

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206619Orig1s000**

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

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 206619	<b>Biopharmaceutics Reviewer:</b> Elsbeth Chikhale, Ph.D.	
<b>Submission Date:</b>	April 21, 2014		
<b>Division:</b>	Division of Antiviral Products	<b>Biopharmaceutics Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	AbbVie, Inc.	<b>Acting Supervisor:</b> Paul Seo, Ph.D.	
<b>Trade Name:</b>	Viekira Pak	<b>Date Assigned:</b>	April 16, 2014
<b>Generic Name:</b>	Ombitasvir, Paritaprevir and Ritonavir Tablets / copackaged with Dasabuvir Tablets	<b>Date of Review:</b>	September 21, 2014
<b>Indication:</b>	Treatment of hepatitis C infection, including patients with cirrhosis	<b>Type of Submission:</b> 505(b)(1) Original (rolling) New Drug Application - Priority	
<b>Dosage form/strengths</b>	Ombitasvir, Paritaprevir and Ritonavir Tablets (12.5 mg/75 mg/50 mg) co-packaged with Dasabuvir Tablets (250mg)		
<b>Route of Administration</b>	Oral		

## **SUMMARY**

### ***Submission:***

The Applicant is seeking approval of a 505(b)(1) New Drug Application (NDA 206619) for a fixed dose combination (FDC) film coated tablet containing 75 mg paritaprevir (ABT-450), 50 mg ritonavir, and 12.5 mg ombitasvir (ABT-267), co-packaged with a film coated tablet containing 250 mg dasabuvir (ABT-333), indicated for the treatment of genotype-1 chronic hepatitis C infection, including patients with cirrhosis. During the development of the FDC tablet and the ABT-333 tablet, a variety of investigational formulations were used and in vitro (dissolution) and/or in vivo (bioavailability/bioequivalence) studies supported the bridging of formulations throughout the product's development.

### ***Review:***

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology for each active in the proposed product
- 2) the proposed dissolution acceptance criteria for each active in the proposed product
- 3) the bridging of the formulations throughout development
- 4) pivotal BE study M14-196 and the 3 relative BA studies: M12-683, M13-391, and M13-331
- 5) the bio-analytical methods of each active and their method validation



## **CONCLUSIONS:**

ONDQA-Biopharmaceutics had evaluated the information provided in NDA 206619 and concludes the following:

### **1) Dissolution methods:**

The following dissolution methods are acceptable:

For Ombitasvir, Paritaprevir and Ritonavir Tablets 12.5mg/75mg/50mg:

Apparatus 2 (paddle) at 75 rpm; 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 0.3% (w/v) polyoxyethylene 10 lauryl ether (POE10LE or equivalent decaethylene glycol mono dodecyl ether) at 37°C

For Dasabuvir Tablets 250mg:

Apparatus 2 (paddle) at 75 rpm; 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 15 mM cetyl triethylammonium bromide (CTAB) at 37°C

### **2) Dissolution acceptance criteria:**

The following dissolution acceptance criteria are acceptable for release and on stability:

Ombitasvir, Paritaprevir and Ritonavir (using USP <711> Table 2):

At 30 minutes, NMT (b) (4) %

At 90 minutes, NLT = (b) (4) %

At 150 minutes, NLT = (b) (4) %

Dasabuvir (using USP <711> Table 1):

Q = (b) (4) % at 15 minutes

### **3) Bridging of the formulations:**

Adequate bridging was performed throughout the product's development.

### **4) Bioequivalence/Relative Bioavailability studies:**

- The pivotal bioequivalence study M14-196 indicate that the 250 mg ABT-333 tablets manufactured in North Chicago, IL, used in the Phase 3 study, and the 250 mg ABT-333 tablets manufactured at the commercial drug product manufacturing site in Sligo, Ireland, are bioequivalent.
- The results from study M13-331 indicate that the ABT-333 250 mg (b) (4) Phase 3 tablets are bioequivalent to the ABT-333 400 mg Phase 2b tablets.
- For the ombitasvir, paritaprevir and ritonavir FDC tablets, relative bioavailability studies M12-683 and M13-391 indicate that several single component and FDC formulations of the ombitasvir, paritaprevir and ritonavir tablets used during the product's development have different ABT-450 bioavailabilities due to the boosting effect of ritonavir on ABT-450 or due to the manufacturing process changes (b) (4)

**5) Bio-analytical methods:**

The bio-analytical methods used to measure concentrations of Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir and its metabolite in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the five analytes was demonstrated during sample processing and long-term storage.

**RECOMMENDATION:**

From a Biopharmaceutics perspective NDA 206619 for ombitasvir/paritaprevir/ritonavir FDC Tablets (12.5mg/75mg/50mg) co-packaged with dasabuvir Tablets (250 mg) is recommended for **APPROVAL**.

**Elsbeth Chikhale, Ph.D.**

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Office of New Drug Quality Assessment

## **BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES**

### **SUBMISSION:**

The Applicant is seeking approval of a 505(b)(1) New Drug Application (NDA) for a fixed dose combination (FDC) film coated tablet containing 75 mg paritaprevir (ABT-450), 50 mg ritonavir, and 12.5 mg ombitasvir (ABT-267), co-packaged with a film coated tablet containing 250 mg dasabuvir (ABT-333), indicated for the treatment of genotype-1 chronic hepatitis C infection, including patients with cirrhosis. The Applicant developed 3 new molecular entities (NMEs), which are all direct-acting antiviral agents (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection: ABT-450 (dosed with ritonavir (r) as a pharmacokinetic enhancer), ABT-267, and ABT-333.

The FDC ombitasvir/ paritaprevir /ritonavir tablet is comprised of [REDACTED] to form the final tablet.

(b) (4)

(b) (4)

The ABT-333 tablet contains dasabuvir (ABT-333) [REDACTED]

(b) (4)

Dissolution is considered a critical quality attribute for the proposed tablets and will be tested as part of the drug product release and stability testing.

### **REVIEW:**

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:

- 1) the proposed dissolution methodology
- 2) dissolution acceptance criteria for each active and each tablet
- 3) the bridging of the formulations
- 4) the pivotal BE study M14-196 and relative BA studies: M12-683, M13-391, and M13-331
- 5) the bio-analytical method and method validation

**BIOPHARMACEUTICS INFORMATION:****PROPOSED FORMULATION:**

The qualitative and quantitative composition of the proposed co-packaged tablets is shown in the two tables below:

**Ombitasvir, Paritaprevir (ABT-450) and Ritonavir Tablets, 12.5mg / 75mg / 50mg:**

Component	Quality Standard	Function	Amount (mg)/Tablet
(b) (4)			
Ombitasvir	In-house standard	Active	12.5
Copovidone, K value 28	NF/Ph. Eur. and In-house standard	(b) (4)	(b) (4)
Vitamin E Polyethylene Glycol Succinate	NF and In-house standard		
Colloidal Silicon Dioxide/ Colloidal Anhydrous Silica	NF/Ph. Eur.		
(b) (4)			
ABT-450	In-house standard	Active	75.0
(b) (4)			
Propylene Glycol Monolaurate Type I	NF/Ph. Eur.	(b) (4)	
(b) (4)			
Ritonavir	USP/Ph. Eur.	PK Enhancer	50.0
(b) (4)			
Sorbitan Monolaurate	NF/Ph. Eur.	(b) (4)	
(b) (4)			
Sodium Stearyl Fumarate	NF/Ph. Eur.	(b) (4)	
Film-Coating			
(b) (4)			
(b) (4)			
(b) (4)			

**Dasabuvir Tablets, 250 mg:**

Component	Quality Standard	Function	Amount (mg)/Tablet
(b) (4)			
Dasabuvir Sodium	In-house	Active	270.26
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.	(b) (4)	(b) (4)
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.		
Lactose Monohydrate	NF/Ph.Eur.		
Copovidone (b) (4)	NF/Ph. Eur.		
Croscarmellose Sodium	NF/Ph. Eur.		
Colloidal Silicon Dioxide / Anhydrous Colloidal Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)			
Film-Coating			
(b) (4)			

(b) (4)

The proposed dosing is to take two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with food without regard to fat or calorie content.

## **PROPOSED DISSOLUTION METHODS AND ACCEPTANCE CRITERIA:**

### **The proposed dissolution method (RTM.C5203) for Ombitasvir/ABT-450/Ritonavir FDC Tablets is:**

Apparatus 2 (paddle) at 75 rpm; 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 0.3% (w/v) polyoxyethylene 10 lauryl ether (or equivalent decaethylene glycol mono dodecyl ether) at 37°C.

### **Dissolution Method Development Report for Ombitasvir, ABT-450 and Ritonavir Tablets 12.5 mg/75 mg/50 mg:**

The dissolution method development reports includes the following information:

#### **Background:**

The Applicant states that the proposed FDC ombitasvir/ paritaprevir / ritonavir drug product is formulated as an immediate release film coated tablet. (b) (4)

Eight dissolution methods were developed to characterize the individual clinical formulations. The dissolution parameters for these methods are summarized in the table below. (b) (4)

#### **➤ Apparatus:**

Apparatus 2 (paddle) was chosen (b) (4)

#### **➤ Solubility:**

(b) (4) ombitasvir, paritaprevir (ABT-450), and ritonavir are all poorly (aqueous) soluble drug substances. (b) (4)

(b) (4)

**Reviewer's Note:**

(b) (4)

*The Applicant is not claiming a BCS class for these 3 compounds, but based on the provided information, these compounds belong to BCS class II/IV.*

➤ **Selection of Dissolution Medium:**

The dissolution method for Ombitasvir/ Paritaprevir (ABT-450)/Ritonavir Tablets was developed

(b) (4)

(b) (4)

(b) (4)

Thus, pH of 6.8 was further evaluated as a possible pH for the dissolution medium.

(b) (4)

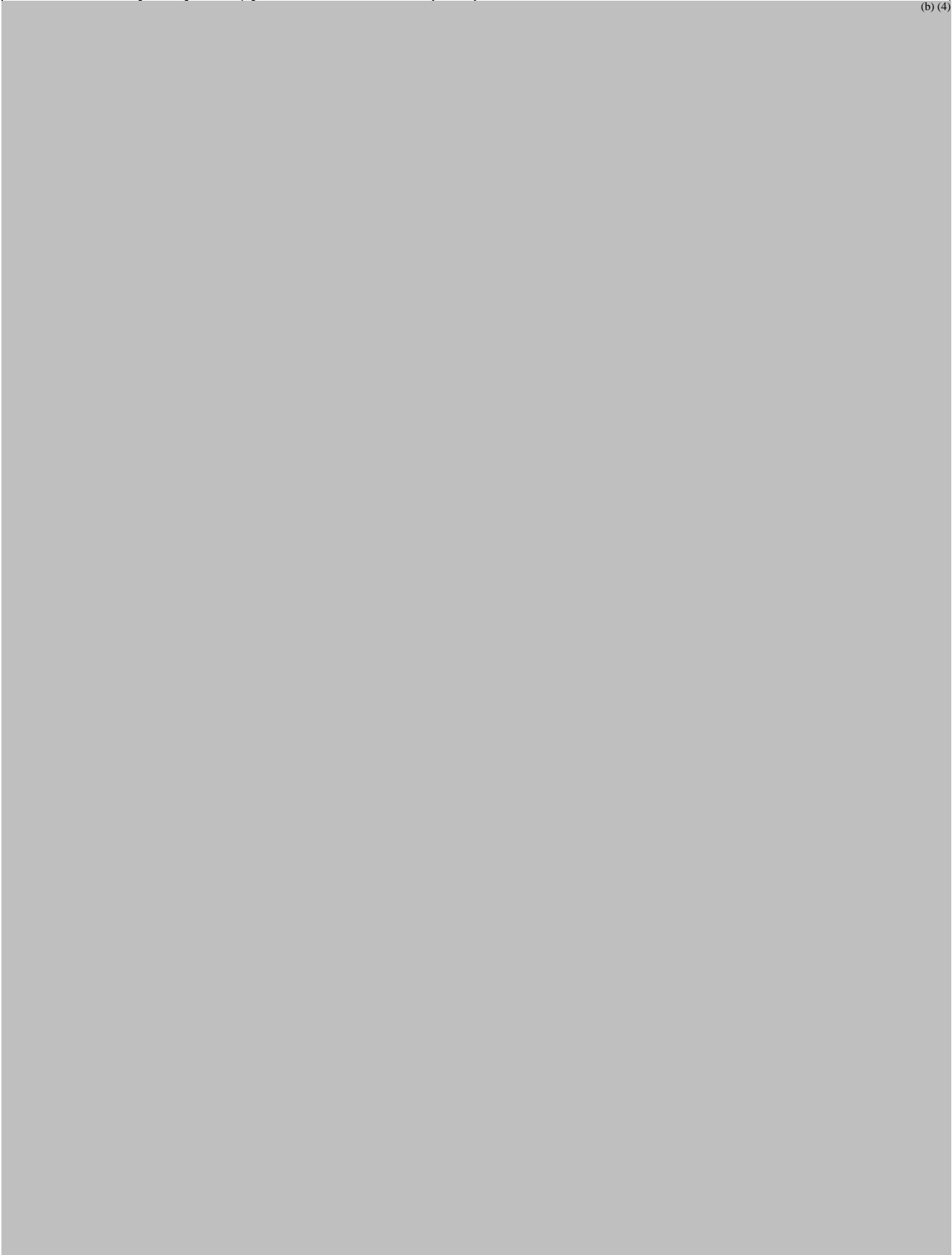
**Solubility of (b) (4) Drug Substances as a function of POE10LE at pH 6.8 and 37 °C:**

(b) (4)



**Kinetic Solubility of (b) (4) Ombitasvir, ABT-450, and Ritonavir Drug Substances in 50 mM sodium phosphate, pH 6.8 with 0.3% (w/v) POE10LE at 37 °C:**

(b) (4)



(b) (4)

➤ **Paddle Speed:**

A paddle speed of 75 rpm was chosen

(b) (4)

(b) (4)

➤ ***Discriminating power of the proposed dissolution method:***

(b) (4)

obtained:

The following dissolution profiles were

Mean Drug Release with (b) (4) ABT-450 in Tablets

(b) (4)

Mean Drug Release with (b) (4) ABT-267 in Tablets

(b) (4)

Mean Drug Release with (b) (4)  
Ritonavir in Tablets

(b) (4)

In order to further evaluate the discriminatory power of the method, tablets [REDACTED] were manufactured and evaluated.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Furthermore, the effect of (b) (4) on drug release from the proposed commercial tablet formulation was studied. (b) (4)

(b) (4)

**Reviewer's assessment of the proposed dissolution method for Ombitasvir, ABT-450 and Ritonavir Tablets 12.5 mg/75 mg/50 mg: ACCEPTABLE**

Based on the physical-chemical properties of ABT-450, ritonavir and ombitasvir, (b) (4), the proposed Ombitasvir/ABT-450/Ritonavir film coated tablet dissolution test parameters have been justified with respect the selected dissolution media pH and media (b) (4) concentration.

**Reviewer's Notes**

- The Clinical Pharmacology Reviewer was informed (b) (4)
- It is noted that the Applicant has not proposed (b) (4)

**Proposed dissolution acceptance criterion for Ombitasvir/ABT-450/Ritonavir FDC Tablets:**

Q= (b) (4) % at (b) (4) for all 3 actives

**Applicant's justification for the proposed dissolution acceptance criterion for Ombitasvir/ABT-450/Ritonavir FDC Tablets:**

The Applicant claims that,

(b) (4)

the tablets give in vivo performance that is equivalent to that of an immediate release formulation. (b) (4)

(b) (4)

Three primary stability batches of Ombitasvir/ABT-450/Ritonavir Tablets (including the pivotal biobatch lot 12-00644) have been tested with the proposed commercial dissolution test procedure. The drug-release profiles of these batches are shown in the graphics below.



**Reviewer's initial assessment of the proposed dissolution acceptance criterion for Ombitasvir/ABT-450/Ritonavir FDC Tablets: *NOT ACCEPTABLE***

***The following information request was sent to the Applicant on July 11, 2014:***

*Although we acknowledge that your proposed product is an immediate release dosage form, (b) (4) ombitasvir, ABT-450, and ritonavir*

(12.5/75/50 mg) tablets, the dissolution acceptance criteria for these drugs requires more than one sampling time point. Therefore, based on the dissolution profile data of these three drug substances (b) (4) we recommend the inclusion of additional dissolution testing time points at 30 minutes and 60 minutes, (b) (4). Specifically, we recommend that the following dissolution acceptance criteria be implemented for these three actives:

FDA's Recommended Dissolution Acceptance Criteria for Ombitasvir, ABT-450, and Ritonavir	
Sampling Time	% Drug Dissolved
30 minutes	(b) (4)
60 minutes	(b) (4)
180 minutes	(b) (4)

Either revise your specifications table for the ombitasvir, ABT-450, and ritonavir FDC tablet accordingly and provide an updated drug product specification sheet for the ombitasvir, ABT-450, and ritonavir FDC tablet or request a telephone conference to discuss our recommendation.

A **teleconference** was held between representatives of FDA and the Applicant on **July 24, 2014**. During the teleconference, the Applicant and FDA agreed on the recommended acceptance criteria for the two early time points of the dissolution test (using Acceptance Table 2 in the USP <711>) for all 3 drug substance as follows:

Time Point	% Drug Dissolved
30 minutes	(b) (4)
90 minutes	(b) (4)

**Reviewer Notes:**

- Although the Acceptance Table 2 in USP<711> recommends specification ranges, this table is recommended for extended release products and therefore is NOT fully applicable to the proposed product under review, which is a (b) (4) immediate release tablet.
- Therefore, for the setting of the dissolution acceptance criteria of this product, Biopharmaceutics considers that the use of an innovative-risk based approach is appropriate and therefore the Applicant's proposal of two time points at 30 and 90 minutes with only one sided limit, instead of a range is adequate because it provides adequate/sufficient control of the initial and middle phases of the dissolution profile of the proposed Ombitasvir, ABT-450, and Ritonavir Tablets.
- For the final (third) dissolution time point, during the teleconference it was agreed that the Applicant will collect dissolution data at the 150 minute time point for the primary stability batches and any additional clinical samples.

The additional dissolution data for the 150 minute time point were submitted in the Applicant's response dated **August 25, 2014**.

In their response, the Applicant states that at the 150 minute time point, all samples went to Stage 2 testing and met the Stage 2 acceptance criteria if Acceptance Table 1 of USP<711> was used. The Applicant claims that a Monte Carlo simulation analysis was performed and showed that a  $Q = (b)(4)\%$  at 150 minutes acceptance criterion using USP <711> Acceptance Table 1 would require Stage 2 testing with a frequency of up to  $(b)(4)\%$ ; however, no samples were predicted to require Stage 3 testing. Based on the frequency of Stage 2 testing, the Applicant performed another analysis using a  $(b)(4)\%$  criterion at 150 minutes using USP <711> Acceptance Table 2. This analysis predicted Stage 2 testing with a frequency of up to  $(b)(4)\%$  and would require Stage 3 testing with a frequency of up to  $(b)(4)\%$ ; the analysis predicts 0% failure for this limit. Therefore, the Applicant proposes a  $(b)(4)\%$  criteria at the 150 minute time point using USP <711> Acceptance Table 2. The Applicant proposed the following revised dissolution acceptance criteria for Ombitasvir/Paritaprevir (ABT-450)/Ritonavir Tablets:

Time Point	% Drug Released	
30 minutes		(b) (4)
90 minutes		
150 minutes		
As per USP <711>, Acceptance Table 2		

*Reference is made to USP<711> Acceptance Tables 1 and 2  
USP<711> Acceptance Table 1 (for immediate-release dosage forms):*

Stage	Number Tested	Acceptance Criteria
S <sub>1</sub>	6	Each unit is not less than $Q + 5\%$ .
S <sub>2</sub>	6	Average of 12 units ( $S_1 + S_2$ ) is equal to or greater than $Q$ , and no unit is less than $Q - 15\%$ .
S <sub>3</sub>	12	Average of 24 units ( $S_1 + S_2 + S_3$ ) is equal to or greater than $Q$ , not more than 2 units are less than $Q - 15\%$ , and no unit is less than $Q - 25\%$ .

*USP<711> Acceptance Table 2 (for extended-release dosage forms):*

Level	Number Tested	Criteria
L <sub>1</sub>	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L <sub>2</sub>	6	The average value of the 12 units ( $L_1 + L_2$ ) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.

	L <sub>3</sub>	12	The average value of the 24 units (L <sub>1</sub> + L <sub>2</sub> + L <sub>3</sub> ) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.
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Taking the innovative-risk based approach of using dissolution sampling time points (b) (4) for the proposed immediate release drug product will provide adequate control of the shape of the dissolution profile of the proposed product at release and on stability. Therefore, the following proposed revised dissolution acceptance criteria for Ombitasvir/Paritaprevir (ABT-450)/Ritonavir Tablets are found to be acceptable.

Time Point	% Drug Released
30 minutes	(b) (4)
90 minutes	(b) (4)
150 minutes	(b) (4)
As per USP <711>, Acceptance Table 2	

**Reviewer's overall assessment of the response with the proposed revised dissolution acceptance criteria for Ombitasvir/ABT-450/Ritonavir FDC Tablets: *ACCEPTABLE***

**The proposed dissolution method (RTM.C5103) for Dasabuvir (ABT-333) Tablets is:**  
Apparatus 2 (paddle), 75 rpm; 900 mL of 0.05M phosphate buffer, pH 6.8 with 15 mM cetyl triethylammonium bromide (CTAB) at 37°C.

**Dissolution Development Report for Dasabuvir Tablets 250mg:**

The dissolution method development report includes the following information:

**Background:**

The proposed commercial dissolution method and specification were developed (b) (4)

The Applicant states that two other dissolution methods were developed to characterize the clinical formulations. A summary of the dissolution methods used during the drug product development is provided in the following table:

➤ **Apparatus:**

USP Apparatus 2 was chosen

(b) (4)

➤ **Solubility:**

(b) (4)

Dasabuvir drug substance is a sodium salt, which has higher apparent aqueous solubility.

(b) (4)

Reviewer's note:

(b) (4)

The Applicant is not claiming a BCS class for ABT-333, but based on the provided information, ABT-333 belong to BCS class II.

➤ **Selection of dissolution medium:**

Based on the ABT-333 drug substance solubility

(b) (4)

claims

Applicant

(b) (4)

as shown in the following table:



(b) (4) the use of 15 mM CTAB as dissolution media is adequate and justified. Therefore, 0.05 M Sodium phosphate buffer, pH 6.8 with 15 mM CTAB is proposed as the dissolution media.

➤ ***Paddle Speed:***

(b) (4)  
To determine the optimal paddle speed (b) (4)  
dissolution experiments were performed at (b) (4) and 75 rpm with the primary stability lot of 250 mg dasabuvir tablets:

(b) (4) The Applicant selected 75 rpm for the development of Dasabuvir Tablets. Based on the studies conducted during development, and the data generated for the primary stability lots of the 250 mg dosage strength, Apparatus 2 at 75 rpm is proposed for the dissolution testing of Dasabuvir Tablets.

➤ ***Discriminating power of the proposed dissolution method:***

(b) (4)

(b) (4) The mean dissolution profiles generated for Dasabuvir Tablets using the proposed dissolution method are shown below.

(b) (4)



Dasabuvir Tablets was evaluated by manufacturing formulations containing drug substance with particle size (b) (4) using the proposed dissolution method. (b) (4)

The mean dissolution profiles are shown in the next plot.

(b) (4)

(b) (4)

The proposed dissolution method

(b) (4)

as shown here.

(b) (4)

*Reviewer's assessment of the proposed dissolution method for Dasabuvir Tablets 250mg:*  
***ACCEPTABLE***

*Based on the provided data, the proposed dissolution method is suitable as a quality control test.*

(b) (4)

**Proposed dissolution acceptance criterion for Dasabuvir (ABT-333) Tablets:**

Q= (b) (4) % at 15 minutes

**Applicant's justification for the proposed dissolution acceptance criterion for ABT-333 Tablets:**

Release and stability testing for the primary stability batches of the 250 mg tablets manufactured at AbbVie's in North Chicago (formerly Abbott, Abbott Park), lot numbers 12-003123, 12-003124 and 12-003125, were performed using the proposed commercial dissolution method in 0.05 M sodium phosphate buffer, pH 6.8 with 15 mM CTAB. The primary stability batches, including the batch used in the pivotal BE study (lot 12-003123), were also used as clinical supplies for the Phase 3 clinical trials.

(b) (4)

**Reviewer's initial assessment of the proposed dissolution acceptance criterion for Dasabuvir Tablets: NOT ACCEPTABLE**

***The following information request was sent to the Applicant on July 11, 2014:***

*Provide an assessment of the percentage of batches of ABT-333 drug product that would require stage 2 and stage 3 testing at lot release if the dissolution acceptance criterion would be set at  $Q = (b) (4)\%$  at 15 minutes. Please perform this assessment with and without lot #12-007842.*

***Applicant's response dated 7/25/14:***

A Monte Carlo Simulation was performed on all of the data with an acceptance criteria of  $Q = (b) (4)\%$  at 15 minutes. As requested by FDA, the simulation was conducted with and without lot #12-007842. As expected, the removal of lot #12-007842 from the analysis resulted in a lower instance of batches going to Stage 2 and 3 testing. The table below presents the Monte Carlo Simulation results.

All Lots			Without Lot 12-007842		
Requires Stage 2		(b) (4)	Requires Stage 2		(b) (4)
Requires Stage 3			Requires Stage 3		
Failure at Stage 3			Failure at Stage 3		

During the teleconference held between the Applicant and FDA, on July 24, 2014, the Applicant agreed to implement an acceptance criterion of  $Q = \text{(b) (4)}\%$  in 15 minutes for Dasabuvir Tablets (ABT-333).

**Reviewer's overall assessment for the proposed revised dissolution acceptance criterion for Dasabuvir (ABT-333) Tablets: *ACCEPTABLE***

*For ABT-333 Tablets, the revised dissolution acceptance criterion of  $Q = \text{(b) (4)}\%$  at 15 minutes is acceptable.*

**BRIDGING OF THE FORMULATIONS:**

The following formulations were used during the development of the Ombitasvir/ABT-450/Ritonavir Tablets:

(b) (4)

The following formulations were used during the development of ABT-333 Tablets.

(b) (4)

The in vitro dissolution profiles for the Phase 3 ABT-333 (250 mg) (b) (4) tablets that were assessed in the relative bioavailability/bioequivalence studies, Study M13-330 (food effect on the ABT-333 250 mg (b) (4) tablet manufactured in North Chicago, IL) (Lot No. 12-003123), Study M13-331 (which compared ABT-333 250 mg (b) (4) tablet, Lot No. 12-003057, to the reference 400 mg tablet) and the to-be-marketed formulation that was assessed in Study M14-196 (which compared ABT-333 250 mg to-be-marketed tablet manufactured at the Sligo, Ireland site to the reference ABT-333 250 mg (b) (4) Phase 3 tablet manufactured at the North Chicago, IL site, Lot No. 13-002795), are illustrated in the following figure.

The bioavailability and bioequivalence studies bridging several developmental and commercial formulations of the Ombitasvir/Paritaprevir (ABT-450)/Ritonavir Tablets as well as the ABT-333 Tablets, are discussed in a separate section of this review (see below under bioavailability and bioequivalence studies).

**Reviewer's assessment of the bridging studies: *SATISFACTORY***

*For the FDC drug product, there was no change between the Phase 3 drug product and the proposed drug product. Nevertheless, dissolution data were provided to indicate that tablet coating did not significantly affect the dissolution profiles of this FDC tablet. For the ABT-333 tablet, the Phase 3 drug product and the proposed drug product were manufactured at different drug product manufacturing sites. The BE study that support this manufacturing site change (M14-196) is discussed and evaluated in a separate section of this review (see below). Additional bridging bioequivalence/relative bioavailability studies (M-13-331, M12-683 and M13-391) are also discussed in a separate section of this review (see below). Overall, adequate bridging was performed throughout drug product development.*



## **BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES:**

The main (pivotal) bioequivalence study is Study M14-196, bridging the 250 mg ABT-333 tablets manufactured in North Chicago, IL with the 250 mg ABT-333 tablets manufactured in Sligo, Ireland. In addition, Biopharmaceutics was asked to review the bioequivalence study M13-331 for ABT-333 tablets, and the relative bioavailability studies, M 12-683 and M-13-391 for the Ombitasvir/ ABT-450/Ritonavir Tablets.

### ➤ **BIOEQUIVALENCE STUDY No. 14-196:**

This study was designed to determine the bioequivalence between the 250 mg ABT-333 tablets manufactured in North Chicago, IL, used in the Phase 3 study, and the 250 mg ABT-333 tablets manufactured at the commercial drug product manufacturing site in Sligo, Ireland. These tablets are identical in composition but manufactured at different sites using a similar process.

The study synopsis and provided results are copied here:

<b>Study Protocol No. (Country):</b> <a href="#">M14-196</a> (USA)	<b>Location:</b> R&D/13/674
<b>Product ID/Bulk Product Lot No.</b>	ABT-333 (250 mg tablet, commercial)/13-002795; ABT-333 (250 mg tablet, Phase 3)/12-003123
<b>Study Objective</b>	To determine the bioequivalence of the ABT-333 commercial formulation with reference to the ABT-333 clinical Phase 3 formulation. For additional information on the assessment of bioequivalence, see Section <a href="#">2.7.1.2.4</a> .
<b>Study Design</b>	Non-fasting, open-label, two-period, randomized, crossover study
<b>Number Subjects Entered/ Number Completed (M/F)</b>	(25 M/7 F)/(23 M/7 F)
<b>Healthy Volunteers/Patients (Age: mean, range)</b>	Healthy volunteers, N = 32: (35.6 years, 20 – 55 years)

#### **Mean ± SD Pharmacokinetic Parameters of ABT-333 and ABT-333 M1 Metabolite**

<b>Regimen</b>	<b>N</b>	<b>C<sub>max</sub> (ng/mL)</b>	<b>T<sub>max</sub> (h)</b>	<b>t<sub>1/2</sub><sup>a</sup> (h)</b>	<b>AUC<sub>t</sub> (ng•h/mL)</b>	<b>AUC<sub>inf</sub> (ng•h/mL)</b>
<b>ABT-333</b>						
Regimen A	30	699 ± 309	3.47 ± 1.31	7.07 ± 1.13	5980 ± 2760	6050 ± 2790
Regimen B	30	749 ± 310	3.33 ± 1.06	7.16 ± 1.24	6110 ± 2540	6180 ± 2570
<b>ABT-333 M1 Metabolite</b>						
Regimen A	30	244 ± 107	4.00 ± 1.26	6.40 ± 1.46	2090 ± 940	2120 ± 942
Regimen B	30	249 ± 87.1	3.87 ± 1.01	6.31 ± 0.94	2140 ± 889	2170 ± 894

Regimen A: ABT-333 250 mg tablet, commercial formulation under non-fasting conditions (test).

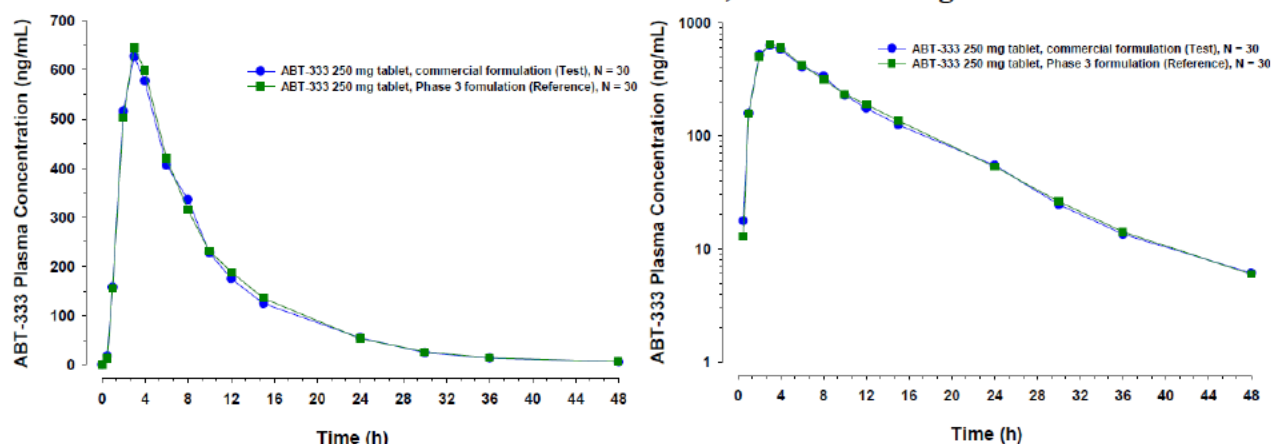
Regimen B: ABT-333 250 mg tablet, clinical Phase 3 formulation under non-fasting conditions (reference).

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

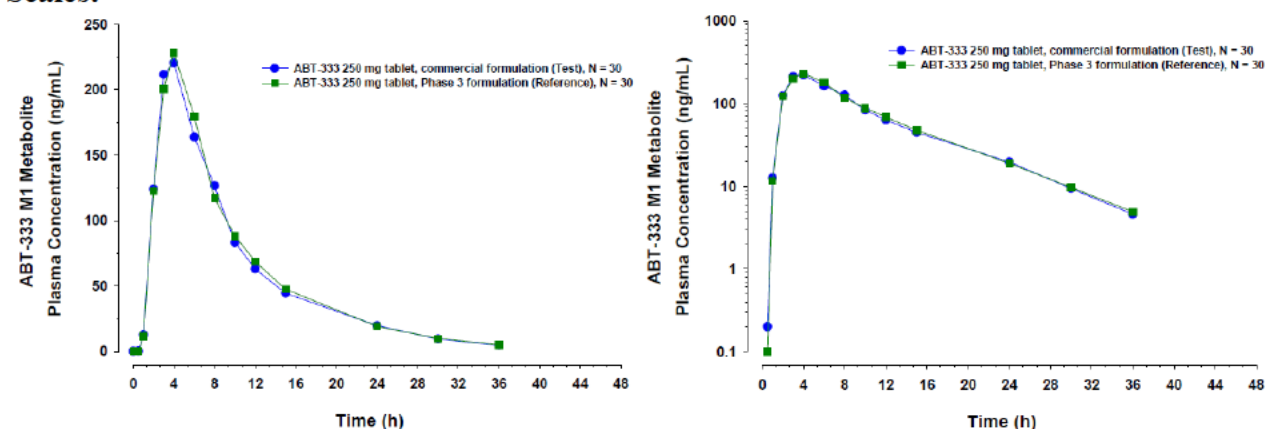
	ABT-333 Test Formulation	ABT-333 Reference Formulation
Dosage Form	Tablet	Tablet
Formulation	Commercial	Clinical Phase 3
Strength	250 mg	250 mg
Bulk Product Lot Number	13-002795	12-003123
Potency (% of Label Claim)	(b) (4)	
Manufacturing Site	AbbVie Sligo, Ireland	AbbVie North Chicago, IL
Manufacturing Date	(b) (4)	

This bioequivalence study was conducted under fed conditions because ABT-333 was administered with food across the clinical program in Phase 1 through 3 studies, which provide bioavailability comparisons in a clinically relevant setting.

#### Mean ABT-333 Plasma Concentration-Time Profiles, Linear and Log-linear Scales:



#### Mean ABT-333 M1 Metabolite Plasma Concentration-Time Profiles, Linear and Log-linear Scales:



The results of the study indicate ABT-333 250 mg commercial tablet (Regimen A) was bioequivalent to the reference ABT-333 250 mg Phase 3 tablet (Regimen B), because the 90% confidence intervals from the analyses of the relative bioavailability ratios for  $C_{max}$  and AUC were contained within the bioequivalence range of 80 to 125%.

**Reviewer's assessment of BE study M14-196 under fed conditions: ACCEPTABLE**

In general, the manufacturing site changes for immediate release drug products are usually supported by comparative in vitro dissolution profile data and bioequivalence studies are usually only required to support manufacturing site changes for extended-release drug products. However, it is noted that in this case, the Applicant performed a bioequivalence (BE) study to support the drug product manufacturing site change for the ABT-333 Tablets and reported the following results:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
ABT-333					
A vs. B	C <sub>max</sub>	638	687	0.929	0.873 – 0.989
	AUC <sub>t</sub>	5442	5636	0.966	0.925 – 1.009
	AUC <sub>∞</sub>	5503	5697	0.966	0.925 – 1.008
ABT-333 M1 Metabolite					
A vs. B	C <sub>max</sub>	225	236	0.954	0.884 – 1.030
	AUC <sub>t</sub>	1903	1984	0.959	0.911 – 1.010
	AUC <sub>∞</sub>	1940	2017	0.962	0.915 – 1.012

Regimen A = ABT-333 250 mg tablet, commercial formulation under non-fasting conditions (Test)

Regimen B = ABT-333 250 mg tablet, clinical Phase 3 formulation under non-fasting conditions (Reference)

- Exponentiation of the least squares means for logarithms.
- Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
- Exponentiation of the endpoints of confidence intervals for the difference of logarithm means.

*This Reviewer confirmed the BE results for the parent drug using phoenix software and the following results were obtained for Dasabuvir (ABT-333) Tablets.*

	90% confidence interval
C <sub>max</sub>	88.45-100.24
AUC <sub>0-t</sub>	92.26-100.42
AUC <sub>0-inf</sub>	92.45-100.51

*These results are in agreement with those reported by the Applicant.*

*Based on the provided data, it can be concluded that the 250 mg ABT-333 tablets manufactured in North Chicago, IL, used in the Phase 3 study, and the 250 mg ABT-333 tablets manufactured at the commercial drug product manufacturing site in Sligo, Ireland are bioequivalent.*

*It was noted that 32 adult male and female subjects (N = 32) were enrolled in the study, and only 30 subjects (23 males and 7 females) completed the study. Subject 126, a 36 year-old white male, was lost to follow-up because he did not return for Period 2. Subject 130, a 27 year-old black male, was discontinued from the study due to an elevated alanine aminotransferase (ALT) level at the Period 2/Day –1 visit (7 days after dosing in Period 1).*

➤ **BIOEQUIVALENCE STUDY No. 13-331:**

This Phase 1, two-period crossover study was designed to evaluate the bioavailability of ABT-333 250 mg (b) (4) test tablet relative to the ABT-333 400 mg Phase 2b reference tablet under fed conditions.

The study synopsis and provided results are copied here:

Study Protocol No. (Country): <a href="#">M13-331</a> (USA)	Location: R&D/12/1005
Product ID/Bulk Product Lot No.	ABT-333 (250 mg tablet, (b) (4))/12-003057; ABT-333 (400 mg tablet, Phase 2b)/11-002720
Study Objective	To assess the relative bioavailability of the 250 mg ABT-333 (b) (4) formulation used in Phase 3 studies as compared to the 400 mg ABT-333 formulation used in Phase 2b
Study Design	Non-fasting, open-label, two-period, randomized, crossover study
Number Subjects Entered/ Number Completed (M/F)	(28 M/4 F)/(28 M/4 F)
Healthy Volunteers/Patients (Age: mean, range)	Healthy volunteers, N = 32: (35.9 years, 20 – 54 years)

Mean ± SD Pharmacokinetic Parameters of ABT-333 and ABT-333 M1 Metabolite						
Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
ABT-333						
Regimen A	32	818 ± 337	3.5 ± 1.0 <sup>b</sup>	7.66 ± 1.55	6060 ± 2220	6100 ± 2240
Regimen B	32	887 ± 274	2.9 ± 0.8	7.44 ± 1.32	6230 ± 1730	6280 ± 1750
ABT-333 M1 Metabolite						
Regimen A	32	288 ± 117	4.1 ± 0.9 <sup>b</sup>	5.99 ± 0.74	2120 ± 951	2140 ± 954
Regimen B	32	310 ± 112	3.7 ± 0.8	6.08 ± 0.78	2250 ± 831	2280 ± 831

Regimen A: ABT-333 250 mg (b) (4) Phase 3 tablet under non-fasting conditions (test).

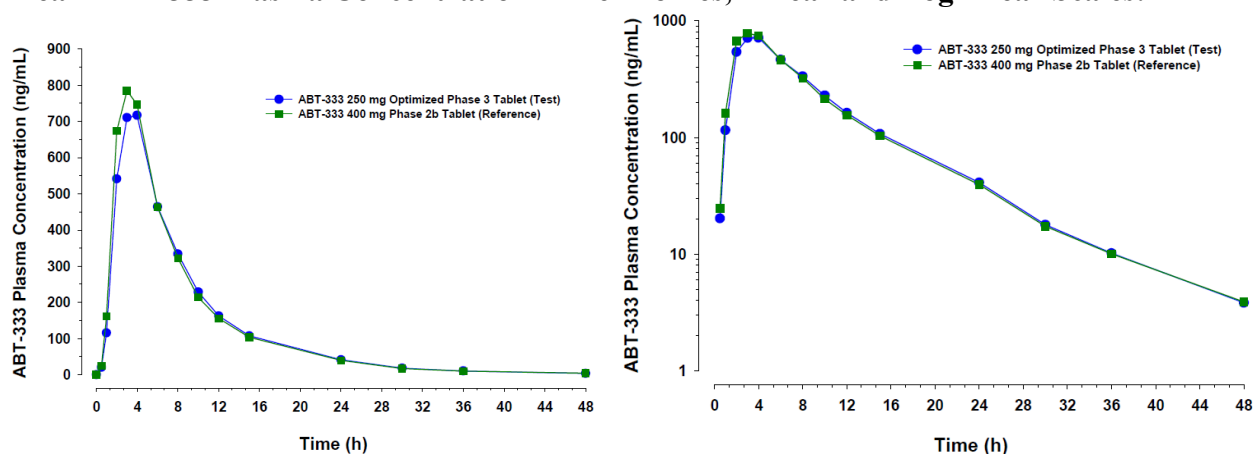
Regimen B: ABT-333 400 mg Phase 2b tablet under non-fasting conditions (reference).

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

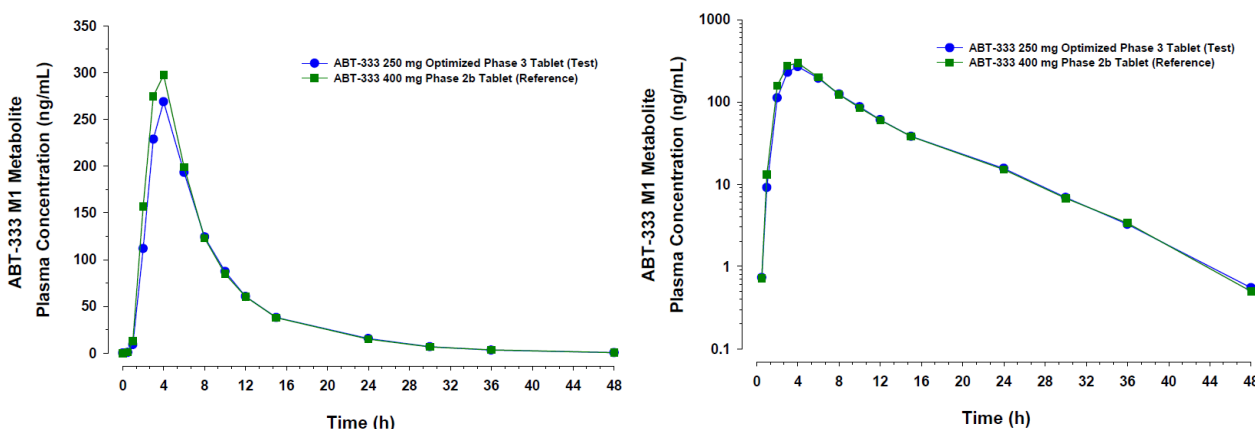
b. Statistically significantly different from reference regimen (Regimen B, ANOVA, p < 0.05).

	<b>ABT-333 Test Formulation</b>	<b>ABT-333 Reference Formulation</b>
Dosage Form	Tablet	Tablet
Formulation	(b) (4)	Phase 2b
Strength (mg)	250 mg	400 mg
Bulk Product Lot Number	12-003057	11-002720
Manufacturing Site	Abbott Abbott Park, IL	Abbott Abbott Park, IL
Finishing Lot Number	12-005426	12-005425

### Mean ABT-333 Plasma Concentration-Time Profiles, Linear and Log-linear Scales:



### Mean ABT-333 M1 Metabolite Plasma Concentration-Time Profiles, Linear and Log-linear Scales:



The results of the study indicate that the administration of the ABT-333 250 mg (b) (4) Phase 3 tablet (Regimen A) under fed conditions resulted in  $\leq 10\%$  decrease in ABT-333 and ABT-333 M1 metabolite  $C_{\max}$  and AUC central values relative to the reference ABT-333 400 mg Phase 2b tablet (Regimen B). The test ABT-333 250 mg (b) (4) Phase 3 tablet (Regimen A) was bioequivalent under fed conditions, to the reference ABT-333 400 mg Phase 2b tablet (Regimen B) as the 90% confidence intervals from the analyses of the relative bioavailability ratios for  $C_{\max}$  and AUC were within the bioequivalence range of 0.80 to 1.25.



**Reviewer's assessment of BE study M13-331 under fed conditions: ACCEPTABLE**

The following table includes the study results:

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-333					
A vs. B	C <sub>max</sub>	762	847	0.900	0.820 - 0.987
	AUC <sub>t</sub>	5755	6018	0.956	0.892 - 1.025
	AUC <sub>∞</sub>	5799	6061	0.957	0.893 - 1.025
ABT-333 M1 Metabolite					
A vs. B	C <sub>max</sub>	268	290	0.921	0.853 - 0.996
	AUC <sub>t</sub>	1971	2108	0.935	0.879 - 0.994
	AUC <sub>∞</sub>	2000	2140	0.934	0.880 - 0.992

Regimen A = ABT-333 250 mg (b) (4) Phase 3 tablet under non-fasting conditions (Test)

Regimen B = ABT-333 400 mg Phase 2b tablet under non-fasting conditions (Reference)

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The study results from M13-331 indicate that the ABT-333 250 mg (b) (4) Phase 3 tablets are bioequivalent to the ABT-333 400 mg Phase 2b tablets because the 90% confidence intervals from the analyses for C<sub>max</sub> and AUC were within the bioequivalence range of 80 to 125%. These results support the bridging of the formulations for the ABT-333 Tablets.

It is noted that all 32 subjects enrolled in this study, completed the study and no discontinuations were reported.

➤ **BIOAVAILABILITY STUDY No. 12-683:**

This is a relative bioavailability study designed to assess the bioavailability of ABT-450 when taking tablets of ABT-450 co-formulated with ritonavir in the same tablet vs. using single tablets for ABT-450 and ritonavir. Based on results from previous Phase 2 studies and initial results from an ABT-450/ritonavir co-formulation (Study M11-388), four different ABT-450/ ritonavir co-formulated tablets were developed and tested in this study.

The Applicant states that the pharmacokinetics of ABT-450 are nonlinear and increase supra-proportionally with dose when administered with ritonavir. A 2.7-fold increase in dose from 75 mg to 200 mg increased ABT-450 AUC by 30-fold. ABT-450 is co-dosed with ritonavir to boost its pharmacokinetics. Separate ABT-450 and ritonavir formulations have been co-administered in Phase 1 and Phase 2 studies. ABT-450 is being co-formulated with ritonavir for convenience and to reduce dosing errors. Phase 2 studies have evaluated ABT-450 doses ranging from 50 mg to 250 mg with 100 mg ritonavir. The doses of ABT-450/ ritonavir co-formulated tablets tested in this study were 75/100 mg, 100/100 mg, 150/100 mg, and 200/100 mg. The doses were within the projected range of potentially efficacious doses that could be used in Phase 2 and Phase 3 clinical studies. ABT-450 doses of 100 mg, 150 mg, and 200 mg co-dosed with ritonavir 100 mg capsules are being evaluated in the proposed Phase 2b study.

The study synopsis and provided results are copied here:

<b>Study Protocol No. (Country):</b> <a href="#">M12-683</a> (USA)	<b>Location:</b> R&D/11/974
<b>Product ID/Bulk Product Lot No.</b>	ABT-450/r (37.5 mg/50 mg, total dose: 75 mg/100 mg co-formulated tablet)/10-004471; ABT-450/r (50 mg/50 mg, total dose: 100 mg/100 mg co-formulated tablet)/11-002402; ABT-450/r (75 mg/50 mg, total dose: 150 mg/100 mg co-formulated tablet)/10-004472; ABT-450/r (100 mg/50 mg, total dose: 200 mg/100 mg co-formulated tablet)/11-002024; ABT-450 (50 mg <sup>(b) (4)</sup> tablet)/10-003507; ritonavir (100 mg SGC)/10-002930
<b>Study Objective</b>	To assess the bioavailability of four different dosage strengths of ABT-450 administered with ritonavir (ABT-450/r) co-formulated tablets compared to the reference ABT-450 <sup>(b) (4)</sup> tablet formulation coadministered with ritonavir 100 mg capsule
<b>Study Design</b>	Single-dose, non-fasting, open-label, randomized, 2-group, 4-period crossover study design. ABT-450 formulation: co-formulated ABT-450/r and ABT-450 <sup>(b) (4)</sup> tablets
<b>Number Subjects Entered/Number Completed (M/F)</b>	(37 M/3 F)/ (36 M/3 F)
<b>Healthy Volunteers/Patients (Age: mean, range)</b>	Healthy volunteers, N = 40: (32.0 years, 19 – 45 years)

**Mean ± SD Pharmacokinetic Parameters of ABT-450**

Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
<b>ABT-450</b>						
Regimen A	20	41.2 ± 21.0	3.8 ± 1.3	6.81 ± 1.92	409 ± 198	420 ± 199
Regimen B	20	116 ± 78.5	4.3 ± 1.9	6.58 ± 1.95	948 ± 506	961 ± 508
Regimen C	20	74.0 ± 40.1	4.8 ± 1.4	6.45 ± 1.61	711 ± 308	721 ± 310
Regimen D	20	370 ± 428	5.4 ± 1.9	5.98 ± 1.25	2500 ± 2200	2520 ± 2210
Regimen E	20	544 ± 373	6.6 ± 2.2	5.25 ± 1.09	3390 ± 2290	3400 ± 2290
Regimen F	19	2440 ± 1050	5.6 ± 1.7	4.40 ± 0.86	12900 ± 6220	12900 ± 6220
Regimen G	20	381 ± 328	7.1 ± 2.2	5.83 ± 1.06	2660 ± 2450	2670 ± 2450
Regimen H	20	1400 ± 1060	5.9 ± 1.8	4.91 ± 1.44	7590 ± 4930	7600 ± 4930

Study Protocol No. (Country):  
M12-683 (USA)

Mean ± SD Pharmacokinetic Parameters of Ritonavir

Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
Ritonavir						
Regimen A	20	509 ± 215	4.8 ± 1.2	5.28 ± 1.56	3940 ± 2110	4010 ± 2110
Regimen B	20	772 ± 389	4.1 ± 1.3	5.13 ± 1.14	5050 ± 2460	5120 ± 2470
Regimen C	20	632 ± 374	5.4 ± 2.0	5.10 ± 0.93	4640 ± 2760	4720 ± 2760
Regimen D	20	839 ± 436	6.3 ± 2.6	4.60 ± 0.67	5630 ± 3080	5710 ± 3080
Regimen E	20	895 ± 431	6.2 ± 2.3	4.23 ± 0.84	6070 ± 3260	6140 ± 3320
Regimen F	19	1190 ± 336	5.5 ± 1.6	3.74 ± 0.66	8100 ± 3270	8160 ± 3290
Regimen G	20	760 ± 402	7.2 ± 2.1	4.48 ± 0.76	5560 ± 2740	5630 ± 2750
Regimen H	20	1030 ± 428	5.4 ± 1.7	4.15 ± 0.76	7210 ± 3100	7270 ± 3110

Regimen A: Two ABT-450/r 37.5 mg/50 mg co-formulated tablets administered under non-fasting conditions (test formulation).

Regimen B: Two ABT-450/r 50 mg/50 mg co-formulated tablets administered under non-fasting conditions (test formulation).

Regimen C: Two ABT-450 50 mg (b) (4) tablets and one ritonavir 100 mg capsule administered under non-fasting conditions (reference formulation).

Regimen D: Three ABT-450 50 mg (b) (4) tablets and one ritonavir 100 mg capsule administered under non-fasting conditions (reference formulation).

Regimen E: Two ABT-450/r 75 mg/50 mg co-formulated tablets administered under non-fasting conditions (test formulation).

Regimen F: Two ABT-450/r 100 mg/50 mg co-formulated tablets administered under non-fasting conditions (test formulation).

Regimen G: Three ABT-450 50 mg (b) (4) tablets and one ritonavir 100 mg capsule administered under non-fasting conditions (reference formulation).

Regimen H: Four ABT-450 50 mg (b) (4) tablets and one ritonavir 100 mg capsule administered under non-fasting conditions (reference formulation).

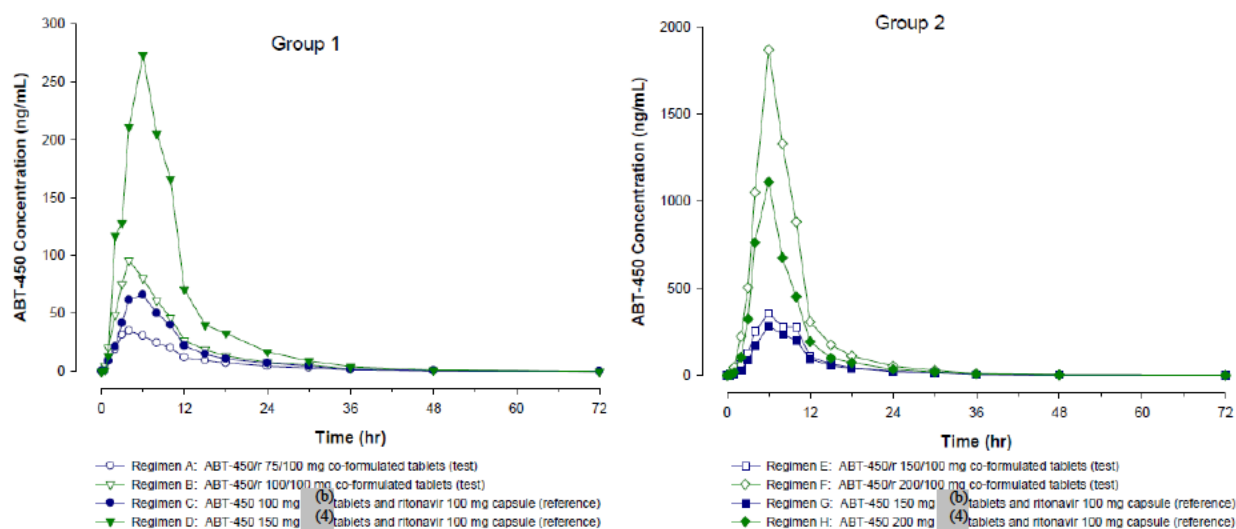
a. Harmonic mean ± pseudo-standard deviation.

	Test Formulation for ABT-450/r		Reference Formulation (Regimens C and D)	
	Co-formulated Tablets		ABT-450	Ritonavir
	75/100 mg Co-formulated Tablet (Regimen A)	100/100 mg Co-formulated Tablet (Regimen B)	Reference	Reference
Dosage Form	Co-formulated Tablet	Co-formulated Tablet	(b) (4) Tablet	Soft Gelatin Capsule
Strength (mg)	37.5 mg/50 mg	50 mg/50 mg	50 mg	100 mg
Bulk Product Lot Number	10-004471	11-002402	10-003507	10-002930
Potency (% of Label Claim)	(b) (4)			
Manufacturing Site	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois

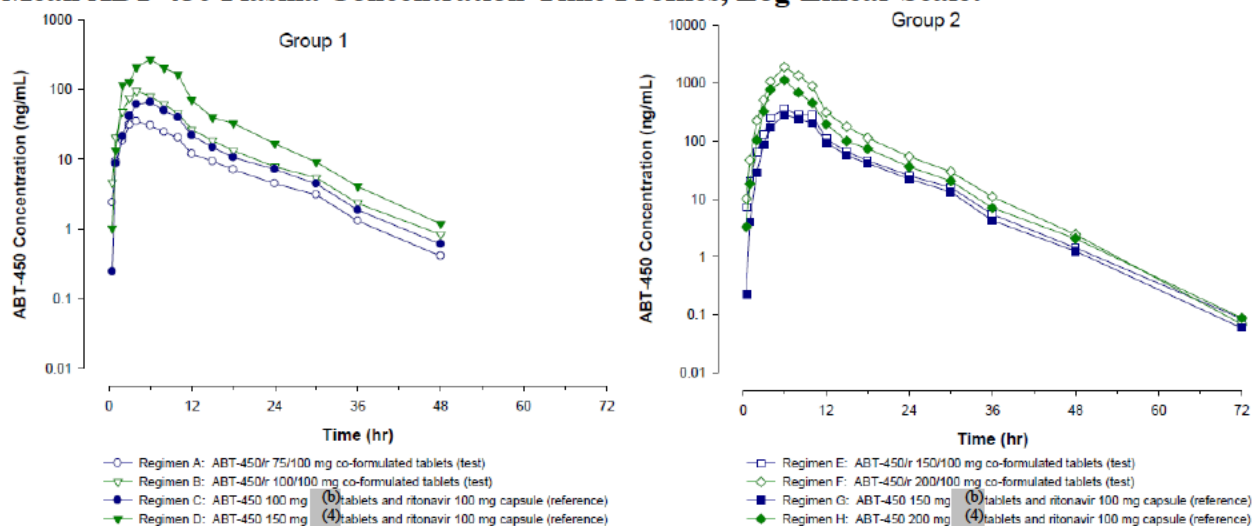


	Test Formulation for ABT-450/r		Reference Formulation (Regimens G and H)	
	Co-formulated Tablets		ABT-450	Ritonavir
	150/100 mg Co-formulated Tablet (Regimen E)	200/100 mg Co-formulated Tablet (Regimen F)	Reference	Reference
	Co-formulated Tablet	Co-formulated Tablet	(b) (4) Tablet	Soft Gelatin Capsule
Dosage Form				
Strength (mg)	75 mg/50 mg	100 mg/50 mg	50 mg	100 mg
Bulk Product Lot Number	10-004472	11-002024	10-003507	10-002930
Potency (% of Label Claim)	(b) (4)			
Manufacturing Site	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois	Abbott Laboratories Lake County, Illinois

### Mean ABT-450 Plasma Concentration-Time Profiles, Linear Scale:



### Mean ABT-450 Plasma Concentration-Time Profiles, Log-Linear Scale:



ABT-450 exposures (AUC and  $C_{max}$ ) from the 75/100 mg ABT-450/ritonavir co-formulated tablets ( $2 \times 37.5/50$  mg) were about 45% lower compared to the 100 mg ABT-450 (b) (4) tablets ( $2 \times 50$  mg) administered with the 100 mg ritonavir capsule ( $1 \times 100$  mg); ritonavir exposures (AUC and  $C_{max}$ ) from the 75/100 mg ABT-450/r co-formulated tablets ( $2 \times 37.5/50$  mg) were around 15% lower compared to the 100 mg ABT-450 (b) (4) tablets ( $2 \times 50$  mg) administered

with the 100 mg ritonavir capsule (1 × 100 mg). ABT-450 exposures (AUC and C<sub>max</sub>) from the 100/100 mg ABT-450/r co-formulated tablets (2 × 50/50 mg) were around 30~50% higher compared to the 100 mg ABT-450 (b) (4) tablets (2 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg); ritonavir exposures (AUC and C<sub>max</sub>) from the 100/100 mg ABT-450/r co-formulated tablets (2 × 50/50 mg) were about 12~25% higher compared to the 100 mg ABT-450 (b) (4) tablets (2 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg).

ABT-450 exposures (AUC and C<sub>max</sub>) from the 150/100 mg ABT-450/r co-formulated tablets (2 × 75/50 mg) were about 35~53% higher compared to the 150 mg ABT-450 (b) (4) tablets (3 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg); ritonavir exposures (AUC and C<sub>max</sub>) from the 150/100 mg ABT-450/r co-formulated tablets (2 × 75/50 mg) were approximately 7~22% higher compared to the 150 mg ABT-450 (b) (4) tablets (3 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg). ABT-450 exposures (AUC and C<sub>max</sub>) from the 200/100 mg ABT-450/r co-formulated tablets (2 × 100/50 mg) were around 2-fold of the 200 mg ABT-450 (b) (4) tablets (4 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg); ritonavir exposures (AUC and C<sub>max</sub>) from the 200/100 mg ABT-450/r co-formulated tablets (2 × 100/50 mg) were around 13~23% higher compared to the 200 mg ABT-450 (b) (4) tablets (4 × 50 mg) administered with the 100 mg ritonavir capsule (1 × 100 mg).

The pharmacokinetics of ABT-450 are nonlinear and increase supra-proportionally with dose when co-administered with ritonavir. A 2.7-fold increase in dose from 75 mg to 200 mg increased ABT-450 AUC by 30-fold. ABT-450 T<sub>max</sub> (3.8 ~ 7.1 hours) and harmonic mean t<sub>1/2</sub> (4.4 ~ 6.8 hours) were similar across formulations. The variability in C<sub>max</sub> and AUC observed following ABT-450 administration was comparable between the two formulations, ranging from 43% to 117%.

**Reviewer's assessment of study 12-683: ACCEPTABLE**

*The Applicant reported the following results for ABT-450:*

**Group 1:**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>b</sup>	90% Confidence Interval
A vs. C 75/100 mg Co-formulation vs. 100 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	C <sub>max</sub>	36.1	64.5	0.560	0.467 - 0.672
	AUC <sub>t</sub>	370.3	654.1	0.566	0.505 - 0.634
	AUC <sub>∞</sub>	382.6	664.7	0.576	0.516 - 0.642
B vs. C 100/100 mg Co-formulation vs. 100 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	C <sub>max</sub>	96.7	64.5	1.498	1.237 - 1.815
	AUC <sub>t</sub>	847.3	654.1	1.295	1.155 - 1.453
	AUC <sub>∞</sub>	860.7	664.7	1.295	1.157 - 1.449
B vs. D 100/100 mg Co-formulation vs. 150 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	C <sub>max</sub>	96.7	237.4	0.407	0.308 - 0.539
	AUC <sub>t</sub>	847.3	1903.2	0.445	0.368 - 0.539
	AUC <sub>∞</sub>	860.7	1918.8	0.449	0.371 - 0.542

**Group 2:**

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>b</sup>	90% Confidence Interval
E vs. G	C <sub>max</sub>	418.4	273.8	1.528	1.165 – 2.005
150/100 mg	AUC <sub>t</sub>	2805.5	2073.0	1.353	1.117 – 1.639
Co-formulation vs. 150 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	AUC <sub>∞</sub>	2819.2	2088.0	1.350	1.116 – 1.634
E vs. H	C <sub>max</sub>	418.4	1021.7	0.410	0.312 – 0.537
150/100 mg	AUC <sub>t</sub>	2805.5	6067.4	0.462	0.382 – 0.560
Co-formulation vs. 200 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	AUC <sub>∞</sub>	2819.2	6083.1	0.463	0.383 – 0.561
F vs. H	C <sub>max</sub>	2203.7	1021.7	2.157	1.636 – 2.843
200/100 mg	AUC <sub>t</sub>	11553.1	6067.4	1.904	1.567 – 2.314
Co-formulation vs. 200 mg ABT-450 (b) (4) plus 100 mg ritonavir capsule	AUC <sub>∞</sub>	11560.1	6083.1	1.900	1.565 – 2.307

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

*ABT-450/ritonavir co-formulated tablets have 30-53% higher ABT-450 bioavailability than the ABT-450 tablets co-administered with ritonavir at doses of 100/100 mg and 150/100 mg. However, at the 200/100 mg dose, the relative ABT-450 bioavailability of the co-formulated tablets of ABT-450/ritonavir is approximately 2-fold of the exposure from the ABT-450 tablets co-administered with ritonavir. Since ritonavir is a booster and does not have direct antiviral activity at the studied doses, the relative bioavailability of ritonavir itself is not considered clinically relevant in this study. This study supports the bridging of the developmental formulations for the ABT-450/r/ABT-267 Tablets.*

*It is noted that 39 of 40 subjects (36 males and 3 females) completed the study. One subject in Group 1 completed all study activities but did not return for the follow-up safety visit. Therefore, one subject was lost to follow-up and did not complete the study.*

➤ **BIOAVAILABILITY STUDY No. 13-391:**

During the clinical development program, four different ABT-450 formulations were used: ABT-450 (b) (4) ABT-450 (b) (4) tablet, ABT-450 and ritonavir co-formulated (b) (4) tablet (ABT-450/r) and ABT-450/r/ABT-267 co-formulated tablet (coated (b) (4)). Of these, the (b) (4) and (b) (4) tablets were evaluated in Phase 2 studies (co-administered with ritonavir soft gelatin capsules [SGC]). The (b) (4) ABT-450/r/ABT-267 co-formulated tablets (75/50/12.5 mg) and (100/50/12.5 mg) were evaluated in this relative bioavailability study where they were compared to the ABT-450 (b) (4) tablet co-administered with ritonavir and ABT-267, and ABT-450/r co-formulated tablets co-administered with ABT-267. Note that the to-be-marketed coated ABT-450/ritonavir/ABT-267 tablet was evaluated in the Phase 3 studies.



The study synopsis and provided results are copied here:

<b>Study Protocol No. (Country):</b> M13-391 (USA)	<b>Location:</b> R&D/12/514
<b>Product ID/Bulk Product Lot No.</b>	ABT-450 (50 mg (b) (4))/11-000781; Ritonavir (100 mg SGC)/11-005635; ABT-267 (25 mg (b) (4))/11-000867; ABT-450/r (75/50 mg)/10-004472; ABT-450/r (100/50 mg)/11-002024; ABT-450/r/ABT-267 (75/50/12.5 mg)/12-000382; ABT-450/r/ABT-267 (100/50/12.5 g)/12-000457
<b>Study Objective</b>	To assess the bioavailability of 2 different dosage strengths of ABT-450/r/ABT-267 co-formulated tablets compared to the reference ABT-450 (b) (4) tablets coadministered with ritonavir and ABT-267, and the reference ABT-450/r co-formulated tablets coadministered with ABT-267
<b>Study Design</b>	Single-dose, open-label, non-fasting study was conducted according to a three-period, randomized, complete crossover design in two groups
<b>Number Subjects Entered/ Number Completed (M/F)</b>	Group 1: (18 M/3 F)/(14 M/3 F); Group 2: (19 M/2 F)/(18 M/2 F)
<b>Healthy Volunteers/Patients (Age: mean, range)</b>	Healthy volunteers, Group 1, N = 21: (38.9 years, 24 – 54 years) Healthy volunteers, Group 2, N = 21: (38.9 years, 20 – 56 years)

**Mean ± SD Pharmacokinetic Parameters of ABT-450**

Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
<b>Group 1: ABT-450/r/ABT-267 150/100/25 mg</b>						
Regimen A; ABT-450	19	713 ± 536	4.2 ± 1.2	5.50 ± 1.51	3930 ± 2170	3950 ± 2170
Regimen B; ABT-450	18	370 ± 339	4.2 ± 1.4	6.39 ± 1.59	2260 ± 1340	2280 ± 1340
Regimen C; ABT-450	19	701 ± 498	4.4 ± 1.3	5.29 ± 1.44	4140 ± 2270	4160 ± 2270
<b>Group 2: ABT-450/r/ABT-267 200/100/25 mg</b>						
Regimen D; ABT-450	20	2010 ± 2030	4.3 ± 0.8	5.35 ± 1.28	10700 ± 10400	10700 ± 10400
Regimen E; ABT-450	21	1590 ± 2350	4.6 ± 2.1	5.60 ± 1.64	7660 ± 9880	7680 ± 9880
Regimen F; ABT-450	21	2450 ± 2540	4.3 ± 1.1	5.36 ± 1.17	13100 ± 12700	13100 ± 12700

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (Test Formulation 1).

Regimen B: Three ABT-450 50 mg (b) (4) tablets + one ritonavir 100 mg capsule + one ABT-267 25 mg (b) (4) tablet (Reference 1).

Regimen C: Two ABT-450/r 75/50 mg co-formulated tablets + one ABT-267 25 mg (b) (4) tablet (Reference 2).

Regimen D: Two ABT-450/r/ABT-267 100/50/12.5 mg co-formulated tablets (Test Formulation 2).

Regimen E: Four ABT-450 50 mg (b) (4) tablets + one ritonavir 100 mg capsule + one ABT-267 25 mg (b) (4) tablet (Reference 3).

Regimen F: Two ABT-450/r 100/50 mg co-formulated tablets + one ABT-267 25 mg (b) (4) tablet (Reference 4).

a. Harmonic mean ± pseudo-standard deviation.

Study Protocol No. (Country):  
M13-391 (USA)

**Mean ± SD Pharmacokinetic Parameters of Ritonavir**

Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
<b>Group 1: ABT-450/r/ABT-267 150/100/25 mg</b>						
Regimen A; Ritonavir	19	1420 ± 521	4.0 ± 1.0	4.53 ± 0.81	8720 ± 3610	8780 ± 3620
Regimen B; Ritonavir	18	1180 ± 551	4.6 ± 2.2	4.84 ± 1.05	7580 ± 3010	7650 ± 3040
Regimen C; Ritonavir	19	1380 ± 512	4.2 ± 1.2	4.51 ± 1.07	8520 ± 3620	8580 ± 3640
<b>Group 2: ABT-450/r/ABT-267 200/100/25 mg</b>						
Regimen D; Ritonavir	20	1560 ± 610	4.4 ± 0.8	4.44 ± 1.06	10300 ± 4710	10400 ± 4710
Regimen E; Ritonavir	21	1340 ± 561	4.7 ± 3.1	4.69 ± 0.74	9310 ± 4480	9380 ± 4490
Regimen F; Ritonavir	21	1530 ± 632	4.2 ± 0.8	4.29 ± 0.69	10600 ± 4790	10600 ± 4800

**Mean ± SD Pharmacokinetic Parameters of ABT-267**

Regimen	N	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	t <sub>1/2</sub> <sup>a</sup> (h)	AUC <sub>t</sub> (ng•h/mL)	AUC <sub>inf</sub> (ng•h/mL)
<b>Group 1: ABT-450/r/ABT-267 150/100/25 mg</b>						
Regimen A; ABT-267	19	106 ± 26.7	4.9 ± 0.8	23.4 ± 5.89	1330 ± 306	1460 ± 364
Regimen B; ABT-267	18	113 ± 28.4	4.8 ± 0.9	22.5 ± 4.90	1390 ± 270	1500 ± 308
Regimen C; ABT-267	19	124 ± 33.1	4.4 ± 1.1	23.7 ± 7.01	1490 ± 358	1630 ± 400
<b>Group 2: ABT-450/r/ABT-267 200/100/25 mg</b>						
Regimen D; ABT-267	20	117 ± 30.3	5.1 ± 0.5	22.5 ± 5.44	1480 ± 395	1620 ± 514
Regimen E; ABT-267	21	116 ± 29.4	4.9 ± 0.5	23.2 ± 5.43	1450 ± 404	1590 ± 531
Regimen F; ABT-267	21	124 ± 33.8	4.5 ± 1.0	22.8 ± 5.70	1530 ± 415	1670 ± 511

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (Test Formulation 1).

Regimen B: Three ABT-450 50 mg (b) (4) tablets + one ritonavir 100 mg capsule + one ABT-267 25 mg (b) (4) tablet (Reference 1).

Regimen C: Two ABT-450/r 75/50 mg co-formulated tablets + one ABT-267 25 mg (b) (4) tablet (Reference 2).

Regimen D: Two ABT-450/r/ABT-267 100/50/12.5 mg co-formulated tablets (Test Formulation 2).

Regimen E: Four ABT-450 50 mg (b) (4) tablets + one ritonavir 100 mg capsule + one ABT-267 25 mg (b) (4) tablet (Reference 3).

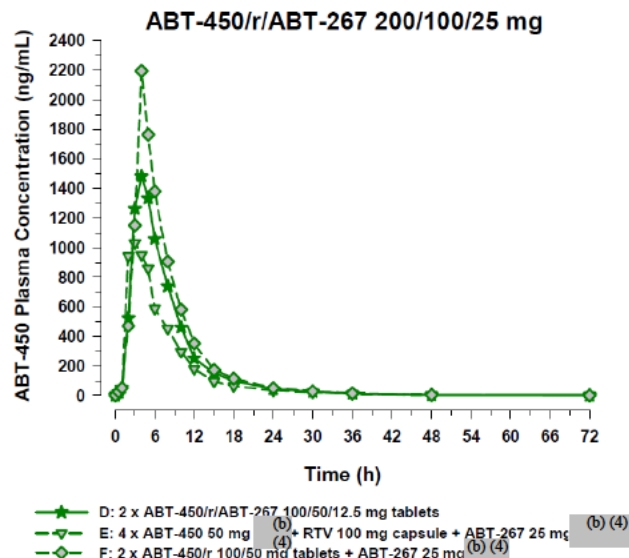
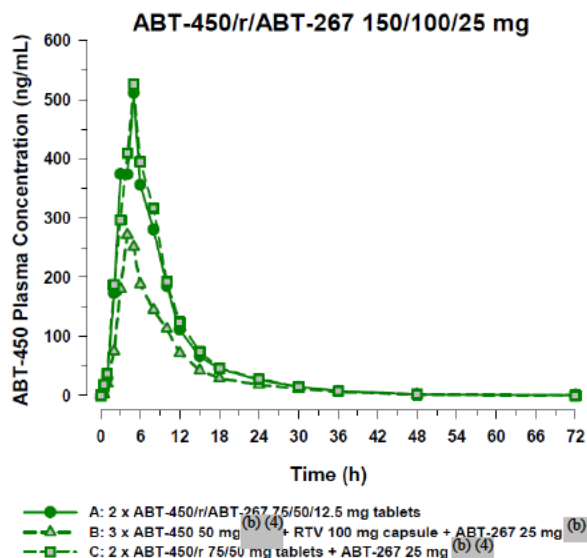
Regimen F: Two ABT-450/r 100/50 mg co-formulated tablets + one ABT-267 25 mg (b) (4) tablet (Reference 4).

a. Harmonic mean ± pseudo-standard deviation.

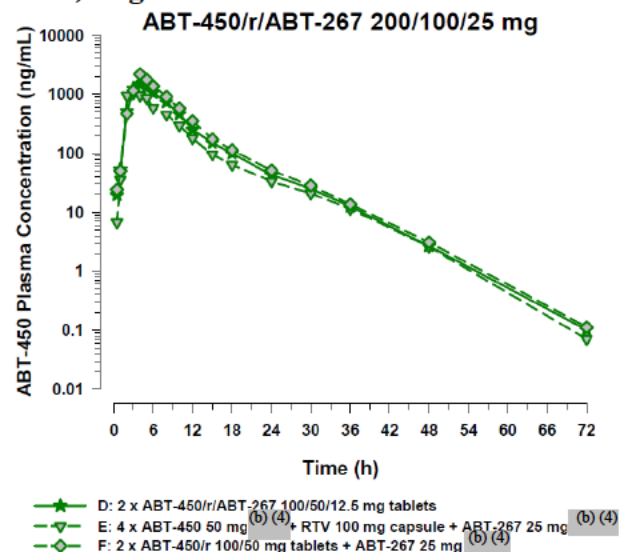
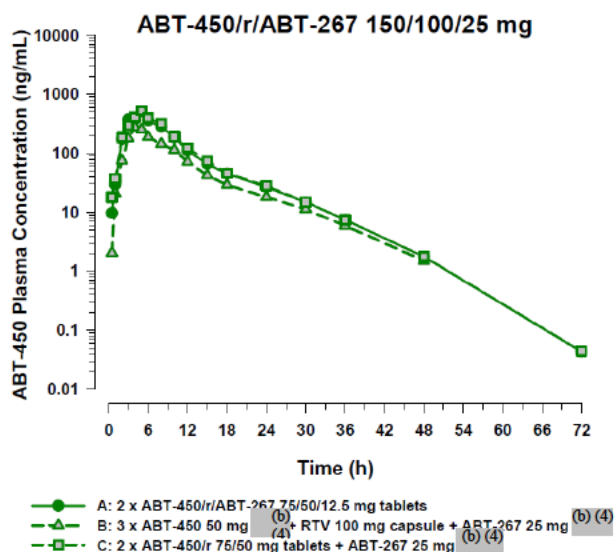
	ABT-450	Ritonavir	ABT-267
Dosage Form	(b) (4) Tablet	Soft Gelatin Capsule	(b) (4) Tablet
Strength	50 mg	100 mg	25 mg
Bulk Product Lot Number	11-000781	11-005635	11-000867
Manufacturing Site	Abbott Abbott Park, IL	Abbott Abbott Park, IL	Abbott (b) (4)
Finishing Lot Number	12-001621	12-001622	12-001620

	ABT-450/r (Reference 2)	ABT-450/r (Reference 4)	ABT-450/r/ABT-267 (Test 1)	ABT-450/r/ABT-267 (Test 2)
Dosage Form	Tablet	Tablet	Tablet	Tablet
Strength	75/50 mg	100/50 mg	75/50/12.5 mg	100/50/12.5 mg
Bulk Product Lot Number	10-004472	11-002024	12-000382	12-000457
Manufacturing Site	Abbott Abbott Park, IL	Abbott Abbott Park, IL	Abbott Abbott Park, IL	Abbott Abbott Park, IL
Finishing Lot Number	12-001624	12-001625	12-001618	12-001619

### Mean ABT-450 Plasma Concentration-Time Profiles, Linear Scale:

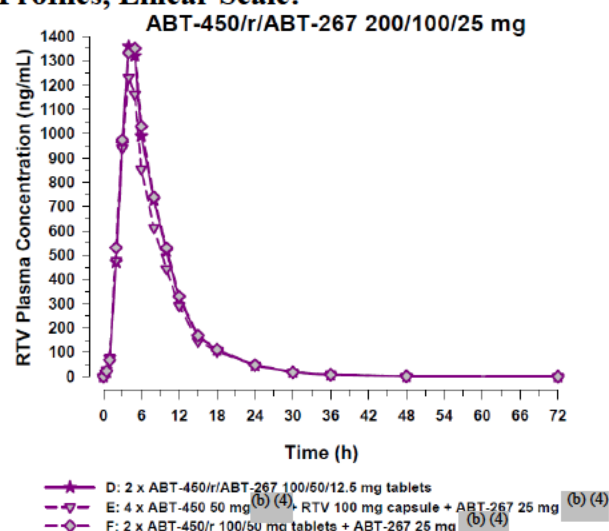
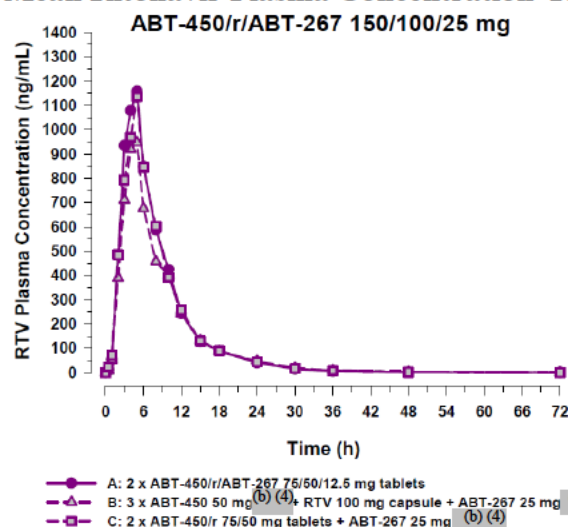


### Mean ABT-450 Plasma Concentration-Time Profiles, Log-linear Scale:

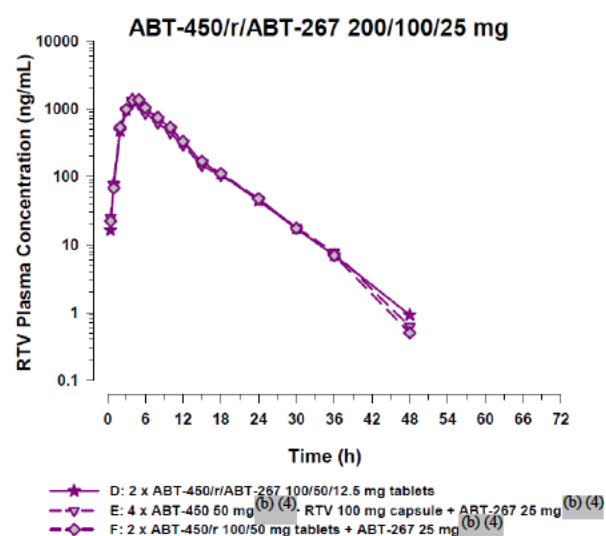
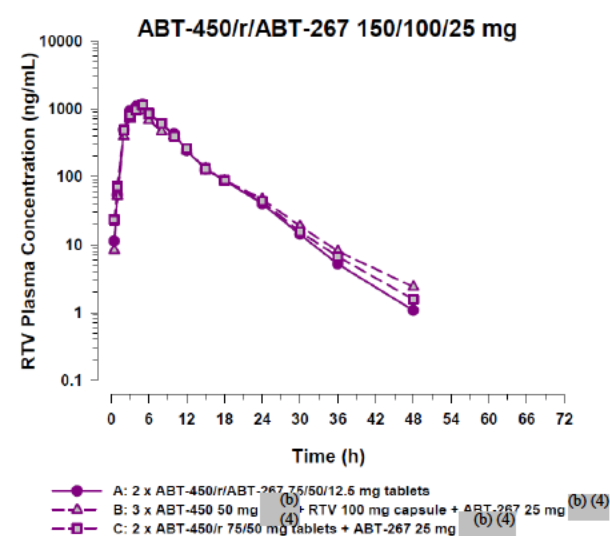




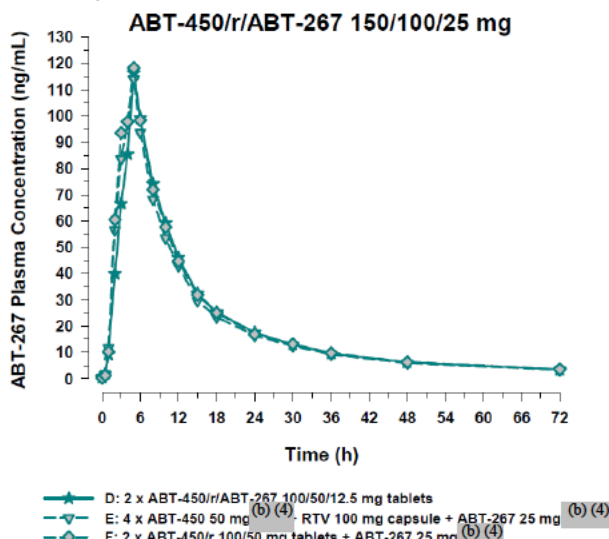
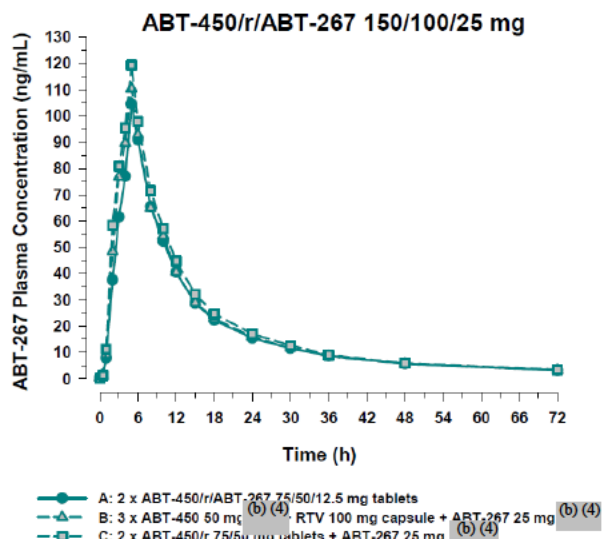
## Mean Ritonavir Plasma Concentration-Time Profiles, Linear Scale:



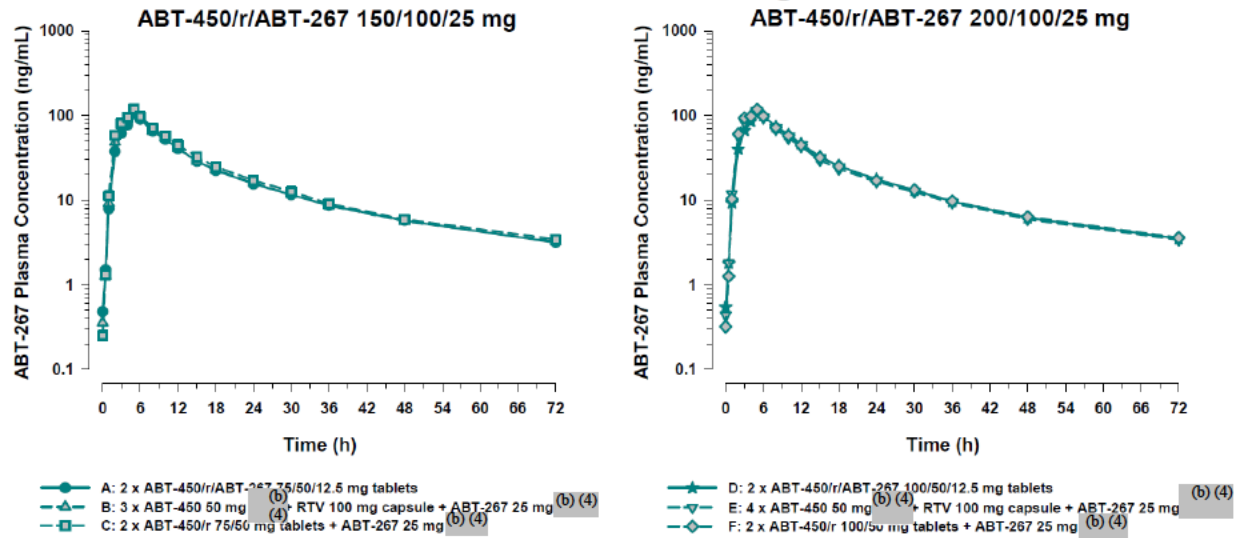
## Mean Ritonavir Plasma Concentration-Time Profiles, Log-linear Scale:



## Mean ABT-267 Plasma Concentration-Time Profiles, Linear Scale:



### Mean ABT-267 Plasma Concentration-Time Profiles, Log-linear Scale:



The Applicant concluded that, at the 150/100/25 mg and 200/100/25 mg dose levels of ABT-450/r/ABT-267:

- ABT-450 exposures from the co-formulated ABT 450/r/ABT-267 (75/50/12.5 mg) and (100/50/12.5 mg) tablets were comparable to the co-formulated ABT 450/r tablets, but were 63 to 93% and 54 to 65% higher than the ABT-450 (b)(4) tablets (co-administered with ritonavir capsule plus ABT-267 (b)(4) tablet) at the ABT-450 150 mg and 200 mg dose levels, respectively.
- Ritonavir exposures from the co-formulated ABT 450/r/ABT-267 (75/50/12.5 mg) and (100/50/12.5 mg) tablets were comparable to the ritonavir capsule (co-administered with ABT-450 (b)(4) tablets plus ABT-267 (b)(4) tablet) and bioequivalent to the co-formulated ABT-450/r 75/50 mg and 100/50 mg tablets (co-administered with ABT-267 (b)(4) tablet).
- ABT-267 exposures from the co-formulated ABT 450/r/ABT-267 (75/50/12.5 mg and 100/50/12.5 mg tablet were bioequivalent to the ABT-267 (b)(4) tablet (co-administered with ABT-450 (b)(4) tablets plus ritonavir capsule) and comparable to the ABT-267 (b)(4) tablet (co-administered with co-formulated ABT-450/r tablets).

**Reviewer's assessment of Fed BA study 13-391: ACCEPTABLE**

The Applicant reported the following results for ABT-450:

#### Relative Bioavailability and 90% Confidence Intervals for ABT-450:

Regimens Test vs. Reference	ABT-450 Pharmacokinetic Parameter	Relative Bioavailability			
		Central Value <sup>a</sup>		Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
		Test	Reference		
Group 1: ABT-450/r/ABT-267 150/100/25 mg					
A vs. B	C <sub>max</sub>	524	272	1.926	1.469 - 2.524
	AUC <sub>t</sub>	3306	2021	1.636	1.392 - 1.923
	AUC <sub>∞</sub>	3328	2044	1.628	1.386 - 1.911
A vs. C	C <sub>max</sub>	524	571	0.917	0.699 - 1.202
	AUC <sub>t</sub>	3306	3736	0.885	0.753 - 1.040
	AUC <sub>∞</sub>	3328	3754	0.886	0.755 - 1.041



		Group 2: ABT-450/r/ABT-267 200/100/25 mg			
D vs. E	C <sub>max</sub>	1276	773	1.650	1.220 - 2.233
	AUC <sub>t</sub>	7518	4878	1.541	1.243 - 1.911
	AUC <sub>∞</sub>	7547	4903	1.539	1.243 - 1.907
D vs. F	C <sub>max</sub>	1276	1448	0.881	0.651 - 1.192
	AUC <sub>t</sub>	7518	8902	0.845	0.681 - 1.047
	AUC <sub>∞</sub>	7547	8927	0.845	0.682 - 1.047

a. Exponentiation of the least squares means for logarithms.  
b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.  
c. Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.

*The Applicant reported the following results for ABT-267:*  
**Relative Bioavailability and 90% Confidence Intervals for ABT-267:**

Regimens Test vs. Reference	ABT-267 Pharmacokinetic Parameter	Relative Bioavailability			
		Central Value <sup>a</sup>		Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
		Test	Reference		
Group 1: ABT-450/r/ABT-267 150/100/25 mg					
A vs. B	C <sub>max</sub>	102	111	0.924	0.848 – 1.007
	AUC <sub>t</sub>	1285	1356	0.947	0.895 – 1.002
	AUC <sub>∞</sub>	1408	1468	0.959	0.907 – 1.014
A vs. C	C <sub>max</sub>	102	121	0.845	0.776 – 0.921
	AUC <sub>t</sub>	1285	1458	0.881	0.833 – 0.932
	AUC <sub>∞</sub>	1408	1582	0.890	0.842 – 0.941
Group 2: ABT-450/r/ABT-267 200/100/25 mg					
D vs. E	C <sub>max</sub>	114	112	1.021	0.963 – 1.084
	AUC <sub>t</sub>	1445	1404	1.029	0.985 – 1.074
	AUC <sub>∞</sub>	1564	1523	1.027	0.983 – 1.073
D vs. F	C <sub>max</sub>	114	120	0.954	0.899 – 1.012
	AUC <sub>t</sub>	1445	1488	0.971	0.930 – 1.014
	AUC <sub>∞</sub>	1564	1614	0.969	0.928 – 1.012

*This study shows that at the 150 mg ABT-450 dose, following administration of the ABT-450/ritonavir/ABT-267 co-formulated tablet, ABT-450 has 93% and 63% higher maximum observed plasma concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (AUC) values, respectively, compared to the (b) (4) tablet (with ritonavir SGC and ABT-267 (b) (4)).*

*The bioavailability of ABT-267 from the (b) (4) ABT-450/r/ABT-267 co-formulated tablets is comparable (C<sub>max</sub> and AUC met the bioequivalence criteria) to that from the ABT-267 (b) (4) tablets at the 25 mg dose. This study supports the bridging of the developmental formulations for the ABT-450/ritonavir/ABT-267 Tablets. Since ritonavir is a booster and does not have direct antiviral activity at the studied doses, the relative bioavailability of ritonavir itself is not considered clinically relevant in this study.*

*It is noted that 42 adult male and female subjects (N = 42) were enrolled in the study, and 37 subjects (32 males and 5 females) completed all three periods of the study.*

*The following 5 subjects prematurely discontinued from the study:*

- *Subject 1001 (42 year-old White male) discontinued from the study due to a family emergency after receiving Regimen C on Day 1 of Period 1.*
- *Subject 1004 (46 year-old White male) discontinued from the study due to a schedule conflict after receiving Regimen C on Day 1 of Period 2.*
- *Subject 1015 (24 year-old White male) discontinued from the study due to elevated alkaline phosphatase levels ( $> 116$  U/L) on Day 2 (118 U/L) and Day 7 (119 and 120 U/L) after receiving Regimen A on Day 1 of Period 1. The subject was confined from the afternoon of Day –1 through the morning of Day 4 of Period 1. The elevated alkaline phosphatase levels were not considered adverse events.*
- *Subject 1021 (24 year-old Black male) discontinued from the study due to an elevated creatinine level ( $> 115$   $\mu$ Mol/L) on Day 7 (127  $\mu$ Mol/L) after receiving Regimen A on Day 1 of Period 1. The subject had been released from confinement on Day 4 of Period 1. The elevated creatinine level was not considered an adverse event.*
- *Subject 1056 (22 year-old White male) discontinued from the study due to adverse events of elevated ALT and AST values ( $> 3$  times ULN) on Days 7 through 11 of Period 2 (Table 19) after receiving Regimen F on Day 1 of Period 2. The subject had been released from confinement on Day 4 of Period 2.*

**Reviewer's Note:** *The inspections for the clinical and analytical sites of the previously presented bioavailability/ bioequivalence studies were not needed and therefore were not requested to the Office of Scientific Investigations.*

#### **BIO-ANALYTICAL METHOD:**

**The following information request was sent to the Applicant on 7/11/14:**

*Provide the location of the Bio-analytical methods (description and validation) used for the analysis of ombitasvir, ABT-450 and ritonavir in studies 13-391 and 12-683, and the location of the Bio-analytical methods (description and validation) used for the analysis of ABT-333 and it's metabolite in studies 13-331 and 14-196. For each method, provide a summary table.*

**Applicant's response dated 7/25/14:**

The following compound identifications were used:

Ombitasvir:	ABT-267, A-1233617, A1233617
ABT-450:	A-1043422, A1043422
ABT-333:	A-998821, A998821
ABT-333 metabolite (M1):	A-1041392, A1041392
Ritonavir:	A-84538, A84538, Ritonavir, or RTV

- **Study M-13-391:** The bio-analytical method **1** for study M-13-391, for the measurement of ABT-450 (A-1043422) and ritonavir (A-84538) and ABT-267 (A1233617) in human plasma uses a protein precipitation and on-line solid phase extraction HPLC tandem mass spectrometric method.
- **Study M12-683:** The bio-analytical method **2** (for study M12-683) for the measurement of ABT-450 (A-1043422) and ritonavir (A-84538) in human plasma uses a salting-out assisted liquid/liquid extraction HPLC tandem mass spectrometric method.

- **Studies M13-331 and M14-196:** The bio-analytical method **3** (for studies M13-331 and M14-196) for the measurement of ABT-333 in human plasma uses an on-line solid phase extraction HPLC tandem mass spectrometric method.
- **Studies M13-331 and M14-196:** The bio-analytical method **4** (for studies M13-331 and M14-196) for the measurement of ABT-333 metabolite in human plasma also uses an on-line solid phase extraction HPLC tandem mass spectrometric method.

Summaries of the bio-analytical methods and the method validation parameters were provided and are included in Attachment 1.

***Reviewer's assessment of the bio-analytical method and method validation: ACCEPTABLE***

*The bio-analytical methods used to measure concentrations of ombitasvir, paritaprevir, ritonavir, and dasabuvir and its metabolite in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the five analytes was demonstrated during sample processing and long-term storage.*

***RISK EVALUATION: ACCEPTABLE***

The risk assessment evaluation for the dissolution CQA component of Ombitasvir/ Paritaprevir/ Ritonavir Tablets and Dasabuvir Tablets is presented in the next tables.

**Risk Assessment of Ombitasvir/Paritaprevir/Ritonavir Tablets**

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments**
Dissolution					

\*Risk ranking applies to product attribute/CQA

\*\*For example, post marketing commitment, knowledge management post approval, etc.

### Risk Assessment of Dasabuvir Tablets

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments**
Dissolution					

(b) (4)

\*Risk ranking applies to product attribute/CQA

\*\*For example, post marketing commitment, knowledge management post approval, etc.

### REVIEWER'S OVERALL CONCLUSIONS:

#### 1) **Dissolution methods:**

The following dissolution methods are acceptable:

For Ombitasvir, Paritaprevir and Ritonavir Tablets 12.5mg/75mg/50mg:

Apparatus 2 (paddle) at 75 rpm; 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 0.3% (w/v) polyoxyethylene 10 lauryl ether (POE10LE or equivalent decaethylene glycol mono dodecyl ether) at 37°C.

For Dasabuvir Tablets 250mg:

Apparatus 2 (paddle) at 75 rpm; 900 mL of 0.05M sodium phosphate buffer, pH 6.8 with 15 mM cetyl triethylammonium bromide (CTAB) at 37°C.

#### 2) **Dissolution acceptance criteria:**

The following dissolution acceptance criteria are acceptable:

Ombitasvir, Paritaprevir and Ritonavir (using USP <711> Table 2):

At 30 minutes, NMT (b) (4) %

At 90 minutes, NLT (b) (4) %

At 150 minutes, NLT (b) (4) %

Dasabuvir (using USP <711> Table 1):

$Q = \frac{(b)(4)}{(4)} \% \text{ at 15 minutes}$

**3) Bridging of the formulations:**

Adequate bridging was performed throughout the drug product development.

**4) Bioequivalence/Relative Bioavailability studies:**

- The results for pivotal bioequivalence study M14-196 indicate that the 250 mg ABT-333 tablets manufactured in North Chicago, IL, used in the Phase 3 study, and the 250 mg ABT-333 tablets manufactured at the commercial drug product manufacturing site in Sligo, Ireland, are bioequivalent.
- The results from study M13-331 indicate that the ABT-333 250 mg (b)(4) Phase 3 tablets are bioequivalent to the ABT-333 400 mg Phase 2b tablets.
- For the ombitasvir, paritaprevir and ritonavir FDC tablets, the results from relative bioavailability studies M12-683 and M13-391 indicate that several single component and FDC formulations of the ombitasvir, paritaprevir and ritonavir tablets used during the drug product development have different ABT-450 bioavailabilities due to the boosting effect of ritonavir on ABT-450 or due to the manufacturing process changes (b)(4).

**5) Bio-analytical method:**

The bio-analytical methods used to measure concentrations of Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir and its metabolite in human plasma were sensitive, selective, accurate and reproducible. The proposed bio-analytical methods are suitable and validated. The stability of each of the five analytes was demonstrated during sample processing and long-term storage.

**RECOMMENDATION:**

From a Biopharmaceutics perspective NDA 206619 for ombitasvir, paritaprevir and ritonavir FDC Tablets (12.5mg/75mg/50mg) co-packaged with dasabuvir Tablets (250 mg) is recommended for **APPROVAL**.

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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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ELSBETH G CHIKHALE  
09/21/2014

ANGELICA DORANTES  
09/21/2014

## OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

<b>NDA: 206619</b>	Submission Date: April 22, 2014
<b>Brand Name</b>	VIEKIRA PAK™
<b>Generic Names</b>	Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ Ritonavir and Dasabuvir (ABT-333)
<b>Clinical Pharmacology Review Team</b>	Vikram Arya, Ph.D., FCP, Seong Jang , Ph.D., Dhananjay Marathe, Ph.D, Jeffry Florian, Ph.D, Islam Younis, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology 4
<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; 250 mg ABT-333 tablets.
<b>Proposed Indication</b>	Treatment of HCV Genotype 1 Infection
<b>Review Type</b>	505 (b)(1) New Drug Application, Priority Review

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## 1 Executive Summary

Abbvie Inc. is seeking approval of VIEKIRA PAK™, a combination of Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ritonavir co-formulated tablets and Dasabuvir (ABT-333) tablets for the treatment of genotype 1 chronic hepatitis C infection. The remainder of this review will refer to ombitasvir as ABT-267, paritaprevir as ABT-450, and dasabuvir as ABT-333; the combination of ABT-267/ABT-450/ritonavir and ABT-333 will be referred to as the “3-DAA regimen” or VIEKIRA PAK™.

ABT-267 is a non-structural protein 5A [NS5A] inhibitor, ABT-450 is a NS3/4A protease inhibitor, and ABT-333 is a NS5B polymerase inhibitor.

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) and the proposed total daily dose of ABT-333 is 500 mg (1 X 250 mg tablet given orally twice daily). Depending on the HCV genotype-subtype (genotype 1a or 1b) and cirrhosis status (presence or absence of cirrhosis), ribavirin 1000 mg (for patients < 75 kg) and 1200 mg (for patients ≥ 75 kg) should be administered orally in two equally divided doses for 12 weeks or 24 weeks.

Table 1 shows the summary of the treatment regimen and patient population proposed by the applicant at the time of the original NDA submission:

**Table 1: Summary of Treatment Regimen and Patient Population (regimens apply to both treatment naïve- and treatment experienced patients)**



(b) (4)

Source: Annotated Draft Labeling Submitted with the NDA

Of note, the need for ribavirin in all genotype 1a patients without cirrhosis and the duration of therapy in all genotype 1a patients with cirrhosis was under discussion at the time of finalizing this review.

The clinical development program for the 3-DAA regimen included data from 6 Phase 3 randomized and controlled trials. The 3-DAA regimen ± ribavirin was administered (using the to-be-marketed formulations) to patients with genotype 1 chronic hepatitis C



infection. The primary efficacy endpoint of all pivotal trials was SVR<sub>12</sub> defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after the last dose. Overall, SVR<sub>12</sub> > 90 % was observed across the 6 clinical trials.

## **1.1 Recommendation**

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 label:

### **Extrinsic Factor (Drug-Drug Interactions):**

1. Co-administration of VIEKIRA PAK™ with estrogen containing products is contraindicated because of the observed higher rate of ALT elevations after co-administration of VIEKIRA PAK™ with estrogen containing products in the drug-drug interaction trial, Phase 2 trials, and Phase 3 trials.
2. Co-administration of VIEKIRA PAK™ with darunavir is not recommended due to the decrease in the mean C<sub>trough</sub> of darunavir observed in the drug-drug interaction trial after administration of VIEKIRA PAK™ with various darunavir regimens.
3. When VIEKIRA PAK™ is co-administered with amlodipine, the following recommendation is proposed, "Exposure to amlodipine was increased when amlodipine was co-administered with VIEKIRA PAK™. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended".
4. When VIEKIRA PAK™ is co-administered with furosemide, the following recommendation is proposed, "Clinical monitoring of patients is recommended and therapy should be individualized according to patient's response".
5. When VIEKIRA PAK™ is co-administered with buprenorphine/naloxone, clinical monitoring for sedation and cognitive effects is recommended and a dose reduction of buprenorphine may be considered.
6. The final clinical recommendations regarding the use of VIEKIRA PAK™ with cyclosporine, tacrolimus, and omeprazole were under discussion at the time of finalizing this review.

### **Intrinsic Factor (Hepatic Impairment):**

1. VIEKIRA PAK™ is contraindicated for use in subjects with severe hepatic impairment.
2. The safety and efficacy of VIEKIRA PAK™ after multiple dose administration has not been established in HCV infected patients with decompensated cirrhosis. Hence, VIEKIRA PAK™ is not recommended to be used in patients with moderate hepatic impairment.

## **Dose and Treatment Duration (Overall Population):**

1. VIEKIRA PAK™ should always be co-administered with ribavirin for 12 weeks for the entire cohort of GT1a infected non-cirrhotic HCV patients in order to minimize virologic failures (both on-treatment and relapse).
2. VIEKIRA PAK™ plus ribavirin should be co-administered for 24 weeks for all GT1a infected (treatment naïve and treatment experienced) cirrhotic HCV patients to minimize virologic failures due to relapse.

## **1.2 Postmarketing Commitments or Requirements**

None

## **1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings**

### **1.3.1 Dose Selection and Exposure-response (efficacy) analyses**

#### **Dose selection**

Dose selection was based on efficacy, safety and resistance variables and exposure-response analyses utilizing data from:

- Dose ranging studies with each of the DAA (ABT-450, ABT-267, ABT-33) as monotherapy and in combination with pegIFN + RBV,
- Dose ranging evaluation for pegIFN-free regimens utilizing different DAA combinations with a range of ABT-450 doses, with/without ABT-333 (250 mg BID), with/without ABT-267 (25 mg QD) along with or without Ribavirin (RBV) in different arms. This strategy was based on the greater potency of ABT-450 in decreasing the viral load following monotherapy in treatment-naïve HCV-infected subjects. Final dosing regimen to carry forward in phase 3 trials were determined based on study M11-652 which contained both GT1a and GT1b infected treatment naïve and treatment experienced patients.

In GT1b infected patients, the % SVR<sub>12</sub> were high both in presence or absence of RBV with the 3-DAA regimen and the virological failures were too low to judge whether RBV provided any additional value. Thus 3-DAA regimen without RBV was proposed to be suitable for this population.

In GT1a infected patients, absence of either RBV or any DAA component (ABT-233 or ABT-267) resulted in incrementally higher virological failure. Removal of either ABT-333 or ABT-267 from the 3-DAA + RBV regimen was associated with a substantially higher virologic failure rate in HCV GT1a-infected treatment-experienced subjects (19.2% to 50%, compared to 4% for 3-DAA+RBV regimen). Thus, RBV containing 3-DAA regimen was found to be suitable for the majority of these patients.

In cirrhotic subjects, only RBV containing regimens were evaluated since these patients are known to be hard to treat and there is lack of suitable follow-on treatment options. The different duration of treatment (12 week vs 24-weeks) were tested (Study M13-099) in these cirrhotic patients to come up with final dosing proposal.

### **Exposure-efficacy relationship**

#### GT1a-infected subjects receiving 3-DAA+RBV:

No trends in % SVR<sub>12</sub> were observed for ABT-333 exposures. There was a shallow E-R relationship for % SVR<sub>12</sub> for ABT-450, ABT-267 and RBV exposures. Females had numerically higher (5-9%) efficacy response than males in respective lower quartiles of exposures (Q1/Q2) of ABT-450, ABT-267 or RBV, which could be attributable to exposure differences since females had higher exposures of ABT-450 (1.8-fold AUC) and ABT-267 (1.7-fold AUC) than males for the same dosing regimen. Alternatively, these relationship trends were not peculiar to gender and may be attributable to body weight differences, since similar E-R relationship trends were observed in subgroup based on baseline body weight threshold of 80 kg.

The Applicant's multivariate logistic regression analysis for SVR<sub>12</sub> response identified ABT-267 exposure, RBV exposure, absence of RBV, baseline viral load, IL28B genotype and Hispanic/Latino ethnicity as the significant predictors of probability of SVR<sub>12</sub>. This model predicts that a 50% decrease in ABT-267 AUC would result in a decrease of 3.4% in SVR<sub>12</sub> and a 2-fold increase in ABT-267 AUC would result in an increase of 1.3% in SVR<sub>12</sub> for a reference population. The ABT-450 exposure was not statistically significantly correlated to the SVR<sub>12</sub> after inclusion of ABT-267 and RBV exposures in the model. Combining with the fact that ABT-450 showed the highest potency in decreasing viral load in monotherapy trials with each of the three DAAs, this suggests that the efficacy response is on saturation part of E-R relationship curve with respect to ABT-450 exposure. Thus a reduction in exposure to 50% from the mean exposure in the population for ABT-267 / ABT-450 may not reduce the overall efficacy by a substantial margin. Overall, the lowest quartiles of exposures of ABT-267 and RBV still had SVR<sub>12</sub> above 90% across different subgroups (gender/body weight) and thus no dose adjustment is recommended for these subgroups based on the exposure-efficacy analyses.

#### GT1a-infected naïve subjects without cirrhosis receiving 3-DAA:

No trends in % SVR<sub>12</sub> were observed for ABT-333 or ABT-450 exposures. There was a shallow E-R relationship for % SVR<sub>12</sub> with respect to ABT-267 exposures. Due to higher rates of relapse with this regimen in GT1a-infected subjects (5.4%) compared to 3 DAA + RBV (1.7%) and higher rates of on treatment virologic failure (3.0% versus 0.5%) this regimen is not recommended for subjects for GT1a-infected naïve subjects without cirrhosis.

### GT1b-infected subjects receiving 3-DAA or 3-DAA + RBV:

No exposure-response (E-R) relationship was observed for % SVR<sub>12</sub> for any of the ABT-450, ABT-333, ABT-267 or RBV exposures and % SVR<sub>12</sub> were uniformly high (97%-100%) across all the exposure quartiles.

#### **1.3.2 Exposure-safety relationship**

There was positive exposure-response relationship for safety signals of drug induced rash, ALT elevations, total bilirubin elevations and hemoglobin reductions with ABT-450 exposures. Also there was an E-R relationship for total bilirubin elevations and hemoglobin reductions with ABT-333 and ribavirin exposures.

#### Drug-Induced Rash (Moderate/Severe):

Incidence of drug-induced rash was higher in 3-DAA ± RBV treatment compared to placebo. Presence of RBV in the treatment regimen was associated with higher incidence of rash compared to no RBV. This safety event had higher incidences for higher ABT-450 exposures (AUC).

#### ALT Elevations:

ABT-450 AUC and baseline ALT levels were significantly associated as predictors of post-baseline ≥Grade 3 ALT (>5×ULN) elevations. Also hormonal use was associated with an increased likelihood of on-treatment ≥Grade 3 ALT elevations. The multivariate logistic regression analysis of this safety signal predict a 2-fold increase in ABT-450 exposure would increase the incidence of ≥Grade 3 ALT elevations from the observed 0.91% incidence to 1.4%. For comparison, approximately 2.6% of the Phase 3 population used hormonal products and the observed incidence rate of ≥Grade 3 ALT elevations was 5.5% in this population.

#### Bilirubin Elevations:

Presence of RBV in the treatment regimen was strongly associated with more ≥ Grade 3 (> 3×ULN) total bilirubin elevation. Only 0.39% subjects (n/N=2/509) had ≥ Grade 3 total bilirubin elevations in the absence of RBV compared to 5.1% subjects (n/N=81/1584) in the presence of RBV. ABT-450, ribavirin exposures and baseline elevated bilirubin levels were associated with post-baseline ≥ Grade 2/3 bilirubin elevations. Multivariate logistic regression predicted that increasing ABT-450 exposure by 2-fold would increase the incidence of ≥Grade 3 total bilirubin elevations to ~6.0% from an observed incidence of 4.0% for the population mean ALT-450 exposures.

#### Decreases in Hemoglobin Levels (Anemia):

Presence of ribavirin and higher ribavirin exposures were significant predictors of decreases in hemoglobin levels to ≥Grade 2 levels (< 10 g/dL) of hemoglobin) in addition to sex (female), baseline hemoglobin (baseline ≥Grade 1), and hormonal use. There was no association between ABT-333 or ritonavir exposures and reduction in hemoglobin levels in the multivariate logistic regression analysis. ABT-450 and ribavirin had shallow E-R relationship while ABT-267 and hormone use have shallow negative relationship.

Given the observed  $\geq$  Grade 2 decrease in hemoglobin level incidence of 5.21% (n/N=109/2093) corresponding to the mean ABT-450 exposure, a 2-fold increase from mean in ABT-450 exposure is predicted to produce  $\sim$ 6.9% incidence of  $\geq$  Grade 2 hemoglobin decrease events.

Overall, from the E-R relationships for safety and efficacy, a change in exposure within the window of 0.5- to 2.0-fold from the population mean exposures for ABT-450, ABT-267 or ABT-333 are not anticipated to alter the benefit/risk profile to an extent which would necessitate any dosing changes.

### 1.3.3 **Absorption, Distribution, Metabolism, and Excretion**

#### ABT-450

*Absorption:* ABT-450 shows moderate permeability. The absolute bioavailability of ABT-450 was not determined. ABT-450 is a substrate of P-glycoprotein (P-gp) transporters. The  $t_{\max}$  of ABT-450 is approximately 4-5 hours.

*Distribution:* The protein binding of ABT-450 is  $> 97\%$  over a concentration range of 0.1  $\mu\text{M}$  to 10  $\mu\text{M}$  (0.08-8  $\mu\text{g/mL}$ ). The blood-to-plasma concentration ratio was 0.7 in humans, indicating that ABT-450 is preferentially distributed in the plasma compartment of whole blood. The results of renal- and hepatic impairment trials showed that the unbound fraction of ABT-450 was similar across the various renal- and hepatic impairment groups, except for mild and moderate hepatic impairment groups where fraction unbound was  $\sim$ 30% lower relative to subjects with normal liver function.

*Metabolism:* ABT-450 is primarily metabolized by CYP3A enzymes. ABT-450 was the predominant circulating radioactive species ( $\sim$ 88.9 % of the drug related radioactivity) in plasma. In plasma, 5 ABT-450 metabolites were identified, including M2, M29, and trace levels of M3, M13, and M6. In urine, M13 is the major component (accounting for 8.57 % of the administered radioactive dose) and in feces, M29 is the major component (accounting for 59.9 % of the administered radioactive dose).

*Excretion:* Approximately 88 % of the administered radioactive dose was recovered in feces and 8.76 % of the administered radioactive dose was recovered in the urine. Unchanged ABT-450 accounted for 1.1 % of the radioactivity in the feces and 0.05 % of the radioactivity in the urine.

#### ABT-267

*Absorption:* ABT-267 shows moderate permeability. The absolute bioavailability of ABT-267 was not determined. ABT-267 is a substrate of P-gp transporters. The  $t_{\max}$  of ABT-267 is approximately 4-5 hours.

*Distribution:* The protein binding of ABT-267 is 99.9 % over a concentration range of 0.1  $\mu\text{M}$  to 10  $\mu\text{M}$  (0.09-9  $\mu\text{g/mL}$ ). The blood-to-plasma concentration ratio was 0.49 in

humans, indicating that ABT-267 is preferentially distributed in the plasma compartment of whole blood. The results of renal- and hepatic impairment trials showed that the unbound fraction of ABT-267 was similar across the various renal- and hepatic impairment groups, except for severe renal impairment group and severe hepatic impairment group where fraction unbound was ~ 2-folds higher than fraction unbound in subjects with normal renal function or normal hepatic function.

*Metabolism:* ABT-267 undergoes amide hydrolysis. Unchanged ABT-267 accounted for 8.85 % of the total radioactivity in plasma. In plasma, 13 metabolites were identified; M23, M29, M36, and M37 were present as major circulating metabolites.

*Excretion:* Approximately 90 % of the administered radioactive dose was recovered in feces and 1.91 % of the administered radioactive dose was recovered in the urine. Unchanged ABT-267 accounted for 87.8 % of the radioactivity in the feces and 0.03 % in the urine.

### ABT-333

*Absorption:* ABT-267 shows high permeability. The absolute bioavailability of a single oral 250 mg dose of ABT-333 under non-fasting conditions was estimated to be 46 %. ABT-333 is a substrate of P-gp transporters. The  $t_{\max}$  of ABT-333 is approximately 3 hours.

*Distribution:* The protein binding of ABT-333 is 99.9 % over a concentration range of 0.1  $\mu$ M to 10  $\mu$ M (0.05-5  $\mu$ g/mL). The blood-to-plasma concentration ratio was 0.7 in humans, indicating that ABT-333 is preferentially distributed in the plasma compartment of whole blood. The results of hepatic impairment trial showed that the unbound fraction of ABT-333 in subjects with mild- and moderate hepatic impairment was approximately 50 % lower as compared to subjects with normal hepatic function. The unbound fraction of ABT-333 in subjects with severe hepatic impairment was ~27% lower than the unbound fraction in subjects with normal hepatic function. The results of the renal impairment trial showed that the unbound fraction of ABT-333 was similar across the various renal impairment groups.

*Metabolism:* ABT-333 is primarily metabolized by CYP2C8 enzymes. Unchanged ABT-333 accounted for approximately 60 % of the total radioactivity in plasma. 7 metabolites (M1, M2, M3, M4, M5, M6, and M11) were observed in plasma;  $AUC_{0-\infty}$  of M1 was about 22 % of the total drug related material in plasma. M1 was the major component in the feces with a mean of ~32 % of the administered radioactive dose, followed by unchanged parent drug (26 %), M2 (15 %), and M5 (11 %). M1 was the major component in the urine (0.85 %).

*Excretion:* Approximately 94 % of the administered radioactive dose was recovered in feces and 2.05 % of the administered radioactive dose was recovered in the urine (0.03 % as unchanged ABT-333). ABT-333 M1 was the major component in the feces with ~32 % of the administered radioactive dose, followed by unchanged ABT-333 (26 % of the

administered radioactive dose). Unchanged ABT-333 accounted for 0.03 % of the total radioactivity in the urine.

#### 1.3.4 **Intrinsic factors**

##### Hepatic Impairment:

*Mild:* Based on the magnitude of changes observed in the pharmacokinetics of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 in the mild hepatic impairment group (Child-Pugh Category 5-6) and the available efficacy and safety data in patients with compensated cirrhosis (M13-099), VIEKIRA PAK™ can be co-administered to patients with mild hepatic impairment (Child-Pugh Category A, score 5-6).

*Moderate:* Based on available pharmacokinetic data after single dose administration, VIEKIRA PAK™ can be administered to patients with moderate hepatic impairment (Child-Pugh Category B, score 7-9). However, the safety and efficacy of VIEKIRA PAK™ after multiple dose administration has not been established in patients with decompensated cirrhosis. Hence, VIEKIRA PAK™ is not recommended to be used in patients with moderate hepatic impairment (Child-Pugh Category B, score 7-9).

*Severe:* The use of VIEKIRA PAK™ is 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.

##### Renal Impairment:

No dose adjustments of VIEKIRA PAK™ are needed in patients with mild (CrCl 60-89 mL/min), moderate (CrCl 30-59 mL/min), and severe (CrCl 15-29 mL/min) renal impairment. Of note, pharmacokinetic data are not available regarding the use of VIEKIRA PAK™ in patients with End Stage Renal Disease (ESRD).

#### 1.3.5 **Extrinsic factors**

##### Effect of Food:

*Moderate Fat:* After administration of ABT-267/ABT-450/ritonavir coformulated tablets with a moderate fat meal (617 Kcal, 29 % calories from fat), the mean  $C_{max}$  and AUC of ABT-450 increased by 367 % and 210 %, respectively, the mean  $C_{max}$  and AUC of ritonavir increased by 63 % and 48 %, respectively, and the mean  $C_{max}$  and AUC of ABT-267 increased by 127 % and 81 %, respectively. After administration of ABT-333 with a moderate fat meal (612 Kcal, 21 % calories from fat), the mean  $C_{max}$  and AUC of ABT-333 increased by 52 % and 29 %, respectively.

*High Fat:* After administration of ABT-267/ABT-450/ritonavir coformulated tablets with a high fat meal (917 Kcal, 60 % calories from fat), the mean  $C_{max}$  and AUC of ABT-450 increased 300 % and 179 %, respectively, the mean  $C_{max}$  and AUC of ritonavir

increased by 50 % and 43 %, respectively, and the mean  $C_{\max}$  and AUC of ABT-267 increased by 106 % and 76 %, respectively. After administration of ABT-333 with a high fat meal (850 Kcal, 59 % calories from fat), the mean  $C_{\max}$  and AUC of ABT-333 increased by 41 % and 21 %, respectively.

Of note, ABT-267/ABT-450/ritonavir co-formulated tablets and ABT-333 tablets were administered with food in all Phase 1, 2, and 3 trials.

VIEKIRA PAK™ should always be taken with a meal. Differences in exposures of ABT-450, ritonavir, ABT-267, and ABT-333 observed after administration of ABT-267/ABT-450/ritonavir coformulated tablets and ABT-333 tablets under moderate fat conditions and high fat conditions are not expected to be clinically relevant.

### Drug-Drug Interactions

*ABT-450:* Primarily metabolized by CYP3A enzymes. Co-administration of ABT-450 with ritonavir, a potent inhibitor of CYP3A enzymes, increased the mean  $C_{\max}$  and AUC of ABT-450 by 28-fold and 48-fold, respectively. ABT-450 is an inhibitor of CYP2C8 and UGT1A1 enzymes. ABT-450 is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and MRP2 transporters. ABT-450 is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, MRP2, and BSEP transporters. ABT-450 is not an inhibitor of renal transporters (OAT1, OAT3, OCT2, MATE-1, and MATE-2K).

*ABT-267:* CYP3A enzymes play a minor role in the metabolism of ABT-267. It is an inhibitor of UGT1A1 enzymes. ABT-267 is a substrate of P-gp and BCRP. ABT-267 is not an inhibitor of renal transporters (OAT1, OAT3, OCT2, MATE-1, and MATE-2K).

*ABT-333:* Primarily metabolized by CYP2C8 enzymes with minor contributions from CYP3A. ABT-333 is an inhibitor of CYP2C8, CYP2C9, CYP2C19, and UGT1A1 enzymes. ABT-333 is a substrate of P-gp and BCRP and an inhibitor of P-gp, BCRP, and MRP2. ABT-333 is not an inhibitor of renal transporters (OAT1, OAT3, OCT2, MATE-1, and MATE-2K).



Recommendation	Drug [Clinical Recommendation]	Summary of Major Findings
Contraindication	<b>Carbamazepine</b>	Significant decrease in the mean systemic exposure of ABT-450, ritonavir, ABT-267, and ABT-333
	<b>Gemfibrozil</b>	~11-fold increase in the mean systemic exposure of ABT-333
	<b>Efavirenz Containing Regimens</b>	Poor tolerability and ALT elevations observed in drug-drug interaction trial with Atripla®
	<b>Estrogen Containing Products</b>	Higher rates of Grade 3+ALT elevations observed in the drug-drug interaction trial and Phase 3 trials in subjects on estrogen containing products
Co-Administration Not Recommended	<b>Atazanavir/ritonavir</b> once daily (evening administration)	3.2-fold increase in the mean systemic exposures of ABT-450
	<b>Rilpivirine</b>	Increase in the mean $C_{max}$ of rilpivirine by : <ul style="list-style-type: none"> <li>- 2.1-fold- (rilpivirine administered in the evening under non fasting conditions)</li> <li>- 2.5-fold- (rilpivirine administered in the morning under non-fasting conditions)</li> <li>- 3-fold (rilpivirine administered under “semi fasting” conditions [4-hours after food])</li> </ul>
	<b>Darunavir</b> (once daily and twice daily)	Decrease in $C_{trough}$ of darunavir by: <ul style="list-style-type: none"> <li>- 45 % (darunavir administered once daily in the evening with ritonavir)</li> <li>- 43 % (darunavir administered twice daily [darunavir administered in the evening with ritonavir; darunavir administered in the morning with the 3-DAA regimen])</li> <li>- 48 % [darunavir administered once daily in the morning with the 3-DAA regimen]</li> </ul>
	<b>Lopinavir/ritonavir</b> (once daily and twice daily)	Increase in the mean AUC of ABT-450 by : <ul style="list-style-type: none"> <li>- 1.9-fold (after co-administration with lopinavir/ritonavir once daily)</li> <li>- 2.2-fold (after co-administration with lopinavir/ritonavir twice daily)</li> </ul>
	<b>Omeprazole</b> <i>Final Clinical Recommendation was</i>	Decrease in the mean AUC of omeprazole by ~38 %

Recommendation	Drug  [Clinical Recommendation]	Summary of Major Findings
	<i>under discussion at the time of completion of this review</i>	
Dose Adjustment/Monitoring Recommended	<b>Ketoconazole</b>  <i>[When VIEKIRA PAK™ is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg/day]</i>	~2.2 fold increase in the mean AUC of ketoconazole
	<b>Digoxin</b>  <i>[While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended]</i>	No significant changes in digoxin PK were observed in the DDI trial. Monitoring of serum digoxin levels is recommended as digoxin is a narrow therapeutic index drug
	<b>Warfarin</b>  <i>[While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalized ratio (INR) is recommended].</i>	No significant changes in warfarin PK were observed in the DDI trial. Monitoring for INR recommended as warfarin is a narrow therapeutic index drug
	<b>Amlodipine</b>  <i>[Exposure to amlodipine was increased when co-administered with VIEKIRA PAK™. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended].</i>	~2.6 fold increase in the mean AUC of amlodipine
	<b>Furosemide</b>  <i>[Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response].</i>	~42 % increase in furosemide mean C <sub>max</sub>
	<b>Alprazolam</b>  <i>[Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response].</i>	~34 % increase in alprazolam AUC
	<b>Pravastatin</b>  <i>[Pravastatin dose should not exceed 40 mg per day].</i>	~1.8-fold increase in pravastatin AUC
	<b>Rosuvastatin</b>	~2.6-fold increase in rosuvastatin AUC

Recommendation	Drug [Clinical Recommendation]	Summary of Major Findings
	<i>[Rosuvastatin dose should not exceed 10 mg per day].</i>	
	<b>Buprenorphine/Naloxone</b> <i>Clinical monitoring for sedation and cognitive effects is recommended and a dose reduction of buprenorphine may be considered.</i>	~2-fold increase in the mean C <sub>max</sub> and AUC of buprenorphine; 2-fold and 1.8-fold increase in the mean C <sub>max</sub> and AUC of norbuprenorphine
	<b>Cyclosporine</b> <i>Final Clinical Recommendation was under discussion at the time of completion of this review</i>	Dose normalized AUC and C <sub>24</sub> of cyclosporine increased by ~6-fold and 16-fold after co-administration with VIEKIRA PAK <sup>TM</sup>
	<b>Tacrolimus</b> <i>Final Clinical Recommendation was under discussion at the time of completion of this review</i>	Dose normalized AUC and C <sub>24</sub> of cyclosporine increased by ~57-fold and 17-fold after co-administration with VIEKIRA PAK <sup>TM</sup>

No dose adjustments are recommended when VIEKIRA PAK<sup>TM</sup> is co-administered with the following: Methadone, Progestin only contraceptives, Atazanavir (morning administration), Raltegravir, Emtricitabine/Tenofovir, Escitalopram, Duloxetine, and Zolpidam.

## 2 Question based review (QBR)

### 2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

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. ABT-333 film coated tablets contain 250 mg of ABT-333. The molecular weight of ABT-267, ABT-450, ritonavir, and ABT-333 is 894.11 (anhydrate form), 765.88 (anhydrate form), 720.95 and 493.57 (anhydrate form). **Table 2** shows the quantitative composition of ABT-267/ABT-450/ritonavir 12.5/75/50 mg tablets.

**Table 2: Quantitative Composition of ABT-267/ABT-450/ritonavir 12.5/75/50 mg tablets**

Component	Quality Standard	Function	Amount (mg)/Tablet
Ombitasvir	In-house standard	Active	12.5
Copovidone, K value 28	NF/Ph. Eur. and In-house standard		
Vitamin E Polyethylene Glycol Succinate	NF and In-house standard		
Colloidal Silicon Dioxide/ Colloidal Anhydrous Silica	NF/Ph. Eur.		
ABT-450	In-house standard	Active	75.0
Propylene Glycol Monolaurate Type I	NF/Ph. Eur.		
Ritonavir	USP/Ph. Eur.	PK Enhancer	50.0
Sorbitan Monolaurate	NF/Ph. Eur.	Surfactant/Plasticizer	33.3
Sodium Stearyl Fumarate	NF/Ph. Eur.		
Film-Coating			

Source: Section 2.3.P.1 (Description and Composition of Drug Product)

**Table 3** shows the quantitative composition of ABT-333 250 mg tablets.

**Table 3: Quantitative Composition of ABT-333 250 mg tablets**

Component	Quality Standard	Function	Amount (mg)/Tablet
(b) (4)			
Dasabuvir Sodium	In-house	Active	270.26
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.		(b) (4)
Microcrystalline Cellulose (b) (4)	NF/Ph. Eur.		
Lactose Monohydrate (b) (4)	NF/Ph.Eur.		
Copovidone (b) (4)	NF/Ph. Eur.		
Croscarmellose Sodium	NF/Ph. Eur.		
Colloidal Silicon Dioxide / Anhydrous Colloidal Silica	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)			
Film-Coating			
(b) (4)			

Source: Section 2.3.P.1 (Description and Composition of Drug Product)

2.1.2 What is the proposed mechanism of action and therapeutic indication(s)?

ABT-267 is a non-structural protein 5A [NS5A] inhibitor. ABT-450 is a NS3/4A protease inhibitor. ABT-333 is a NS5B polymerase inhibitor.

The proposed indication is the treatment of HCV genotype 1 infection. **Table 4** shows the various treatment regimens proposed by the applicant at the time of NDA submission.

**Table 4: Treatment Regimen and Duration for Various Patient Populations**



Source: Annotated Draft Labeling Submitted with the NDA

Of note, the need for ribavirin in all genotype 1a patients without cirrhosis and the duration of therapy in all genotype 1a patients with cirrhosis was under discussion at the time of finalizing this review.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed total daily dose of ABT-267/ABT-450/ritonavir co-formulated tablets is 25 mg/150 mg/100 mg given orally once daily. The proposed total daily dose of ABT-333 is 500 mg (1X250 mg tablet given orally twice daily).

As shown in **Table 4**, depending on the HCV genotype-subtype (genotype 1a or 1b) and cirrhosis status (presence or absence), ribavirin 1000 mg (for patients < 75 kg) and 1200 mg (for patients ≥ 75 kg) will be administered orally in two equally divided doses.

Of note, the film coated ABT-267/ABT-450/ritonavir 12.5/75/50 mg co-formulated tablets and the film coated ABT-333 250 mg tablets used in all Phase 3 trials are identical to the to-be-marketed formulations.

## 2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical and clinical pharmacology studies used to support dosing or claims?

The clinical development program for the 3-DAA regimen included data from 6 Phase 3 randomized and controlled trials. Efficacy data from 10 arms in which subjects received the 3-DAAs ± RBV were used to compare efficacy results and to perform the integrated efficacy analyses across the trials. All efficacy data through post treatment week 12 for all subjects in the 10 treatment arms were included for assessing SVR<sub>12</sub> [HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after the last dose], the primary efficacy end point. Evaluation of secondary end point of ALT normalization in the placebo controlled analysis set assessed the risk difference of the combined 3-DAA +RBV arms to the combined placebo arms stratified by treatment status (naïve and experienced) and HCV subgenotype. The secondary end point of percentage of subjects with hemoglobin decrease during treatment was compared between subjects in the 3-DAA +RBV and 3-DAA arms stratified by study, prior treatment experience, and HCV subgenotype.

**Table 5** shows the key design features of the Phase 3 trials.

**Table 5: Key Design Features of Phase 3 Trials**

Study	Population	Regimen	Number Treated with DAAs ± RBV
<b>Phase 3</b>			
<a href="#">M11-646</a>	HCV GT1-infected (1a and non-1a), treatment-naïve, noncirrhotic, adult subjects	3-DAA <sup>a</sup> + RBV versus placebo for 12 weeks	630
<a href="#">M13-098</a>	HCV GT1-infected (1a and non-1a), pegIFN and RBV treatment-experienced, noncirrhotic, adult subjects	3-DAA + RBV versus placebo for 12 weeks	393
<a href="#">M13-389</a>	HCV GT1b-infected, pegIFN and RBV treatment-experienced, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	186
<a href="#">M13-961</a>	HCV GT1b-infected, treatment-naïve, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	419
<a href="#">M14-002</a>	HCV GT1a-infected, treatment-naïve, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	305
<a href="#">M13-099</a>	HCV GT1-infected (1a and non-1a), treatment-naïve and previous pegIFN and RBV treatment-experienced adult subjects with compensated cirrhosis (Child-Pugh A)	3-DAA + RBV for 12 weeks versus 24 weeks	380
<b>Phase 2</b>			
<a href="#">M11-652</a>	HCV GT1-infected, treatment-naïve subjects and previous null responders to pegIFN and RBV treatment	ABT-450/r, and ABT-267 and/or ABT-333 ± RBV 8, 12, or 24 weeks	571
<a href="#">M14-103</a>	HCV GT1-infected (1a and non-1a), noncirrhotic, treatment-naïve or pegIFN and RBV treatment-experienced, adult noncirrhotic subjects on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for ≥ 6 months prior to screening	3-DAA <sup>a</sup> + RBV for 12 weeks	38

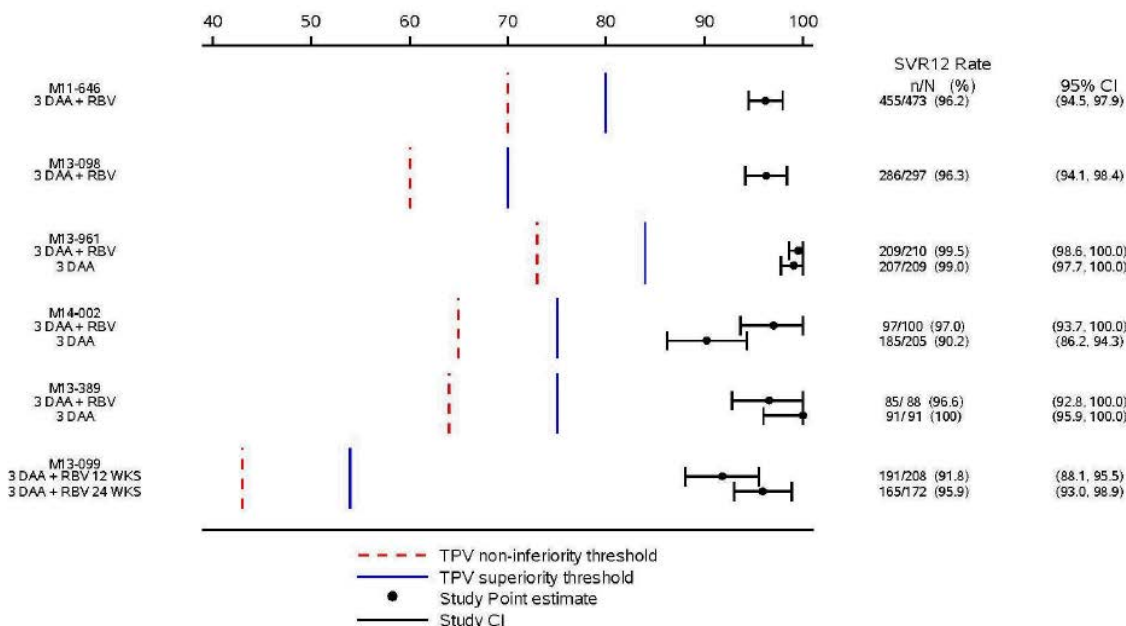
a. 3-DAA is ABT-450/r/ABT-267 (150/100/25 mg QD) + ABT-333 (250 mg BID).

Source: Table 2 on Page 9 of Clinical Overview Section (Section 2.5)



Figure 1 shows the SVR<sub>12</sub> rates observed in the 6 Phase 3 Clinical Trials.

**Figure 1: SVR<sub>12</sub> rates observed in the 6 Phase 3 Clinical Trials**



Source: Fig 4 on Page 52 in the Clinical Overview Section (Section 2.5)

In addition to the 6 Phase 3 trials, data from two supportive, un-controlled Phase 2 trials (M11-652 and M14-103) were used in the overall efficacy assessment of the 3-DAA regimens, however; the data were not included in the primary analysis of efficacy. M11-652 was conducted in HCV GT1-infected, treatment-naïve subjects and previous null responders to pegIFN and RBV treatment. ABT-450 ( (b) (4) tablets), ritonavir, ABT-267 and/or ABT-333 ± RBV were administered for 8, 12 or 24 weeks. M14-103 was conducted in HCV GT1-infected (1a and non-1a), noncirrhotic, pegIFN and RBV treatment-naïve or treatment-experienced, adult subjects on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for ≥ 6 months prior to screening. The 3-DAA+RBV regimen was administered for 12 weeks.

It should be noted that in the entire drug development program, no efficacy or safety data were generated in the HCV-infected patients with decompensated cirrhosis.

The applicant conducted a comprehensive clinical pharmacology program to evaluate the pharmacokinetics (2 trials), ADME properties (3 trials), effect of food (2 trials), effect of renal- and hepatic impairment (2 trials), effect on QT prolongation (1 trial) and potential for drug-drug interactions (25 trials). In addition, intensive and sparse data from Phase 2 and Phase 3 trials were used for population pharmacokinetic analysis and exploring exposure-response (safety and efficacy) relationships.

- 2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy end point of all pivotal trials was SVR<sub>12</sub> defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after the last dose. SVR<sub>12</sub> has been demonstrated to be a validated surrogate marker to demonstrate efficacy of medications being developed to treat HCV infection and is the recommended primary end point in the “Draft Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment”.

- 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The relevant analytes (ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1[active metabolite of ABT-333] and ribavirin) and concomitantly administered drugs (in drug-drug interaction trials) were measured in plasma using validated LC/MS/MS analytical methods. There was a good correlation between the exposures of ABT-333 and ABT-333 M1; therefore, the applicant did not include ABT-333 M1 in the population pharmacokinetic analysis and exposure-response analysis.

- 2.2.4 Exposure-response

- 2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?

GT1b-infected subjects receiving 3-DAA or 3-DAA + RBV:

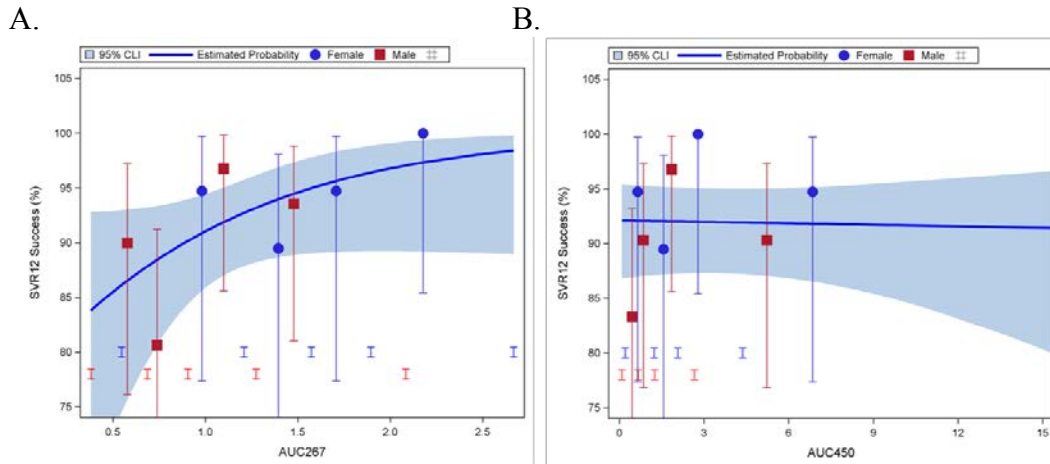
No exposure-response (E-R) relationship was observed for % SVR<sub>12</sub> with respect to ABT-450, ABT-333, ABT-267 or RBV exposure and % SVR<sub>12</sub> were uniformly high (97%-100%) across all the exposure quartiles.

GT1a-infected naïve subjects without cirrhosis receiving 3 DAA:

No trends in % SVR<sub>12</sub> were observed for ABT-333 exposures. There was a shallow E-R relationship for % SVR<sub>12</sub> for ABT-267 exposures and at very low exposures for ABT-450 (**Figure 2**).



**Figure 2: Univariate exposure-response relationship for % SVR<sub>12</sub> in GT1a-infected naïve subjects without cirrhosis receiving 3 DAA (no Ribavirin): panel A for ABT-267 AUC, panel B for ABT-450 AUC. All panels depict efficacy response trends (blue line) for overall population and efficacy response subgrouped by gender (blue/red symbols). The units of AUC are µg\*hr/mL. (The blue and red lines at the bottom of each graph demarcate the range of exposure for each quartile of exposure in each subgroup shown with same colored symbol)**



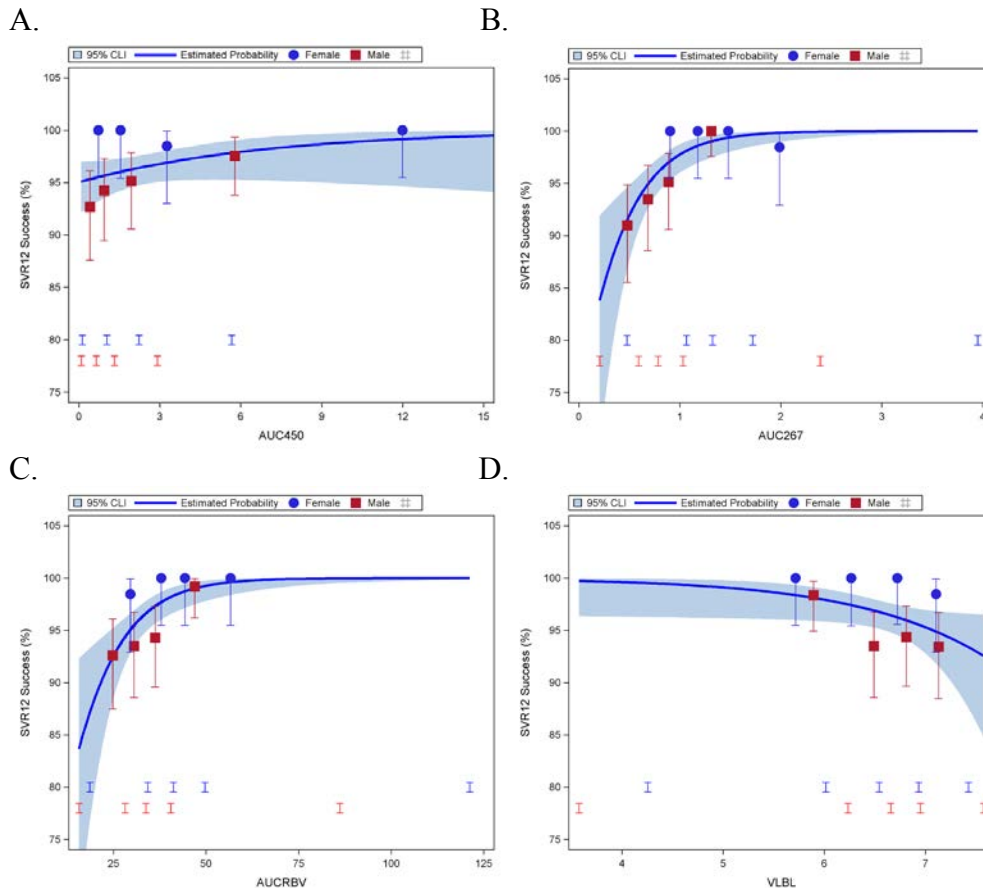
Source: Reviewer's analysis

#### GT1a-infected subjects receiving 3-DAA+RBV:

No trends in % SVR<sub>12</sub> were observed for ABT-333 exposures. There was a shallow E-R relationship for % SVR<sub>12</sub> for ABT-450, ABT-267 and RBV exposures (**Figure 3** panels A-C). When the E-R for efficacy (% SVR<sub>12</sub>) response data was analyzed by subgroups of gender, females had numerically higher efficacy (5-9%) response than males in the respective lower quartiles of exposures (Q1/Q2) of ABT-450, ABT-267 or RBV. On a population basis, females had higher exposures of ABT-450 (1.8-fold AUC) and ABT-267 (1.7-fold AUC) than males for the same dosing regimen. Thus, aligned with the observed E-R relationships, higher exposures to ABT-450 and ABT-267 may have helped females overcome high viral load to achieve numerically better SVR<sub>12</sub> than males (**Figure 3** panel D). These relationship trends were not peculiar to gender and can very well be attributable to body weight differences across genders, since similar E-R relationship trends were observed when the population was subgrouped based on baseline body weight threshold of 80 kg instead of gender (data not shown).

The Applicant's multivariate logistic regression analysis for SVR<sub>12</sub> response identified ABT-267 exposure, RBV exposure, absence of RBV, baseline viral load, IL28B genotype and Hispanic/Latino ethnicity as the significant predictors of probability of SVR<sub>12</sub>. The estimates of logistic regression parameters for the final model and the odds ratios for each of the covariates are shown in **Table 6** and **Table 7** respectively.

**Figure 3: Exposure-response relationship for % SVR<sub>12</sub> in GT1a-infected subjects receiving 3 DAA + Ribavirin: panel A for ABT-450 AUC, panel B for ABT-267 AUC, panel C for RBV AUC; panel D shows relationship of % SVR<sub>12</sub> with baseline viral load. All panels depict efficacy response trends (blue line) for overall population and efficacy response subgrouped by gender (blue/red symbols). The units of AUC are  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and baseline viral load (VLBL) is shown in log scale. (The blue and red lines at the bottom of each graph demarcate the range of exposure for each quartile of exposure in each subgroup shown with same colored symbol)**



Source: Reviewer's analysis

**Table 6: Estimates of logistic regression parameters for SVR<sub>12</sub> response**

Predictor Variable	$\beta$	SE	p-value
Intercept	10.3425	2.2469	< 0.0001
Log ABT-267 AUC	1.4878	0.3607	< 0.0001
Log Ribavirin AUC (centered at geometric mean)	2.1984	0.7632	0.0040
Absence of RBV	-1.5983	0.3773	< 0.0001
Baseline VL	-0.9752	0.3287	0.0030
IL28B (CC)	1.1381	0.4666	0.0147
Ethnicity (Hispanic/Latino)	-0.9467	0.4354	0.0297

Source: Sponsor's Exposure-Response Report R&D/14/0049, page 3

**Table 7: Estimates of odds ratios for each covariate towards SVR<sub>12</sub> response**

Effect	Odds Ratio Estimates		
	Point Estimate	95% Wald Confidence Limits	
Log ABT-267 AUC	4.428	2.183	8.979
Log RBV AUC (centered at geometric mean)	9.101	2.019	40.212
Baseline VL	0.377	0.198	0.718
Ethnicity (Hispanic/Latino)	0.388	0.165	0.911
IL28B (CC)	3.121	1.251	7.787
Absence of RBV	0.202	0.097	0.424

Source: Sponsor's Exposure-Response Report R&D/14/0049, page 4

This model predicts that a 50% decrease in ABT-267 AUC would result in a decrease of 3.4% in SVR<sub>12</sub> and a 2-fold increase in ABT-267 AUC would result in an increase by 1.3% in SVR<sub>12</sub> for a reference population of subjects with IL28B non-CC genotype and non-Hispanic/Latino ethnicity. The ABT-450 exposure was not statistically significantly correlated to the efficacy metric (SVR<sub>12</sub>) after inclusion of ABT-267 and RBV exposures in the model. Combining with the fact that ABT-450 showed the highest potency in decreasing viral load in monotherapy trials with each of the three DAAs, this suggests that the efficacy response is on saturation part of E-R relationship curve with respect to ABT-450 exposure. Thus a 50% reduction in ABT-267 / ABT-450 exposure may not reduce the overall efficacy by a substantial margin. Overall, the lowest quartiles of exposures in males of ABT-267 and RBV still had mean estimates of SVR<sub>12</sub> to be above 90% and thus no dose adjustment is recommended for any of the subgroups based on this E-R analysis for efficacy.

All the E-R analyses mentioned here were carried out with response data from six phase 3 studies (M11-646, M13-098, M13-099, M13-389, M13-96, and M14-002) and a phase 2 study (M14-103) in HCV genotype-1 infected adult subjects (N=2060). The exposure variables were calculated based on individual bayes estimates from population-PK model

for each of the drug molecules. Results from E-R analyses using  $C_{\text{trough}}$  as the exposure metric were consistent with results from AUC as the exposure metric (data not shown).

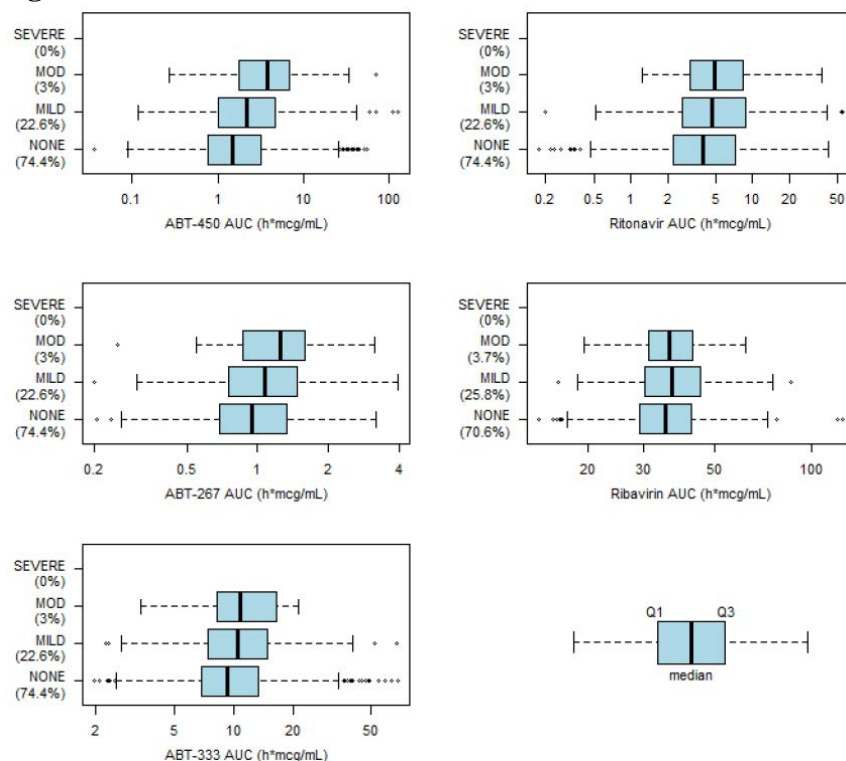
#### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

There was positive exposure-response relationship for safety signals of drug induced rash, ALT elevations, total bilirubin elevations and hemoglobin reductions with ABT-450 exposures. Also there was an E-R relationship for total bilirubin elevations and hemoglobin reductions with ABT-333 and ribavirin exposures.

#### Drug-Induced Rash (Moderate/Severe)

Incidence of drug-induced rash was higher in 3-DAA  $\pm$  RBV treatment compared to placebo. Presence of RBV in the treatment regimen was associated with higher incidence of rash compared to no RBV. This safety event had higher incidences for higher ABT-450 exposures (AUC) as seen in **Figure 4**.

**Figure 4: Drug induced rash vs. exposures (AUC) of components of 3-DAA  $\pm$  RBV regimen**



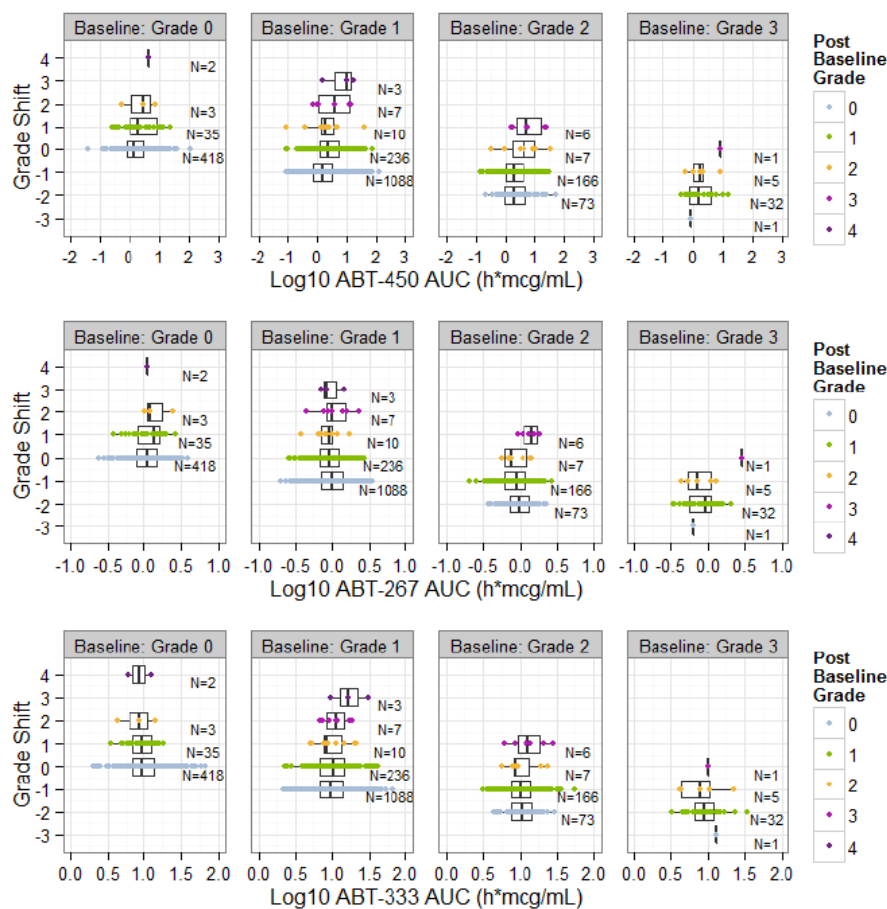
Source: Sponsor's Exposure-Safety Response Report R&D/14/0048, Figure 8, Page 31

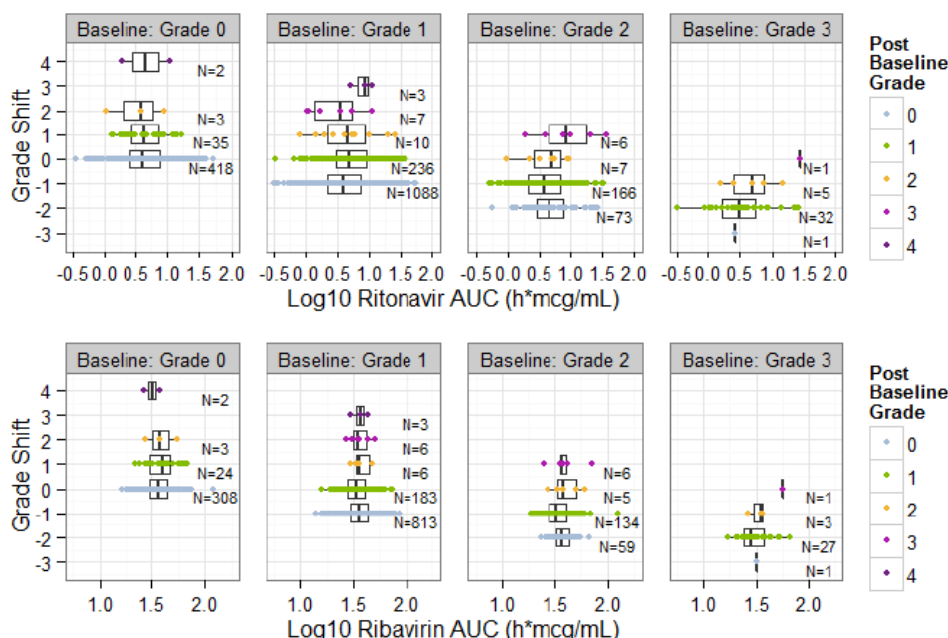
#### ALT Elevations

ABT-450 AUC and baseline ALT levels were significantly associated as predictors of post-baseline elevations in  $\geq$ Grade 3 ALT ( $>5 \times \text{ULN}$ ) levels. Also hormonal use was

associated with an increased likelihood of on-treatment  $\geq$ Grade 3 ALT elevations. Most of the subjects had Grade 1 ALT elevation at baseline and it resolved with treatment, but some patients had exposure dependent further increase in ALT elevation as shown in **Figure 5**. The multivariate logistic regression analysis of this safety signal predict a 2-fold increase in ABT-450 exposure would increase the odds of  $\geq$ Grade 3 ALT elevations by 1.6-fold and thus the incidence of  $\geq$ Grade 3 ALT elevations from the observed 0.91% (n/N=19/2093) incidence to 1.4%. For comparison, approximately 2.6% of the Phase 3 population used hormonal products and the observed incidence rate of  $\geq$ Grade 3 ALT elevations was 5.5% in this population.

**Figure 5: Grade Shift in Lab Abnormality of ALT elevation vs. exposures (AUC) of components of 3-DAA  $\pm$  RBV regimen**





Source: Sponsor's Exposure-Safety Response Report R&D/14/0048, Figure 9, Page 33

### Bilirubin Elevations

Presence of RBV in the treatment regimen was strongly associated with  $\geq$  Grade 3 total bilirubin elevation. Only 0.39% subjects ( $n/N=2/509$ ) had  $\geq$  Grade 3 total bilirubin elevations in the absence of RBV compared to 5.1% subjects ( $n/N=81/1584$ ) in the presence of RBV. ABT-450, ribavirin exposures and baseline elevated bilirubin levels were associated with post-baseline  $\geq$  Grade 2/3 bilirubin elevations (**Figure 6**). Multivariate logistic regression of this safety signal predicted that increasing ABT-450 exposure by 2-fold would increase the odds of  $\geq$  Grade 3 total bilirubin elevations to 1.5-fold and thus the incidence of  $\geq$  Grade 3 total bilirubin elevation from the observed 4.0% ( $n/N=83/2093$ ) incidence to 6.0%.

### Decreases in Hemoglobin Levels (Anemia)

Presence of ribavirin and higher ribavirin exposures were significant predictors of decreases in hemoglobin levels to  $\geq$ Grade 2 ( $<10$  g/dL hemoglobin) (**Figure 7**). Female sex, hemoglobin baseline status (baseline  $\geq$ Grade 1), and estrogen-containing therapy use were associated with decreases in hemoglobin levels ( $\geq$ Grade 2). There was no association between ABT-333 or ritonavir exposures and reduction in hemoglobin levels in the multivariate logistic regression analysis. ABT-450 and ribavirin had shallow E-R relationship to the response of decrease in hemoglobin levels while ABT-267 and hormone use have shallow negative relationship. Given the observed  $\geq$  Grade 2 decrease in hemoglobin level incidence of 5.21% ( $n/N=109/2093$ ) corresponding to the mean ABT-450 exposure, a 2-fold increase from mean in ABT-450 exposure is predicted to produce  $\sim 6.9\%$  incidence of  $\geq$  Grade 2 hemoglobin decrease events.

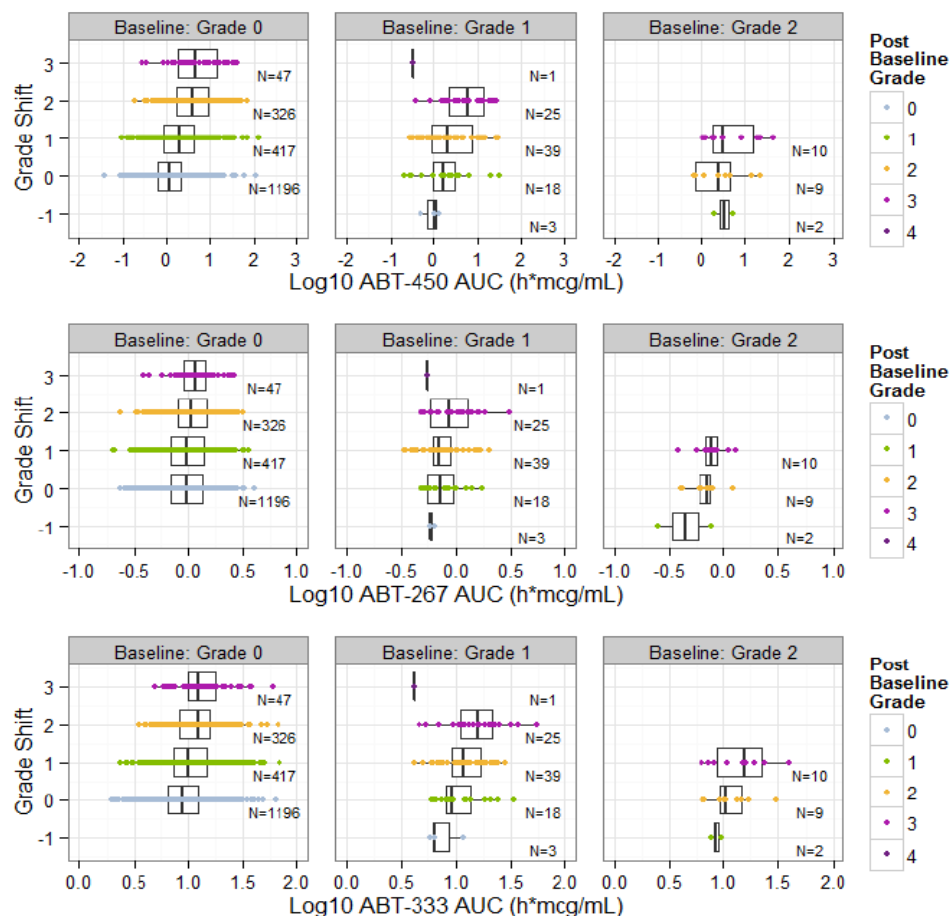
Given the small increase in the predicted incidence of this adverse event with doubling of ABT-450 exposure, increases in ABT-450 exposure by up to 2-fold is not expected to

adversely affect the safety profile substantially.

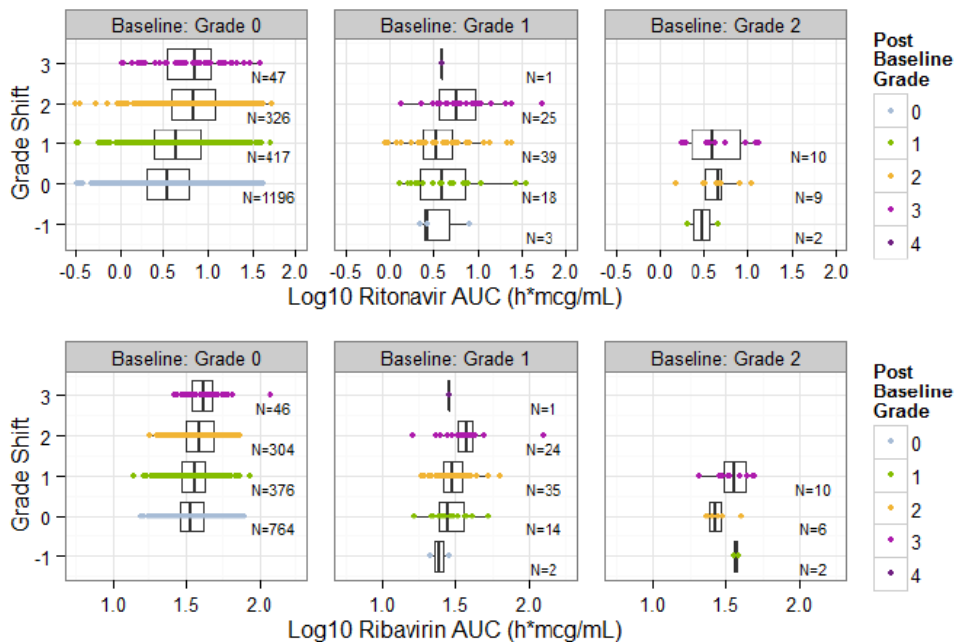
#### 2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect for a combination of ABT-450 with ritonavir plus ABT-267 and ABT-333 was detected in this TQT study (conducted using moxifloxacin as active control). Using individual corrected QT (QT<sub>cF</sub>) interval, the largest upper bounds of the 2-sided 90% CI for the mean differences between therapeutic dose and placebo, and between supratherapeutic doses (ABT-450 350 mg (using (b) (4) tablets) + ABT-267 50 mg + ABT-333 500 mg + Ritonavir 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

**Figure 6: Grade Shift in Lab Abnormality of Total Bilirubin elevation vs. exposures (AUC) of components of 3-DAA ± RBV regimen**

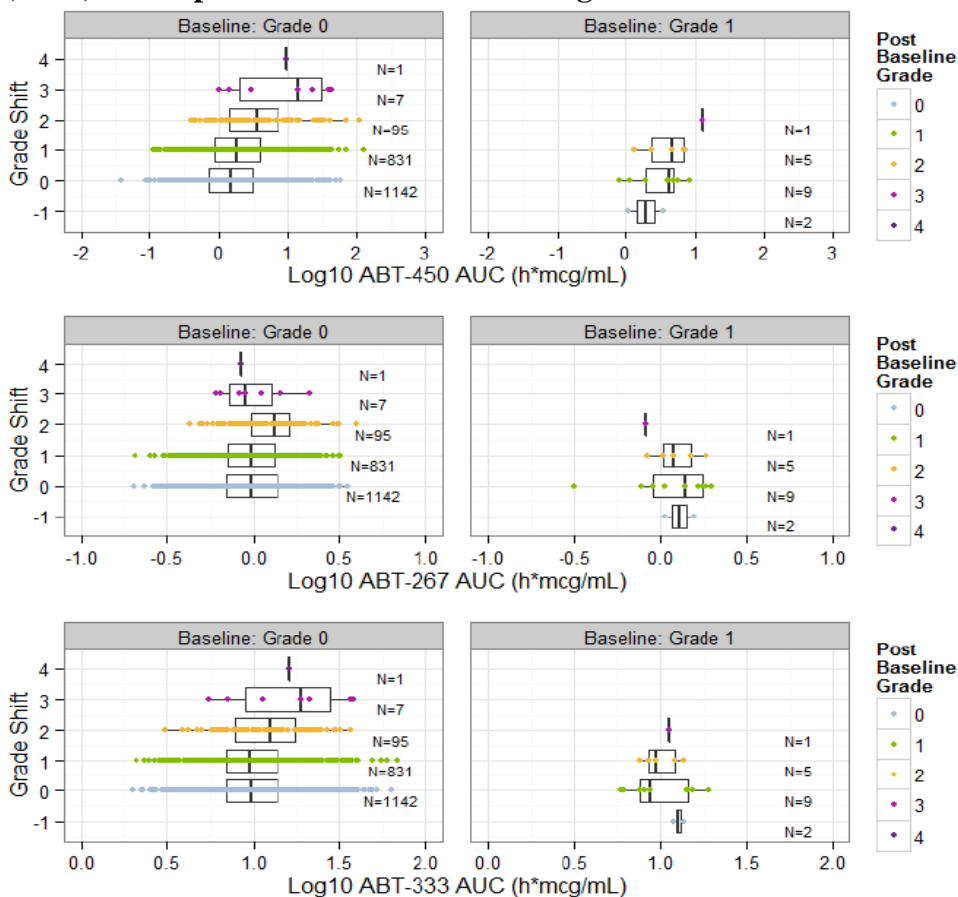




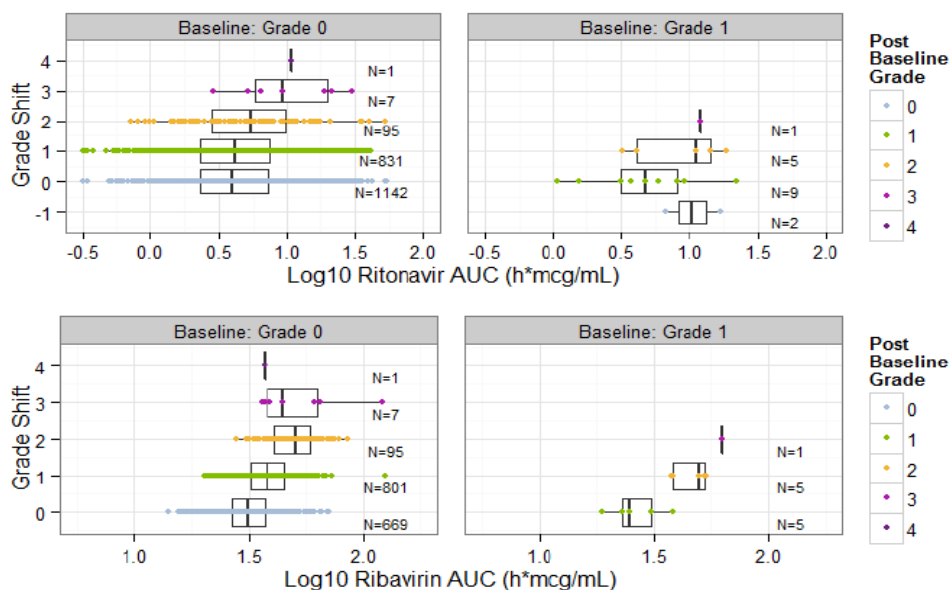


Source: Sponsor's Exposure-Safety Response Report R&D/14/0048, Figure 10, Page 35

**Figure 7: Grade Shift in Lab Abnormality of Hemoglobin Level vs. exposures (AUC) of components of 3-DAA ± RBV regimen**







Source: Sponsor's Exposure-Safety Response Report R&D/14/0048, Figure 11, Page 37

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The benefit/risk based on dose-exposure-response analyses for efficacy and safety support the following dosing recommendations:

**3-DAA regimen (without RBV) for 12 weeks in GT1b-infected non-cirrhotic population:** There was no additional benefit of RBV in this population.

**3-DAA+RBV regimen for 12 weeks in GT1b-infected cirrhotic population:** Study M13-099 had GT1b-infected cirrhotic population treated for either 12-weeks or 24-weeks with 3-DAA+RBV. There was just one relapse incidence in the GT1b population. There was no additional benefit of 24-weeks duration over 12-weeks duration for the relapse incidences across treatment-naïve as well as treatment-experienced population (**Table 8**). Thus, 12-week treatment regimen with 3-DAA+RBV is suitable for this population.

**Table 8: Effect of treatment duration on SVR<sub>12</sub> response and virologic failure due to relapse in GT1b-infected patients with compensated cirrhosis treated with 3-DAA+RBV regimen (Study M13-099)**

n/N (%)	3-DAA + RBV x 12 weeks		3-DAA + RBV x 24 weeks	
	SVR <sub>12</sub>	Relapse	SVR <sub>12</sub>	Relapse
GT 1b naïve	22/22 (100%)	0/22 (0%)	18/18 (100%)	0/18 (0%)
GT 1b experienced	45/46 (97.8%)	1/46 (2.2%)	33/33 (100%)	0/33 (0%)
-prior null	25/25 (100%)	0/25 (0%)	20/20 (100%)	0/20 (0%)
-prior partial	6/7 (85.7%)	1/7 (14.3%)	3/3 (100%)	0/3 (0%)
-prior relapse	14/14 (100%)	0/14 (0%)	10/10 (100%)	0/10 (0%)

Source: Reviewer's analysis

**3-DAA+ RBV regimen for 12 weeks in GT1a-infected treatment-naïve and treatment experienced non-cirrhotic population:** Inclusion of RBV in the treatment regimen was identified as an important predictor of SVR<sub>12</sub> response in a multivariate regression analysis in the GT1a population, with presence of RBV in the treatment regimen associated with a higher SVR<sub>12</sub>. The on-treatment virologic failures were also lower in 3-DAA+ RBV 12 week regimen (0.5% in treatment naïve and 0% in treatment experienced) as compared to the 3-DAA 12 week regimen (3.0%) in GT1a treatment naïve population (**Table 9**). These on-treatment failures with 3-DAA regimen were not localized exclusively in low exposure quartiles of ABT-450, ABT-267 or ABT-333 (**Figure 8**). Therefore, increasing exposures (i.e. doses) of the 3-DAA (ABT-450/ABT-267/ABT-333) may not compensate for the lack of RBV in the treatment regimen for avoiding on-treatment virological failures in this population. The presence of RBV also correlated with lower virological relapse (1.7% in treatment naïve and 3.5% in treatment experienced) as compared to just 3-DAA regimen (5.4%) as shown in **Table 9**. The analysis of relapsers across the GT1a-infected population suggests that all of the relapsers had generally higher baseline viral loads (>5.5 on log<sub>10</sub> scale) as shown in **Figure 9**.

**Table 9: SVR<sub>12</sub> and virological failures in GT1a treatment naïve and treatment experienced non-cirrhotic patients treated with 3-DAA or 3-DAA+RBV regimen for 12 weeks**

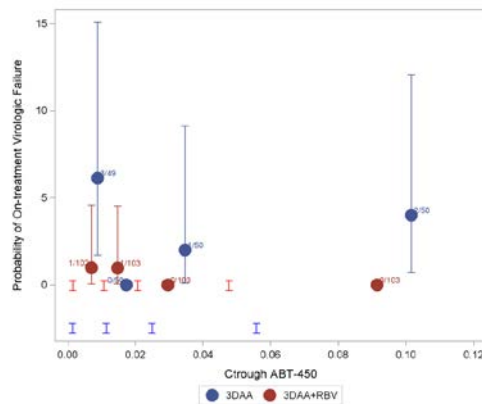
	GT1a Treatment Naïve		GT1a Treatment Experienced
	Study M14-002	Study M14-002 & M11-646	Study M13-098
Treatment	3-DAA + Placebo (n=202)	3-DAA + RBV (n=419)	3-DAA + RBV (n=173)
SVR <sub>12</sub> (ITT)*	182/202 (90.1%)	401/419 (95.7%)	166/173 (96.0%)
On-Treatment Virological failure (virological breakthrough)	6/202 (3.0%)	2/419 (0.5%)	0/173 (0.0%)
Relapse	11/202 (5.4%)	7/419 (1.7%)	6/173 (3.5%) Prior null: 4/87 (4.6%) Prior partial: 0/36 (0.0%) Prior relapse: 2/50 (4.0%)

\*5 cirrhotic patients who were in ITT set were removed from the above study populations to reflect the analysis for just the non-cirrhotic patients.

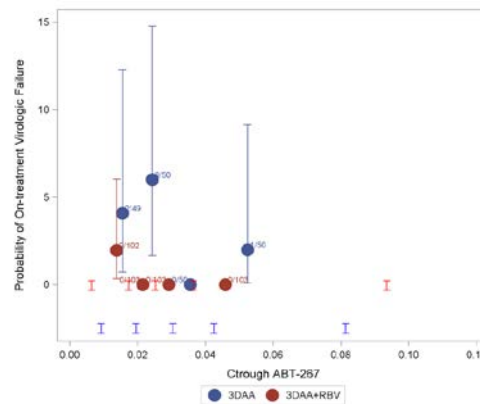
Source: Reviewer's analysis

**Figure 8. Exposure-response relationship for probability of on-treatment virological failure with predicted Ctrough concentrations of different drug components in GT1a-infected treatment-naïve subjects receiving either 3-DAA (blue symbols) or 3-DAA+RBV (red symbols): panel A for ABT-450 Ctrough, panel B for ABT-267 Ctrough, panel C for ABT-333 Ctrough. All Ctrough values are in ug/mL. (The blue and red lines at the bottom of each graph demarcate the range of exposure for each quartile of exposure in each treatment arm shown with same colored symbol)**

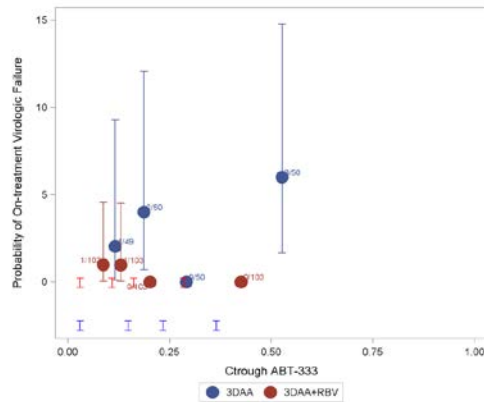
A.



B.

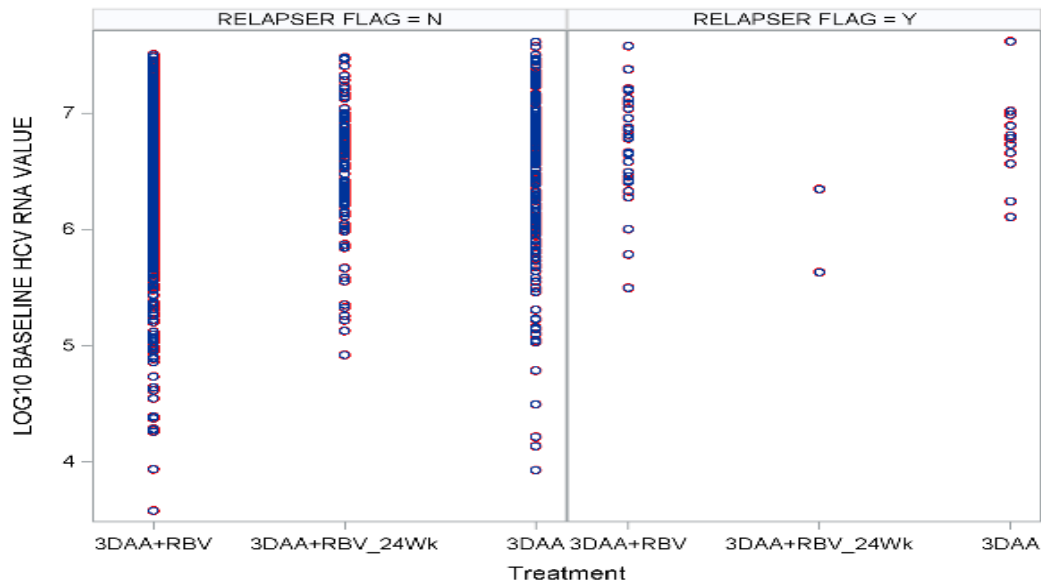


C.



Source: Reviewer's analysis

**Figure 9.** GT1a-infected patients who had relapse on 3-DAA or 3-DAA+RBV regimens have generally a high baseline viral load.



Source: Reviewer's analysis

### 3-DAA+ RBV regimen for 24 weeks in GT1a-infected treatment-naïve and treatment-experienced cirrhotic population:

In GT1a-infected cirrhotic population (study M13-099) treated with 3-DAA+RBV, the 24-week treatment duration resulted in lower relapse incidences compared to 12-week treatment duration across both treatment-naïve (3.6% vs. 7.8%) and treatment-experienced (0% vs. 11.8%) population (**Table 10**). Thus, 24-week treatment regimen with 3-DAA+RBV is suitable for these populations.

**Table 10: Effect of treatment duration on SVR<sub>12</sub> response and virologic failure due to relapse in GT1a-infected patients with compensated cirrhosis treated with 3-DAA+RBV regimen (Study M13-099)**

n/N (%)	3-DAA + RBV x 12 weeks		3-DAA + RBV x 24 weeks	
	SVR <sub>12</sub>	Relapse	SVR <sub>12</sub>	Relapse
GT 1a naïve	59/64 (92.2%)	5/64 (7.8%)	52/56 (92.9%)	2/56 (3.6%)
GT 1a experienced	65/76 (85.5%)	9/76 (11.8%)	62/65 (95.4%)	0/65 (0%)
-prior null	40/50 (80%)	8/50 (16%)	39/42 (92.9%)	0/42 (0%)
-prior partial	11/11 (100%)	1/11 (9.1%) <sup>§</sup>	10/10 (100%)	0/10 (0%)
-prior relapse	14/15 (93.3%)	0/15 (0%)	13/13 (100%)	0/13 (0%)

<sup>§</sup>Reflects 1 patient with post-SVR<sub>12</sub> relapse

Source: Reviewer's analysis

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

**Table 11** shows the comparison of the single dose- and multiple dose pharmacokinetic parameters for ABT-267, ABT-450, ritonavir, ABT-333 and ABT-333 M1 across various trials in which the Phase 3 formulations were administered.

**Table 11: Comparison of Single-Dose and Multiple-Dose Pharmacokinetic Parameters**

Compound	Dose	Number of Studies/ Arms <sup>a</sup>	C <sub>max</sub> <sup>b</sup> ng/mL	AUC <sup>b</sup> ng·h/mL	C <sub>trough</sub> <sup>b</sup> ng/mL	T <sub>max</sub> <sup>c</sup> h	t <sub>1/2</sub> <sup>d</sup> h	V <sub>d</sub> /F <sup>b</sup> L	CL/F <sup>b</sup> L/h
ABT-450	Single	2	1410 (1190 – 1680)	7760 (7000 – 8620)	ND	4.24 (4.17 – 4.30)	5.52 (5.49 – 5.54)	169 (165 – 174)	20 (19 – 21)
	Multiple	8	1470 (686 – 3040)	6990 (3760 – 16500)	20 (14 – 43)	4.40 (4.10 – 5.20)	ND	ND	ND
Ritonavir	Single	2	1670 (1580 – 1770)	9530 (9530 – 9530)	ND	4.05 (4.00 – 4.10)	3.73 (3.65 – 3.81)	59 (58 – 61)	11 (10 – 11)
	Multiple	8	1600 (1190 – 2110)	9470 (7270 – 12700)	33 (29 – 37)	4.24 (4.00 – 4.50)	ND	ND	ND
ABT-267	Single	2	141 (135 – 146)	1030 (1850 – 2010)	ND	4.99 (4.80 – 5.17)	21.1 (18.8 – 23.5)	412 (371 – 457)	13 (13 – 14)
	Multiple	8	127 (84 – 143)	1420 (1050 – 1600)	29 (22 – 34)	5.08 (4.50 – 5.60)	ND	ND	ND
ABT-333	Single	2	1400 (1380 – 1420)	11960 (11500 – 12400)	ND	3.89 (3.70 – 4.08)	5.88 (5.52 – 6.23)	183 (181 – 184)	21 (20 – 23)
	Multiple	8	1030 (826 – 1150)	6840 (5530 – 7740)	269 (229 – 319)	3.64 (3.10 – 4.00)	ND	ND	ND
ABT-333 M1	Single	2	797 (730 – 870)	6240 (5940 – 6560)	ND	4.49 (4.30 – 4.67)	4.68 (4.30 – 5.06)	ND	ND
	Multiple	8	660 (507 – 851)	3890 (2930 – 4720)	127 (102 – 167)	4.32 (3.70 – 4.70)	ND	ND	ND

ND = Not determined

<sup>a</sup> One single dose study was dosed with the (b) (4) ABT-450/r/ABT-267 tablet. The coated (b) (4) tablets had similar dissolution profiles.

<sup>b</sup> Overall cross-study geometric mean (range of geometric means for individual study arms).

<sup>c</sup> Overall cross-study arithmetic mean (range of arithmetic means for individual study arms).

<sup>d</sup> Median (range of harmonic means for individual study arms).

Source: Table 5 on Page 16 of report R&D/14/0050

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

**Table 12** shows the comparison of the steady state exposures between healthy volunteers and HCV genotype 1 infected patients (non-cirrhotics) for the 3-DAA combination administered using the Phase 3 formulations.

**Table 12: Comparison of the steady state exposures between healthy volunteers and HCV genotype 1 infected patients (non-cirrhotics) for the 3-DAA combination administered using the Phase 3 formulation**

Compound in the Phase 3 Formulation	Population	AUC <sub>24,ss</sub> (ng•h/mL) <sup>c</sup>	C <sub>max,ss</sub> (ng/mL)	C <sub>min,ss</sub> (ng/mL)
ABT-450	Healthy <sup>a</sup>	6990 (3760 – 16500)	1470 (686 – 3040)	20 (14 – 43)
ABT-267	Healthy <sup>a</sup>	1420 (1050 – 1600)	127 (84 – 143)	29 (22 – 34)
ABT-333	Healthy <sup>a</sup>	6840 (5530 – 7740)	1030 (826 – 1150)	269 (229 – 318)
Ritonavir	Healthy <sup>a</sup>	9470 (7270 – 12700)	1600 (1190 – 2110)	33 (29 – 37)
ABT-450	HCV <sup>b</sup>	1950	229	18.8
ABT-267	HCV <sup>b</sup>	1030	72.7	25.0
ABT-333	HCV <sup>b</sup>	3110	643	71.3
Ritonavir	HCV <sup>b</sup>	6290	699	33.9

a. Overall Phase 1 study geometric mean (range of observed geometric means for individual study arms)

b. Overall model-predicted cross-study median (based on individual predicted concentrations)

c. Area under the plasma concentration-time curve from time 0 to 12 hours at steady state (AUC<sub>12,ss</sub>) is reported for ABT-333

Source: Table 40 on Page 122 of report R&D/14/0047

Overall, the exposures (AUC) of ABT-267, ABT-450, ritonavir, and ABT-333 were lower in HCV-1 infected patients as compared to healthy volunteers. In contrast, a similar comparison of exposures between HCV-1 infected patients and healthy volunteers from Phase 2 trials indicated that the exposures of ABT-267, ABT-450, ritonavir, and ABT-333 were similar between healthy volunteers and patients.

The lower estimated C<sub>max,ss</sub> observed in Phase 3 studies for ABT-267, ABT-333 and ritonavir and the lower C<sub>max,ss</sub> and AUC<sub>24,ss</sub> for ABT-450 could be due to the pharmacokinetic sample collection scheme used. In the Phase 2 studies, intensive pharmacokinetic samples were collected in a subset of subjects and samples near C<sub>max,ss</sub> (2 hour and 4 hour on Day 1) were collected in all (~600) subjects in the Phase 2b study (Study M11-652). In comparison, only sparse samples were collected in the Phase 3 studies. Dosing information for DAAs was recorded based on the MEMS cap for ribavirin with the assumption that subjects took DAAs and ribavirin at the same time. The only exception was Study M13-099 (cirrhotic subjects), that had a 2 hour pharmacokinetic sample and used a MEMS cap on all DAAs and ribavirin. The exposures for subjects in this study were higher than in other Phase 3 studies but comparable to those in healthy subjects.

Hence, due to the potential impact of differences in pharmacokinetic sampling scheme, no definitive conclusions can be drawn regarding whether there are differences in the pharmacokinetics between HCV-infected patients and healthy volunteers.

Cirrhosis status was a significant covariate for ABT-450 and ABT-333 exposures, but not the ABT-267 or RBV exposure. In the pooled patient population from six phase 3 studies

and a phase 2 study (M14-103), after adjusting for the important PK covariates of sex, concomitant RBV and concomitant methadone use, the exposures (AUC calculated from population-PK model) in cirrhotic patients (n=371) were 2.7-fold for ABT-450 and 1.4-fold for ABT-333 compared to non-cirrhotic patients (n=1689) as shown in **Table 13**.

**Table 13: Comparison of exposures in cirrhotic vs. non-cirrhotic patients after adjusting for sex, concomitant RBV and concomitant methadone use**

Parameter	Comparison	Ratio (90% CI)
ABT-450 AUC	Cirrhotic/Non-Cirrhotic	2.7 (2.44, 3.00)
ABT-333 AUC	Cirrhotic/Non-Cirrhotic	1.4 (1.35, 1.49)
ABT-267 AUC	Cirrhotic/Non-Cirrhotic	1 (0.92, 1.00)
RBV AUC	Cirrhotic/Non-Cirrhotic	0.93 (0.91, 0.96)

Source: Reviewer's analysis

#### 2.2.5.3 What are the characteristics of drug absorption?

##### ABT-450

ABT-450 membrane apparent permeability ( $P_{app}$ ) in Caco-2 cells ranged from  $6.7 - 9.8 \times 10^{-6}$  cm/sec at concentrations  $\leq 10$   $\mu$ M. The absolute bioavailability of ABT-450 was not determined. The  $t_{max}$  of ABT-450 is approximately 4-5 hours.

##### ABT-267

ABT-267 membrane apparent permeability ( $P_{app}$ ) in MDCK cells ranged from  $0.9-3.3 \times 10^{-6}$  cm/sec at concentrations  $\leq 10$   $\mu$ M. The absolute bioavailability of ABT-267 was not determined. The  $t_{max}$  of ABT-267 is approximately 4-5 hours.

##### ABT-333

ABT-333 membrane permeability in Caco-2 cells was independent of pH and concentration, with values which ranged from 36.5 to  $51.9 \times 10^{-6}$  cm/sec at drug concentrations of 0.5 and 5  $\mu$ M. Based on the results of a trial conducted using a single intravenous microdose of 100  $\mu$ g  $^{14}$ C-ABT-333 and ABT-333 400 mg tablet, the absolute bioavailability of ABT-333 under non-fasting conditions was estimated to be 46 %. The  $t_{max}$  of ABT-333 is approximately 3 hours.

#### 2.2.5.4 What are the characteristics of drug distribution?

##### ABT-450

The protein binding of ABT-450 is  $> 97$  % over a concentration range of 0.1  $\mu$ M to 10  $\mu$ M (0.08-8  $\mu$ g/mL). The blood-to-plasma concentration ratio was 0.7 in humans, indicating that ABT-450 was preferentially distributed in the plasma compartment of whole blood. The results of renal- and hepatic impairment trials showed that the unbound fraction of ABT-450 was similar across the various renal- and hepatic impairment

groups, except for mild and moderate hepatic impairment groups where fraction unbound was ~30% lower relative to subjects with normal liver function.

### ABT-267

The protein binding of ABT-267 is 99.9 % over a concentration range of 0.1  $\mu\text{M}$  to 10  $\mu\text{M}$  (0.09-9  $\mu\text{g/mL}$ ). The blood-to-plasma concentration ratio was 0.49 in humans, indicating that ABT-267 was preferentially distributed in the plasma compartment of whole blood. The results of renal- and hepatic impairment trials showed that the unbound fraction of ABT-267 was similar across the various renal- and hepatic impairment groups, except for severe renal impairment group and severe hepatic impairment group where fraction unbound was ~ 2-fold higher than fraction unbound in subjects with normal renal function or normal hepatic function.

### ABT-333

The protein binding of ABT-333 is 99.9 % over a concentration range of 0.1  $\mu\text{M}$  to 10  $\mu\text{M}$  (0.05-5  $\mu\text{g/mL}$ ). The blood-to-plasma concentration ratio was 0.7 in humans, indicating that ABT-333 was preferentially distributed in the plasma compartment of whole blood. The results of the hepatic impairment trial showed that the unbound fraction of ABT-333 in subjects with mild- and moderate hepatic impairment was approximately 50 % lower as compared to subjects with normal hepatic function. The unbound fraction of ABT-333 in subjects with severe hepatic impairment was 27% lower than unbound fraction in subjects with normal hepatic function. The results of the renal impairment trial showed that the unbound fraction of ABT-333 was similar across the various renal impairment groups.

#### 2.2.5.5 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The results of the mass balance trials suggest that ABT-450 (co-administered with ritonavir), ABT-267 and ABT-333 and their metabolites are primarily eliminated through the hepatobiliary route.

#### 2.2.5.6 What are the characteristics of drug metabolism?

### ABT-450 (co-administered with ritonavir)

The results of the mass balance trial showed that ABT-450 was the predominant circulating radioactive species (~88.9 % of the drug related radioactivity) in plasma. In plasma, 5 ABT-450 metabolites were identified, including M2, M29, and trace levels of M3, M13, and M6. In urine, M13 was the major component (accounting for 8.57 % of the administered radioactive dose) and in feces, M29 was the major component (accounting for 59.9 % of the administered radioactive dose).



### ABT-267

The results of the mass balance trial showed that unchanged ABT-267 accounted for 8.85 % of the total radioactivity in plasma. In plasma, 13 metabolites were identified; M23, M29, M36, and M37 were present as major circulating metabolites.

### ABT-333

The results of the mass balance trial showed unchanged ABT-333 accounted for approximately 60 % of the total radioactivity in plasma. 7 metabolites (M1, M2, M3, M4, M5, M6, and M11) were observed in plasma; AUC<sub>0-∞</sub> of M1 (active metabolite) was about 22 % of the total drug related material in plasma. M1 was the major component in the feces with a mean of ~32 % of the administered radioactive dose, followed by unchanged parent drug (26 %), M2 (15 %), and M5 (11 %). M1 was the major component in the urine (0.85 %).

#### 2.2.5.7 What are the characteristics of drug excretion?

### ABT-450 (co-administered with ritonavir)

Approximately 88 % of the administered radioactive dose was recovered in feces and 8.76 % of the administered radioactive dose was recovered in the urine. Unchanged ABT-450 accounted for 1.1 % of the radioactivity in the feces and 0.05 % in the urine.

### ABT-267

Approximately 90 % of the administered radioactive dose was recovered in feces and 1.91 % of the administered radioactive dose was recovered in the urine. Unchanged ABT-267 accounted for 87.8 % of the radioactivity in the feces and 0.03 % in the urine.

### ABT-333

Approximately 94 % of the administered radioactive dose was recovered in feces and 2.05 % of the administered radioactive dose was recovered in the urine (0.03 % as unchanged ABT-333). ABT-333 M1 was the major component in the feces with ~32 % of the administered radioactive dose, followed by unchanged ABT-333 (26 % of the administered radioactive dose). Unchanged ABT-333 accounted for 0.03 % of the total radioactivity in the urine. Of note, ABT-333 M1 showed comparable anti HCV activity in cell culture based on a study conducted using HCV genotype 1a and 1b replicon systems.

#### 2.2.5.8 Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

### ABT-450

For ABT-267/ABT-450/ritonavir co-formulated tablets, increasing the dose of ABT-450 by 33 % increased the mean AUC of ABT-450 by ~2.5 fold. As there were only two doses of ABT-450 available as part of the coformulated tablets, no definitive conclusions

can be drawn regarding the linearity of ABT-450 exposures after administration of ABT-267/ABT-450/ritonavir co-formulated tablets.

#### ABT-267

ABT-267 shows linear pharmacokinetics with dose-proportional increases in exposure over the range from 1.5 mg to 200 mg for (b) (4) tablets and 200 mg to 350 mg for (b) (4) tablets after single-dose administration and over the range of 5 mg to 100 mg once daily after multiple-dose administration.

#### ABT-333

Dose-proportional or slightly less than dose-proportional increases in exposure were observed with the 400 mg tablet formulation up to the 1600 mg dose following single and twice daily multiple dosing.

2.2.5.9 How do the PK parameters change with time following multiple dosing?

Please refer to the response to question 2.2.5.1.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

#### ABT-450

The median [range] inter subject variability (% CV) of ABT-450  $C_{max}$  and  $AUC_{24}$  was 86 % (47 % to 173 %) and 83 % (31 % to 190 %) across the single- and multiple doses conducted with various formulations in healthy volunteers. ABT-450 is a substrate of CYP3A as well as multiple transporters (P-gp, OATP1B1, OATP1B3, MRP-2 and BCRP); hence, the heterogeneity in expression of these enzymes/transporters may explain the variability in ABT-450 exposures. In addition, variability in ritonavir exposures may also help to explain the variability in ABT-450 exposures.

#### ABT-267

The median [range] inter subject variability (% CV) of ABT-267  $C_{max}$  and  $AUC_{24}$  was 27 % (8 % to 52 %) and 27 % (10 % to 55 %) across the single- and multiple doses conducted with various formulations in healthy volunteers.

#### ABT-333

The median [range] inter subject variability (% CV) of ABT-333  $C_{max}$  and  $AUC_{12}$  was 38 % (21% to 69 %) and 38 % (20 % to 71 %) across the single- and multiple doses conducted with various formulations in healthy volunteers.

## ABT-333 M1

The median [range] inter subject variability (% CV) of ABT-333 M1  $C_{\max}$  and  $AUC_{12}$  was 37 % (22% to 57 %) and 40 % (25 % to 69 %) across the single- and multiple doses conducted with various formulations in healthy volunteers.

### **2.3 Intrinsic Factors**

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

#### 2.3.2.1 Elderly

Elderly status (>65 yr) was a statistically significant covariate for ABT-450, ABT-267, ABT-333 and RBV exposures. When adjusted for other important covariates of sex, cirrhosis status, concomitant RBV and concomitant methadone, the exposures ( $AUC$ ) in elderly patients (age>65 yr; n=127) were 1.1- to 1.3-fold compared to non-elderly patients (age ≤65 yr; n=1933) as shown in **Table 14**. These changes in exposures in elderly subjects are not expected to be clinically relevant.

**Table 14: Comparison of exposures in elderly vs. non-elderly population after adjusting for sex, cirrhosis status, and concomitant RBV and concomitant methadone use**

Parameter	Comparison	Ratio (90% CI)
ABT-450 AUC	Elderly/Non-elderly	1.3 (1.12, 1.54)
ABT-333 AUC	Elderly/Non-elderly	1.1 (1.00, 1.16)
ABT-267 AUC	Elderly/Non-elderly	1.2 (1.11, 1.24)
RBV AUC	Elderly/Non-elderly	1.2 (1.11, 1.22)

Source: Reviewer's analysis

#### 2.3.2.2 Pediatrics

The safety and efficacy of the 3-DAA regimen in pediatric chronic hepatitis C infected patients has not been established. In addition, no pharmacokinetic data on the 3-DAA regimen are available in the pediatric chronic hepatitis C infected patients.

### 2.3.2.3 Gender

Gender was a significant covariate for ABT-450, ABT-267, ABT-333 and RBV exposures. When adjusted for other important covariates of cirrhosis status, concomitant RBV and concomitant methadone, the exposures (AUC) in female patients (n=856) were 1.8-fold for ABT-450, 1.3-fold for ABT-333, 1.7-fold for ABT-267 and 1.2-fold for RBV compared to male patients (n=1204) as shown in **Table 15**. Correspondingly the efficacy (SVR<sub>12</sub>) was slightly higher in females as compared to males as shown above in section 2.2.4.1 (E-R relationship for efficacy). Gender, by itself, was not found to be an important covariate for any safety events when considered separately from concomitant hormonal (estrogen/progestin containing products) use (which is mostly in females). Thus, no dose modifications are recommended based on gender.

**Table 15: Comparison of exposures in females vs. males after adjusting for cirrhosis status, concomitant RBV and concomitant methadone use**

Parameter	Comparison	Ratio (90% CI)
ABT-450 AUC	Female/Male	1.8 (1.66, 1.95)
ABT-333 AUC	Female/Male	1.3 (1.27, 1.36)
ABT-267 AUC	Female/Male	1.7 (1.66, 1.76)
RBV AUC	Female/Male	1.2 (1.16, 1.21)

Source: Reviewer's analysis

### 2.3.2.4 Race

Race (Black vs. Other) or ethnicity (Hispanic/Latino ethnicity vs. Others) were not found to be significant covariates for exposures derived from population-pk analyses of Phase 1b/2 or Phase 3 data for the DAAs, ritonavir and ribavirin. In phase 3 studies with the ABT-450/r/ABT-267 co-formulated tablet, when adjusted for other important covariates of sex, cirrhosis status, concomitant RBV and concomitant methadone administration:

- the exposures (AUC) in asian patients (n=34) were 1.3-fold for ABT-450, 1.4-fold for ABT-333, 1.1-fold for ABT-267 and no change for RBV compared to white patients (n=1880)
- the exposures (AUC) in black patients (n=125) were 1.3-fold for ABT-450, 1.1-fold for ABT-333, 1.0-fold for ABT-267 and 1.0-fold for RBV compared to white patients (n=1880)

These differences are not expected to be clinically relevant.

It should be noted that in a study in healthy volunteers (n=18), steady state ABT-450 C<sub>max</sub> and AUC in Chinese and Japanese subjects were 2.5- to 3.2-fold and 2.9- to 3.7-fold of exposures in Caucasian subjects. This increase is not caused by an increase in ritonavir exposure. ABT-267 and ABT-333 were slightly higher in Asians compared to Caucasians. These observed exposures were not adjusted for covariates that are known to affect ABT-450 exposures; therefore, the above recommendations based on population

PK analysis regarding no clinical relevant difference in exposures as a function of race are considered acceptable by the review team.

### 2.3.2.5 Renal impairment

The pharmacokinetics of a single dose of ABT-450/r 150/100 mg and ABT-267 25 mg ± ABT-333 400 mg were 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 16 shows the summary of the mean pharmacokinetic parameters of ABT-450 (based on total concentrations) in the various renal impairment groups after administration of the 3-DAA regimen.

**Table 16: Summary of the Mean Pharmacokinetic Parameters of ABT-450 (based on total concentrations) in the Various Renal Impairment Groups after Administration of the 3-DAA Regimen**

Parameter (units)	Normal Renal Function Subjects	Mild Renal Impairment Subjects	Moderate Renal Impairment Subjects	Severe Renal Impairment Subjects
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)				
N	6	6	6	6
$C_{max}$ (ng/mL)	280 ± 223	1690 ± 1120	1180 ± 1170	557 ± 528
$T_{max}$ (h)	4.7 ± 1.0	4.8 ± 1.8	4.7 ± 0.8	4.8 ± 0.4
$AUC_t$ (ng•h/mL)	1850 ± 1200	8590 ± 5480	6680 ± 5580	4000 ± 3530
$AUC_{\infty}$ (ng•h/mL)	1870 ± 1200	8610 ± 5490	6700 ± 5590	4020 ± 3530
$t_{1/2}^a$ (h)	6.88 ± 2.66	5.58 ± 0.66	5.88 ± 3.92	7.57 ± 3.16
$\beta$ (1/h)	0.101 ± 0.039	0.124 ± 0.015	0.118 ± 0.068	0.092 ± 0.036
$CL/F$ (L/h)	108 ± 56.5	34.4 ± 40.2	57.3 ± 74.9	79.8 ± 67.3
$V_{\beta}/F$ (L)	1390 ± 1150	264 ± 295	995 ± 1790	1070 ± 1140
$f_e$ (%)	0.035 ± 0.030	0.212 ± 0.179	0.046 ± 0.062	0.042 ± 0.061
$CL_R/F$ (L/h)	0.026 ± 0.017	0.034 ± 0.015	0.012 ± 0.015	0.012 ± 0.011

Source: Section of Table 10 (Page 112) from Clinical Study Report of M12-193

Table 17 shows the least squares mean ratio and 90 % CI of ABT-450 pharmacokinetic parameters in the various renal impairment groups.

**Table 17: Least Squares Means Ratio and 90 % CI of ABT-450 Pharmacokinetic Parameters in the Various Renal Impairment Groups**

Group	Pharmacokinetic	Central Value <sup>a</sup>		Point	90% Confidence
Test vs. Reference	Parameter	Test	Reference	Estimate	Interval
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	518	1214	0.426	0.113 – 1.608
	AUC <sub>t</sub> (ng•h/mL)	3715	6040	0.615	0.212 – 1.781
	AUC <sub>∞</sub> (ng•h/mL)	3748	6071	0.617	0.215 – 1.770
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	1925	1214	1.586	0.630 – 3.993
	AUC <sub>t</sub> (ng•h/mL)	10751	6040	1.780	0.850 – 3.729
	AUC <sub>∞</sub> (ng•h/mL)	10806	6071	1.780	0.855 – 3.704
Severe vs. Normal	C <sub>max</sub> (ng/mL)	674	1214	0.555	0.206 – 1.498
	AUC <sub>t</sub> (ng•h/mL)	4914	6040	0.814	0.367 – 1.801
	AUC <sub>∞</sub> (ng•h/mL)	4974	6071	0.819	0.373 – 1.801

Source: Section of Table 13 (Page 116) from Clinical Study Report of M12-193

Table 18 shows the summary of the mean pharmacokinetic parameters of ABT-267 (based on total concentrations) in the various renal impairment groups after administration of the 3-DAA regimen.

**Table 18: Summary of the Mean Pharmacokinetic Parameters of ABT-267 in the Various Renal Impairment Groups after Administration of the 3-DAA Regimen**

Parameter (units)	Normal Renal Function Subjects	Mild Renal Impairment Subjects	Moderate Renal Impairment Subjects	Severe Renal Impairment Subjects
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)				
N	6	6	6	6
C <sub>max</sub> (ng/mL)	129 ± 26	142 ± 40	119 ± 30	131 ± 39
T <sub>max</sub> (h)	5.0 ± 0.6	4.8 ± 0.8	5.0 ± 0.6	5.3 ± 0.8
AUC <sub>t</sub> (ng•h/mL)	1610 ± 195	2090 ± 568	1870 ± 589	2000 ± 712
AUC <sub>∞</sub> (ng•h/mL)	1680 ± 209	2300 ± 682	1980 ± 593	2150 ± 766
t <sub>1/2</sub> <sup>a</sup> (h)	38.1 ± 8.3	47.2 ± 14.1	44.5 ± 8.5	46.0 ± 9.6
β (1/h)	0.018 ± 0.004	0.015 ± 0.004	0.016 ± 0.003	0.015 ± 0.003
CL/F (L/h)	15.1 ± 1.9	11.9 ± 4.2	13.7 ± 4.5	13.4 ± 6.2
V <sub>β</sub> /F (L)	856 ± 186	822 ± 217	909 ± 354	916 ± 410
f <sub>e</sub> (%)	0.023 ± 0.027	0.025 ± 0.013	0.022 ± 0.014	0.025 ± 0.018
CL <sub>R</sub> /F (L/h)	0.003 ± 0.004	0.003 ± 0.001	0.003 ± 0.001	0.003 ± 0.002

Source: Section of Table 24 (Page 146) from Clinical Study Report of M12-193

**Table 19** shows the least squares mean ratio and 90 % CI of ABT-267 pharmacokinetic parameters in the various renal impairment groups.

**Table 19: Least Squares Mean Ratio and 90 % CI of ABT-267 Pharmacokinetic Parameters in the Various Renal Impairment Groups**

Group	Pharmacokinetic	Central Value <sup>a</sup>		Point	90% Confidence
Test vs. Reference	Parameter	Test	Reference	Estimate	Interval
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	117	149	0.790	0.581 – 1.075
	AUC <sub>t</sub> (ng•h/mL)	1700	2315	0.734	0.496 – 1.088
	AUC <sub>∞</sub> (ng•h/mL)	1892	2461	0.769	0.509 – 1.162
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	120	149	0.808	0.631 – 1.037
	AUC <sub>t</sub> (ng•h/mL)	2243	2315	0.969	0.737 – 1.274
	AUC <sub>∞</sub> (ng•h/mL)	2484	2461	1.009	0.757 – 1.345
Severe vs. Normal	C <sub>max</sub> (ng/mL)	120	149	0.810	0.620 – 1.058
	AUC <sub>t</sub> (ng•h/mL)	2163	2315	0.935	0.697 – 1.254
	AUC <sub>∞</sub> (ng•h/mL)	2439	2461	0.991	0.728 – 1.350

Source: Section of Table 27 (Page 150) from Clinical Study Report of M12-193

**Table 20** shows the summary of the mean pharmacokinetic parameters of ABT-333 and ABT-333 M1 in the various renal impairment groups (based on total concentrations) after administration of the 3-DAA regimen.

**Table 20: Summary of the Mean Pharmacokinetic Parameters of ABT-333 and ABT-333 M1 in the Various Renal Impairment Groups after Administration of the 3-DAA Regimen**

Parameter (units)	Normal Renal Function Subjects	Mild Renal Impairment Subjects	Moderate Renal Impairment Subjects	Severe Renal Impairment Subjects
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)				
ABT-333				
N	6	6	6	6
C <sub>max</sub> (ng/mL)	952 ± 276	2470 ± 1240	1390 ± 465	1500 ± 760
T <sub>max</sub> (h)	3.7 ± 1.6	3.5 ± 1.1	4.3 ± 0.5	4.8 ± 0.4
AUC <sub>t</sub> (ng•h/mL)	6410 ± 2480	21200 ± 8200	11100 ± 6050	15600 ± 10000
AUC <sub>∞</sub> (ng•h/mL)	6490 ± 2520	21400 ± 8370	11200 ± 6040	15800 ± 10100
t <sub>1/2</sub> <sup>a</sup> (h)	5.34 ± 0.74	9.02 ± 3.29	10.50 ± 3.54	12.00 ± 5.04
β (1/h)	0.130 ± 0.019	0.077 ± 0.027	0.066 ± 0.021	0.058 ± 0.024
CL/F (L/h)	71.0 ± 31.3	22.4 ± 12.4	41.4 ± 12.7	46.2 ± 48.0
V <sub>p</sub> /F (L)	547 ± 222	294 ± 115	670 ± 295	710 ± 444
f <sub>e</sub> (%)	0.020 ± 0.013	0.088 ± 0.060	0.055 ± 0.057	0.054 ± 0.060
CL <sub>R</sub> /F (L/h)	0.012 ± 0.009	0.015 ± 0.008	0.017 ± 0.008	0.011 ± 0.007
ABT-333 M1 Metabolite				
N	6	6	6	6
C <sub>max</sub> (ng/mL)	508 ± 186	964 ± 315	647 ± 275	352 ± 216
T <sub>max</sub> (h)	4.3 ± 1.2	4.8 ± 0.8	5.3 ± 0.5	5.5 ± 0.6
AUC <sub>t</sub> (ng•h/mL)	3240 ± 1530	8330 ± 2860	5540 ± 3340	3590 ± 2550
AUC <sub>∞</sub> (ng•h/mL)	3290 ± 1530	8410 ± 2880	5610 ± 3340	3710 ± 2560
t <sub>1/2</sub> <sup>a</sup> (h)	4.92 ± 0.82	6.22 ± 0.92	5.58 ± 1.14	7.12 ± 2.67
β (1/h)	0.141 ± 0.024	0.111 ± 0.016	0.124 ± 0.026	0.097 ± 0.037
A <sub>e</sub> (mg) <sup>b</sup>	5.06 ± 2.44	7.40 ± 2.14	2.12 ± 1.76	0.603 ± 0.662

a. Harmonic mean ± pseudo-standard deviation.

b. A<sub>e</sub> represents cumulative amount excreted in urine over collection interval of 0 – 144 hours.

Source: Table 31 (Page 166) from Clinical Study Report of M12-193

Table 21 shows the least squares mean ratio and 90 % CI of ABT-333 and ABT-333 M1 pharmacokinetic parameters in the various renal impairment groups.

**Table 21: Least Squares Mean Ratio and 90 % CI of ABT-333 and ABT-333 M1 Pharmacokinetic Parameters in the Various Renal Impairment Groups**

Group	Pharmacokinetic	Central Value <sup>a</sup>		Point	90% Confidence
Test vs. Reference	Parameter	Test	Reference	Estimate	Interval
ABT-267 25 mg + ABT-450/r 150/100 mg + ABT-333 400 mg (Period 1)					
ABT-333					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	1463	1363	1.073	0.589 – 1.958
	AUC <sub>t</sub> (ng•h/mL)	15285	7763	1.969	0.978 – 3.963
	AUC <sub>∞</sub> (ng•h/mL)	15448	7842	1.970	0.981 – 3.958
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	1444	1363	1.060	0.678 – 1.657
	AUC <sub>t</sub> (ng•h/mL)	10690	7763	1.377	0.782 – 2.424
	AUC <sub>∞</sub> (ng•h/mL)	10814	7842	1.379	0.784 – 2.424
Severe vs. Normal	C <sub>max</sub> (ng/mL)	1197	1363	0.878	0.543 – 1.421
	AUC <sub>t</sub> (ng•h/mL)	11365	7763	1.464	0.797 – 2.688
	AUC <sub>∞</sub> (ng•h/mL)	11527	7842	1.470	0.802 – 2.695
ABT-333 M1 Metabolite					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	659	671	0.983	0.507 – 1.908
	AUC <sub>t</sub> (ng•h/mL)	5576	4128	1.351	0.690 – 2.645
	AUC <sub>∞</sub> (ng•h/mL)	5736	4126	1.390	0.723 – 2.671
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	644	671	0.960	0.562 – 1.642
	AUC <sub>t</sub> (ng•h/mL)	5232	4128	1.267	0.736 – 2.182
	AUC <sub>∞</sub> (ng•h/mL)	5290	4126	1.282	0.756 – 2.174
Severe vs. Normal	C <sub>max</sub> (ng/mL)	246	671	0.366	0.206 – 0.652
	AUC <sub>t</sub> (ng•h/mL)	2560	4128	0.620	0.346 – 1.112
	AUC <sub>∞</sub> (ng•h/mL)	2727	4126	0.661	0.375 – 1.165

a. Antilogarithm of the least squares means for logarithms.

Source: Table 34 (Page 170) from Clinical Study Report of M12-193

The fraction of the dose excreted unchanged in the urine ( $f_e$ ) was < 2 % for all DAAs and ritonavir. Overall, the changes in exposures of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 in subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. Of note, pharmacokinetic data are not available on the use of the 3-DAA regimen in subjects with End Stage Renal Disease (ESRD).

### 2.3.2.6 Hepatic impairment

The pharmacokinetics of a single dose of 200 mg ABT-450 (using (b) (4) tablets), 100 mg ritonavir, 25 mg ABT-267, and 400 mg ABT-333 were evaluated in subjects with mild hepatic impairment (Child-Pugh Category A; score of 5-6), moderate hepatic impairment (Child-Pugh Category B, score of 7-9) and severe hepatic impairment (Child-Pugh Category C, score of 10-15).



Table 22 shows the summary of the mean pharmacokinetic parameters of ABT-450 (based on total concentrations) in the various hepatic impairment groups after administration of the 3-DAA regimen.

**Table 22: Summary of the Mean Pharmacokinetic Parameters of ABT-450 (based on total concentrations) in the Various Hepatic Impairment Groups after Administration of the 3-DAA Regimen**

Parameter (Unit)	ABT-267 25 mg + ABT-450/r 200/100 mg + ABT-333 400 mg			
	Normal Subjects	Mild Hepatic Impaired Subjects	Moderate Hepatic Impaired Subjects	Severe Hepatic Impaired Subjects
N	7	6	6	5
C <sub>max</sub> (ng/mL)	2530 ± 2810	1650 ± 2140	2970 ± 2230	5580 ± 1970
T <sub>max</sub> (h)	4.3 ± 0.49	4.7 ± 2.8	4.2 ± 1.2	5.6 ± 2.5
AUC <sub>t</sub> (ng•hr/mL)	13800 ± 17200	11000 ± 15600	23300 ± 24700	73000 ± 29300
AUC <sub>∞</sub> (ng•hr/mL)	13900 ± 17100	11000 ± 15600	23300 ± 24700	73000 ± 29300
t <sub>1/2</sub> <sup>a</sup> (h)	5.83 ± 1.56	5.94 ± 1.87	6.38 ± 0.70	7.90 ± 1.28
β (1/h)	0.119 ± 0.032	0.117 ± 0.036	0.109 ± 0.012	0.088 ± 0.014
CL/F (L/h)	49.2 ± 48.8	74.6 ± 79.0	23.1 ± 25.8	3.06 ± 1.06
V <sub>D</sub> /F (L)	431 ± 406	693 ± 746	221 ± 250	36.1 ± 16.1

a. Harmonic mean ± pseudo-standard deviation.

Source: Table 10 (Page 87) from Clinical Study Report of M12-215

Table 23 shows the least squares mean ratio and 90 % CI of ABT-450 pharmacokinetic parameters in the various hepatic impairment groups.

**Table 23: Least Squares Means Ratio and 90 % CI of ABT-450 Pharmacokinetic Parameters in the Various Hepatic Impairment Groups**

Group Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Point Estimate	90% Confidence Interval
		Test	Reference		
Mild vs. Normal	C <sub>max</sub> (ng/mL)	738	1423	0.519	0.213 – 1.266
	AUC <sub>t</sub> (ng•hr/mL)	5193	7341	0.707	0.272 – 1.839
	AUC <sub>∞</sub> (ng•hr/mL)	5213	7359	0.708	0.273 – 1.839
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	1794	1423	1.261	0.511 – 3.111
	AUC <sub>t</sub> (ng•hr/mL)	11868	7341	1.617	0.615 – 4.252
	AUC <sub>∞</sub> (ng•hr/mL)	11893	7359	1.616	0.615 – 4.244
Severe vs. Normal	C <sub>max</sub> (ng/mL)	6042	1423	4.247	1.660 – 10.868
	AUC <sub>t</sub> (ng•hr/mL)	76925	7341	10.479	3.831 – 28.661
	AUC <sub>∞</sub> (ng•hr/mL)	76948	7359	10.456	3.828 – 28.559

a. Antilogarithm of the least squares means for logarithms.

Source: Table 13 (Page 89) from Clinical Study Report of M12-215

Table 24 shows the summary of the mean pharmacokinetic parameters of ABT-267 (based on total concentrations) in the various hepatic impairment groups after administration of the 3-DAA regimen.

**Table 24: Summary of the Mean Pharmacokinetic Parameters of ABT-267 (based on total concentrations) in the Various Hepatic Impairment Groups after Administration of the 3-DAA Regimen**

Parameter (Unit)	ABT-267 25 mg + ABT-450/r 200/100 mg + ABT-333 400 mg			
	Normal Subjects	Mild Hepatic Impaired Subjects	Moderate Hepatic Impaired Subjects	Severe Hepatic Impaired Subjects
N	7	6	6	5
C <sub>max</sub> (ng/mL)	108 ± 45.0	104 ± 24.8	83.1 ± 30.8	32.9 ± 11.4
T <sub>max</sub> (h)	4.3 ± 1.1	4.3 ± 0.82	5.2 ± 0.75	4.8 ± 1.3
AUC <sub>t</sub> (ng•hr/mL)	1560 ± 770	1410 ± 496	1220 ± 493	689 ± 293
AUC <sub>∞</sub> (ng•hr/mL)	1720 ± 877	1500 ± 550	1290 ± 538	737 ± 303
t <sub>1/2</sub> <sup>a</sup> (h)	55.1 ± 14.5	46.9 ± 9.88	42.8 ± 17.3	45.4 ± 6.43
β (1/h)	0.013 ± 0.003	0.015 ± 0.003	0.016 ± 0.006	0.015 ± 0.002
CL/F (L/h)	18.0 ± 8.31	18.2 ± 5.31	22.3 ± 8.89	39.6 ± 17.8
V <sub>D</sub> /F (L)	1530 ± 945	1240 ± 318	1520 ± 814	2750 ± 1560

a. Harmonic mean ± pseudo-standard deviation.

Source: Table 20 (Page 107) from Clinical Study Report of M12-215

Table 25 shows the least squares mean ratio and 90 % CI of ABT-267 pharmacokinetic parameters in the various hepatic impairment groups.

**Table 25: Least Squares Means Ratio and 90 % CI of ABT-267 Pharmacokinetic Parameters in the Various Hepatic Impairment Groups**

Group Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Point Estimate	90% Confidence Interval
		Test	Reference		
Mild vs. Normal	C <sub>max</sub> (ng/mL)	103	103	1.002	0.769 – 1.306
	AUC <sub>t</sub> (ng•hr/mL)	1365	1448	0.943	0.694 – 1.282
	AUC <sub>∞</sub> (ng•hr/mL)	1454	1579	0.921	0.669 – 1.269
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	72.9	103	0.708	0.542 – 0.926
	AUC <sub>t</sub> (ng•hr/mL)	1040	1448	0.719	0.527 – 0.980
	AUC <sub>∞</sub> (ng•hr/mL)	1103	1579	0.699	0.505 – 0.966
Severe vs. Normal	C <sub>max</sub> (ng/mL)	32.6	103	0.317	0.240 – 0.419
	AUC <sub>t</sub> (ng•hr/mL)	670	1448	0.462	0.335 – 0.639
	AUC <sub>∞</sub> (ng•hr/mL)	719	1579	0.456	0.325 – 0.638

a. Antilogarithm of the least squares means for logarithms.

Source: Table 20 (Page 109) from Clinical Study Report of M12-215

Table 26 shows the summary of the mean pharmacokinetic parameters of ABT-333 (based on total concentrations) in the various hepatic impairment groups after administration of the 3-DAA regimen.

**Table 26: Summary of the Mean Pharmacokinetic Parameters of ABT-333 (based on total concentrations) in the Various Hepatic Impairment Groups after Administration of the 3-DAA Regimen**

	ABT-267 25 mg + ABT-450/r 200/100 mg + ABT-333 400 mg			
ABT-333 Parameter (Unit)	Normal Subjects	Mild Hepatic Impaired Subjects	Moderate Hepatic Impaired Subjects	Severe Hepatic Impaired Subjects
N	7	6	6	5
$C_{max}$ (ng/mL)	1400 ± 1230	1410 ± 520	743 ± 185	1530 ± 708
$T_{max}$ (h)	3.6 ± 0.98	2.8 ± 0.98	4.3 ± 0.52	4.4 ± 1.1
$AUC_t$ (ng•hr/mL)	10400 ± 8510	10300 ± 4780	8050 ± 3130	36400 ± 15600
$AUC_{\infty}$ (ng•hr/mL)	10400 ± 8510	10300 ± 4780	8120 ± 3130	36500 ± 15700
$t_{1/2}^a$ (h)	9.20 ± 4.09	8.33 ± 4.46	11.1 ± 3.98	16.7 ± 1.43
$\beta$ (1/h)	0.075 ± 0.033	0.083 ± 0.039	0.063 ± 0.023	0.042 ± 0.004
CL/F (L/h)	63.3 ± 47.1	44.6 ± 15.3	57.1 ± 26.5	13.5 ± 8.04
$V_d/F$ (L)	1200 ± 1620	583 ± 241	1120 ± 780	322 ± 178

a. Harmonic mean ± pseudo-standard deviation.

Source: Table 25 (Page 118) from Clinical Study Report of M12-215

Table 27 shows the summary of the mean pharmacokinetic parameters of ABT-333 M1 (based on total concentrations) in the various hepatic impairment groups after administration of the 3-DAA regimen.

**Table 27: Summary of the Mean Pharmacokinetic Parameters of ABT-333 M1 (based on total concentrations) in the Various Hepatic Impairment Groups after Administration of the 3-DAA Regimen**

	ABT-267 25 mg + ABT-450/r 200/100 mg + ABT-333 400 mg			
ABT-333 M1 Parameter (Unit)	Normal Subjects	Mild Hepatic Impaired Subjects	Moderate Hepatic Impaired Subjects	Severe Hepatic Impaired Subjects
N	7	6	6	5
$C_{max}$ (ng/mL)	788 ± 548	659 ± 318	283 ± 173	283 ± 160
$T_{max}$ (h)	4.4 ± 0.53	3.8 ± 0.98	5.7 ± 1.2	11.2 ± 7.6
$AUC_t$ (ng•hr/mL)	5880 ± 5490	5310 ± 3830	2300 ± 1110	8310 ± 4520
$AUC_{\infty}$ (ng•hr/mL)	5920 ± 5510	5350 ± 3870	2340 ± 1120	8420 ± 4500
$t_{1/2}^a$ (h)	5.21 ± 1.01	5.43 ± 1.90	7.60 ± 2.75	16.0 ± 2.17
$\beta$ (1/h)	0.133 ± 0.026	0.128 ± 0.048	0.091 ± 0.032	0.043 ± 0.006

a. Harmonic mean ± pseudo-standard deviation.

Source: Table 26 (Page 118) from Clinical Study Report of M12-215

Table 28 shows the least squares mean ratio and 90 % CI of ABT-333 and ABT-333 M1 pharmacokinetic parameters in the various hepatic impairment groups.

**Table 28: Least Squares Means Ratio and 90 % CI of ABT-333 and ABT-333 M1 Pharmacokinetic Parameters in the Various Hepatic Impairment Groups**

Group Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Point Estimate	90% Confidence Interval
		Test	Reference		
ABT-333					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	1358	1094	1.241	0.795 - 1.937
	AUC <sub>t</sub> (ng•hr/mL)	9658	8226	1.174	0.732 - 1.884
	AUC <sub>∞</sub> (ng•hr/mL)	9694	8269	1.172	0.732 - 1.877
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	666	1094	0.608	0.388 - 0.955
	AUC <sub>t</sub> (ng•hr/mL)	6842	8226	0.832	0.515 - 1.342
	AUC <sub>∞</sub> (ng•hr/mL)	6910	8269	0.836	0.519 - 1.346
Severe vs. Normal	C <sub>max</sub> (ng/mL)	1462	1094	1.336	0.836 - 2.136
	AUC <sub>t</sub> (ng•hr/mL)	35066	8226	4.263	2.590 - 7.015
	AUC <sub>∞</sub> (ng•hr/mL)	35144	8269	4.250	2.589 - 6.978
ABT-333 M1					
Mild vs. Normal	C <sub>max</sub> (ng/mL)	600	671	0.893	0.510 - 1.565
	AUC <sub>t</sub> (ng•hr/mL)	4443	4416	1.006	0.591 - 1.711
	AUC <sub>∞</sub> (ng•hr/mL)	4476	4453	1.005	0.593 - 1.704
Moderate vs. Normal	C <sub>max</sub> (ng/mL)	211	671	0.315	0.178 - 0.556
	AUC <sub>t</sub> (ng•hr/mL)	1875	4416	0.425	0.248 - 0.727
	AUC <sub>∞</sub> (ng•hr/mL)	1907	4453	0.428	0.251 - 0.731
Severe vs. Normal	C <sub>max</sub> (ng/mL)	265	671	0.395	0.219 - 0.713
	AUC <sub>t</sub> (ng•hr/mL)	7723	4416	1.749	0.999 - 3.060
	AUC <sub>∞</sub> (ng•hr/mL)	7861	4453	1.765	1.013 - 3.077

a. Antilogarithm of the least squares means for logarithms.

Source: Table 20 (Page 122) from Clinical Study Report of M12-215

Based on the magnitude of changes observed in the pharmacokinetics of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 in the mild hepatic impairment group and the available efficacy and safety data in subjects with compensated cirrhosis (M13-099), the 3-DAA regimen can be co-administered to subjects with mild hepatic impairment. Based on available pharmacokinetic data after single dose administration, VIEKIRA PAK™ can be administered to patients with moderate hepatic impairment (Child-Pugh Category B, score 7-9), however, the safety and efficacy of VIEKIRA PAK™ after multiple dose administration has not been established in patients with decompensated cirrhosis. Hence, VIEKIRA PAK™ will not be recommended for use in patients with decompensated liver disease. The use of VIEKIRA PAK™ is contraindicated in patients with severe hepatic impairment due to approximately 10-fold increase in the mean AUC of ABT-450 and increase in associated risk of ALT elevations.

#### 2.3.2.7 What pregnancy and lactation use information is there in the application?

There were no trials evaluating the use of the 3-DAA regimen in pregnant or lactating women that were included in the NDA submission.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

The applicant evaluated two extrinsic factors- the effect of food on the pharmacokinetics on ABT-267/ABT-450/ritonavir co-formulated tablets and ABT-333 tablets (discussed in section 2.5.3) and the potential for drug-drug interactions when ABT-267/ABT-450/ritonavir (administered as individual products or as ABT-267/ABT-450/ritonavir coformulated tablets) and ABT-333 were co-administered with other antiviral and non-antiviral drugs (discussed in section 2.4.2).

### 2.4.2 Drug-drug interactions

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes, there is *in vitro* basis to suspect enzyme- and transporter mediated *in vivo* drug-drug interactions. CYP3A plays a major role in the metabolism of ABT-450 and ritonavir, whereas the contribution of CYP3A in the metabolism of ABT-267 and ABT-333 is minor. ABT-267 primarily undergoes amide hydrolysis. CYP2C8 plays a major role in the metabolism of ABT-333 and a minor role in the metabolism of ABT-450 and ABT-267. ABT-450, ABT-333, ABT-333 M1 and ABT-267 are substrates for the efflux transporters P-gp and BCRP. Ritonavir is a substrate of P-gp but not BCRP.

See sections 2.4.2.2 and 2.4.2.3 for additional information.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, ABT-450 and ritonavir are substrates of CYP3A enzymes and ABT-333 is a substrate of CYP2C8 enzymes. There was no impact of CYP2C8 polymorphism on the systemic exposures of ABT-333; the applicant did not evaluate the impact of CYP3A polymorphism on ABT-450 and ritonavir.

#### 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

#### Inhibition of metabolic enzymes by ABT-267, ABT450, ritonavir, and ABT-333

**Table 29** shows the  $[I]/K_i$  estimates of ABT-267, ABT-450, ritonavir, ABT-333 and ABT-333 M1. “[I]” was based on the mean of the total  $C_{max}$  observed across the Phase 1 studies conducted using the Phase 3 formulation.

**Table 29: [I]/K<sub>i</sub> estimates of ABT-267, ABT-450, ritonavir, ABT-333 and ABT-333 M1**

	ABT-450	Ritonavir	ABT-267	ABT-333	ABT-333 M1
[I] (ng/mL)	1470	1600	127	1030	660
CYP Enzyme	<b>I/K<sub>i</sub> values</b>				
CYP2B6	-	4.43	-	0.14	-
CYP2C8	0.29	2.91	0.038	0.25	-
CYP2C9	-	7.76	-	0.48	-
CYP2C19	-	1.03	-	0.23	-
CYP2D6	-	4.26	-	0.09	-
CYP3A4	-	800	-	-	-
UGT1A1	1.06	2.61	0.13	4.53	0.39

K<sub>i</sub>=IC<sub>50</sub>/2; “[I]” is based on the mean of the total C<sub>max</sub> observed across Phase 1 trials conducted using the Phase 3 formulation; “-”: No significant inhibition observed (IC<sub>50</sub> > 30 μM) in *in vitro* studies, hence K<sub>i</sub> values could not be estimated.

Source: Generated by reviewer based on K<sub>i</sub> information provided in table 2 of report R&D/13/893 and the anticipated C<sub>max</sub> of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1.

The applicant also used a mechanistic static model to predict “R” values (the ratio of intrinsic clearance by the metabolic enzyme in the absence and presence of inhibitor).

**Table 30** shows the calculated model parameters and the R values.

**Table 30: Calculated Model Parameters and R Values based on Mechanistic Static Model**

CYP	ABT-450			Ritonavir			ABT-267			ABT-333		
	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R
CYP2B6	-	-	-	30	0.92	1.08	-	-	-	36	0.99	1.00
CYP2C8	71	0.99	1.01	30	0.95	1.05	3.7	1	1.00	36	0.99	1.01
CYP2C9	-	-	-	30	0.87	1.14	-	-	-	36	0.98	1.02
CYP2C19	-	-	-	30	0.98	1.02	-	-	-	36	0.99	1.01
CYP2D6	-	-	-	30	0.93	1.08	-	-	-	36	1.00	1.00
CYP3A4	-	-	-	30	0.06	13.9	-	-	-	-	-	-
UGT1A1	71	0.95	1.05	30	0.95	1.05	3.7	1	1.00	36	0.86	1.16

$$A_h = 1/(1+[I_h]/K_i)$$

Source: Table 3 on Page 7 of report R&D/13/893

**CYP2B6:** In vitro data suggested that ritonavir and ABT-333 are inhibitors of CYP2B6; however, the results of the drug-drug interaction trial (M12-997) of the 3-DAA regimen with methadone (primarily metabolized by CYP2B6) did not show any significant change in the systemic exposures of methadone.

**CYP2C8:** In vitro data suggested that ABT-450, ritonavir, and ABT-333 are weak inhibitors of CYP2C8; however, repaglinide, the recommended CYP2C8 substrate, is also an OATP substrate and the concentrations of repaglinide can be altered by ABT-450 mediated inhibition of OATP transporters. Hence, the impact of the 3-DAA regimen on CYP2C8 was not evaluated.

*CYP2C9*: In vitro data suggested that ritonavir and ABT-333 are inhibitors of CYP2C9; however, the results of the drug-drug interaction trial (M12-198) of the 3-DAA regimen with warfarin (a sensitive substrate of CYP2C9) showed minimal change in the systemic exposure of warfarin ( $\leq 12\%$ ). Hence, the 3-DAA regimen is not expected to alter the exposures of CYP2C9 substrates via inhibition of CYP2C9.

*CYP2C19*: In vitro data suggested that ABT-333 and ritonavir are weak inhibitors of CYP2C19. In contrast, the results of the drug-drug interaction trial (M12-199) with omeprazole suggested that the mean systemic exposure of omeprazole (a sensitive CYP2C19 substrate), decreased when co-administered with the 3-DAA regimen, primarily due to CYP2C19 induction by ritonavir. Hence, the 3-DAA regimen is not expected to increase the exposures of CYP2C19 substrates via inhibition of CYP2C19.

*CYP3A*: Ritonavir is a potent CYP3A inhibitor, hence, the combination of ABT-267/ABT-450/ritonavir and ABT-333 is expected to increase the systemic exposures of CYP3A substrates. The results of drug-drug interaction trials of the 3-DAA regimen with tacrolimus (M13-491) and cyclosporine (CYP3A substrates with narrow therapeutic index; trial M13-103) showed a significant increase in the mean systemic exposure of tacrolimus and cyclosporine.

#### Induction of metabolic enzymes by ABT-267, ABT450, ritonavir, and ABT-333

ABT-450 is not an inducer of CYP1A2 and 2B6 mRNA expression when tested up to 10  $\mu\text{M}$  in cultured human hepatocytes. ABT-450 induces CYP3A4 mRNA expression in vitro (31% of the response of positive control rifampin in human hepatocytes from three donors); however, the co-administration with ritonavir is expected to result in a net inhibitory net effect on CYP3A. In human hepatocytes, ritonavir (1  $\mu\text{M}$ ) induces CYP2B6, CYP2C8, and CYP3A4 mRNA expression; however, the net effect of ritonavir is expected to be CYP inhibition. ABT-267 is not an inducer of CYP1A2, 2B6 or 3A4 mRNA expression at concentrations up to 3  $\mu\text{M}$ . ABT-333 and ABT-333 M1 are not inducers of CYP1A2, CYP2B6 and CYP3A4 at concentrations up to 50  $\mu\text{M}$ .

#### 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

ABT-450, ritonavir, ABT-333, and ABT-333 M1 are substrates of the P-glycoprotein transporters with net efflux ratios of 13.1, 26.1, 6.4, and 32.5, respectively. No *in vitro* efflux by P-gp was observed for ABT-267, however, in the more sensitive triple knockout mouse model, ABT-267 was shown to be a P-gp substrate.

Based on *in vitro* assessments, ABT-450, ABT-333, and ritonavir are inhibitors of P-gp; however, the results of the drug-drug interaction trial of the 3-DAA regimen with digoxin (M12-201) did not show a significant change in the exposure of digoxin, a sensitive substrate of P-gp transporters.

#### 2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Yes, in addition to the CYP and transporter pathways described in sections 2.4.2.2, 2.4.2.3., and 2.4.2.4, there are other metabolic/transporter pathways that may be important.

##### UGT1A1 Enzyme Inhibition:

In vitro, ABT-450, ABT-267, ABT-333, ABT-333 M1 and ritonavir are inhibitors of UGT1A1 (ritonavir is also an inducer of UGT1A1). The results of the drug-drug interaction trial conducted with raltegravir (M13-392) showed that the mean AUC<sub>12hrs</sub> of raltegravir (a UGT1A1 substrate) increased by 135 % when raltegravir was co-administered with the 3-DAA regimen.

##### OATP Transporters

Based on *in vitro* assessments, ABT-450 and ABT-333 M1 are substrates for the hepatic uptake transporters OATP1B1 and OATP1B3. No OATP-mediated uptake was observed for ABT-333, ABT-267 or ritonavir. Only ABT-450 is anticipated to inhibit OATP1B1 and OATP1B3.

##### BSEP and MRP2 Transporters

ABT-450, ABT-333, and ABT-333 M1 are inhibitors of MRP2. ABT-267 and ritonavir are weak inhibitors of MRP2. ABT-450 and ritonavir are inhibitors of BSEP. Weak inhibition of BSEP was observed for ABT-267, ABT-333, and ABT-333 M1.

##### Renal Transporters

Based on *in vitro* assessments, ABT-450, ABT-267, ABT-333, ABT-333 M1 and ritonavir are not anticipated to inhibit OAT1, OAT3, OCT2, MATE-1 and MATE-2K. Of note, the results of the drug-drug interaction trial with tenofovir (M13-783) did not show a significant change in the exposures of tenofovir (a sensitive OAT1 substrate).

#### 2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes, the label will specify the co-administration of VIEKIRA PAK™ with ribavirin depending on the HCV genotype-subtype (genotype 1a or 1b) and cirrhosis status (presence or absence). Please refer to section 2.1.2 for further information.

Ribavirin does not share common disposition pathways with the DAAs and is not expected to contribute to DAA drug interactions. Further, the lack of interaction between DAAs and ribavirin was confirmed in both, Phase 2 as well as Phase 3 population pharmacokinetic analyses.



2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Other medications likely to be co-administered in HCV infected patients include antiretroviral medications for treatment of HIV-1 infection, immunosuppressants, opioid substitution therapy, antidepressants, antihypertensives, and sleep aids. Please refer to the prescribing information for the list of co-medications that are likely to be administered to the target patient population.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The applicant evaluated mechanism based interactions, interactions with concomitant medications used in specific populations, and commonly prescribed concomitant medications. The drug-drug interaction trials were conducted in healthy volunteers using ABT-450, ritonavir, ABT-267, administered with or without ABT-333. Although ribavirin is part of the proposed treatment regimen (depending on genotype-subtype and presence/absence of cirrhosis), it was not used in any healthy volunteer drug-drug interaction trials. Ribavirin does not share common disposition pathways with the DAAs and is not expected to contribute to DAA drug interactions. Furthermore, given the toxicity of ribavirin, it is inappropriate to dose ribavirin in healthy volunteers for the duration of the drug-drug interaction trials.

The majority of the drug-drug interaction assessments were conducted under steady state conditions except in cases where the objective of the trial were to assess the effect of the 3-DAA regimen on sensitive substrates of enzymes (for example DDI trial with warfarin; M12-198) or transporters (for example DDI trial with digoxin; M12-201). In such cases, the effect of steady state pharmacokinetics of the 3-DAA regimen on single dose pharmacokinetics of the sensitive substrate was assessed. Similarly, the effect of steady state pharmacokinetics of potent CYP3A inhibitors (ketoconazole; M12-189) and inducers (carbamazepine; M14-027) on single dose administration of the 3-DAA regimen was assessed.

Several formulations of ABT-450, ABT-267 and ABT-333 were used in drug-drug interaction trials. Of note, after a single dose administration to healthy volunteers under non-fasting conditions, the mean  $AUC_{0-\infty}$  of ABT-450 when administered as ABT-267/ABT-450/ritonavir coformulated tablets (to-be-marketed formulation) was ~60 % higher as compared with ABT-450 exposures when administered as (b) (4) tablets (ABT-450 (b) (4) tablets were used in 11 DDI trials). The mean systemic exposures of ABT-450 and ritonavir (administered as ABT-450/ritonavir co-formulated tablets+ABT-267 tablets) were similar to the mean systemic exposures of ABT-450 and ritonavir after administration of ABT-267/ABT-450/ritonavir coformulated tablets. Further, the mean systemic exposures of ABT-267 and ABT-333 were similar across the various formulations used in the drug-drug interaction trials.

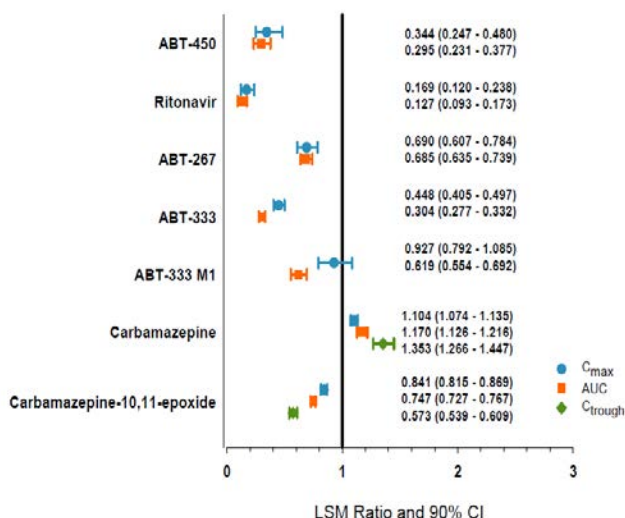
The applicant used a mechanism based approach and a quantitative analysis approach to determine if the clinical recommendations based on data collected in DDI trials using the ABT-450 (b) (4) tablets can be applied to the ABT-267/ABT-450/ritonavir coformulated tablets. Overall, the applicant's proposed approach was found to be acceptable.

### Contraindicated Drugs

#### *Carbamazepine (CYP3A inducer)*

**Figure 10** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and carbamazepine.

**Figure 10: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and carbamazepine**



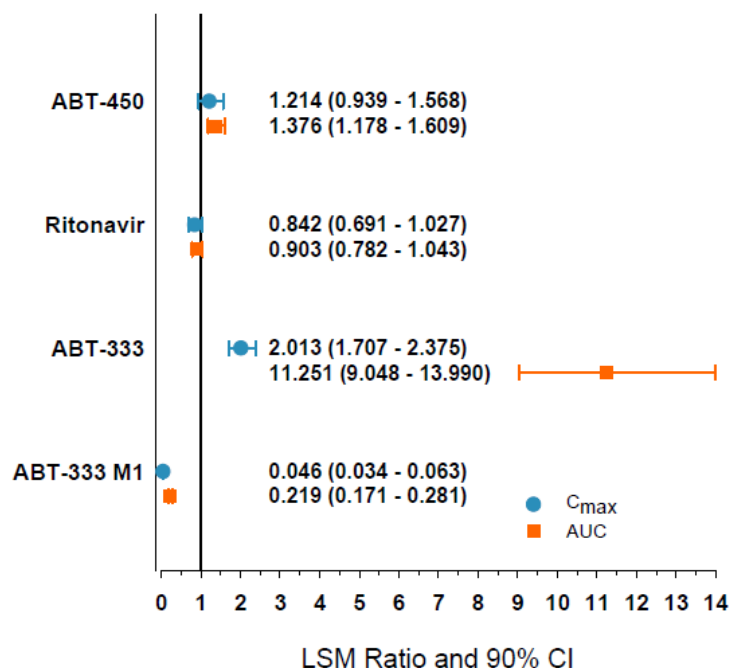
Source: Fig 8 from Clinical Pharmacology Summary (Section 2.7.2), Page 64

**Clinical Recommendation:** The co-administration of VIEKIRA PAK™ and carbamazepine is contraindicated due to significant decrease in the exposures of ABT-450, ABT-267, and ABT-333.

#### *Gemfibrozil (CYP2C8 inhibitor)*

**Figure 11** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-333, and ABT-333 M1 after co-administration of ABT-450, ritonavir, and ABT-333 with gemfibrozil.

**Figure 11: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-333, and ABT-333 M1 after co-administration of ABT-450, ritonavir, and ABT-333 with gemfibrozil**



Source: Fig 4 from Clinical Pharmacology Summary (Section 2.7.2), Page 55

**Clinical Recommendation:** The co-administration of VIEKIRA PAK™ with gemfibrozil is contraindicated due to significant increase in the exposures of ABT-333.

#### *Efavirenz Containing Regimens*

Co-administration of VIEKIRA PAK™ with efavirenz containing regimens is contraindicated due to poor tolerability and cases of ALT elevations observed in the drug-drug interaction trial conducted with Atripla® (M13-104). The applicant conducted trial M13-783 in which the potential for drug-drug interaction between ABT-450, ritonavir, ABT-267, ABT-333 and emtricitabine/tenofovir (Truvada®) was evaluated. The results of the trial showed that that VIEKIRA PAK™ can be co-administered with Truvada® without any dose adjustments. Because Atripla® contains efavirenz (in addition to emtricitabine and tenofovir), the results of trial M13-104 suggest that the adverse events observed in the trial may be attributed to efavirenz in the regimen. Hence, the clinical recommendation applies to all efavirenz containing regimens.

#### *Estrogen Containing Products*

The risk of post baseline ALT elevations was noted to be higher in subjects who received estrogen containing medications. The applicant conducted a drug-drug interaction trial (M12-205) to characterize the potential for drug-drug interaction between the 3-DAA

regimen and oral contraceptives. **Table 31** below outlines the trial design.

**Table 31: Outline of Trial M12-205**

Arms 1 <sup>a</sup> and 2 <sup>b</sup>	Study Day 1 – 9	Study Days 10 – 21	Study Days 22 – 28
DAA	--	X	X
Ortho-Cyclen <sup>®</sup> (EE/NGM 35/250 µg)	X	X	--
Arm 3 <sup>a</sup>	Study Day 1 – 3	Study Days 4 – 17	Study Days 18 – 24
DAA	--	X	X
Jolivet <sup>®</sup> (NET 0.35 mg)	X	X	--
Arm 4 <sup>a</sup>	Study Day 1 – 7	Study Days 8 – 15 <sup>c</sup>	Study Days 22 – 28
DAA	--	X	X
Balziva <sup>®</sup> (EE/NET 35 µg/0.4 mg)	X	X	--

a. Arm 1, 3 and 4 (3 DAAs): ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID.

b. Arm 2 (2 DAAs): ABT-450/r/ABT-267 150/100/25 mg QD.

c. Arm 4 was prematurely discontinued on Study Day 15 due to safety reasons.

All study drugs were administered under non-fasting conditions, and all oral contraceptives were administered QD.

DAA formulations: ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablet, ABT-333 250 mg tablet.

Source: Page 110 of the Clinical Pharmacology Summary (Section 2.7.2)

The summary of pharmacokinetic data does not indicate that the oral contraceptives had a clinically relevant impact on the pharmacokinetics of the individual components of the 3-DAA regimen.

In arms 1 and 2, ALT elevations ( $\geq$  Grade 1) were observed in 6 out of the 9 subjects. Out of the 6 subjects, Grade 3 ALT elevations were observed in 2 subjects. The ALT levels subsequently normalized in these two subjects after discontinuation of both ABT-267/ABT-450/ritonavir and norgestimate/ethinyl estradiol. In the remaining 4 subjects who showed Grade 1 elevations, ALT levels normalized after completion of ABT-267/ABT-450/ritonavir ( $\pm$  ABT-333) dosing.

In Arm 3, there were no discontinuations and all 12 subjects completed the trial. In Arm 4, 9 out of the 12 showed  $\geq$  Grade 1 ALT elevations (2 subjects showed Grade 3 ALT elevations and 1 subject showed Grade 4 ALT elevation).

#### Summary of Grade 3+ ALT elevations observed in Phase 2 and 3 Trials

**Table 32** summarizes the post baseline Grade 3+ ( $> 5 \times$  upper limit of normal) ALT elevations observed in the expanded Phase 2 and 3 clinical trials.

**Table 32: Post baseline Grade 3+ (> 5 X upper limit of normal) ALT elevations observed in the expanded Phase 2 and 3 clinical trials**

Subgroup	Patients with Grade 3+ ALT Elevations	Total Number of Patients	Percentage
Ethinyl estradiol	6	23	26.1%
Other estrogens	1	89	1.1%
No estrogens	28	2927	1.0%
Total	35	3039	1.2%

Note: The expanded Phase 2/3 analysis set included all Phase 2/3 interferon free trials using at least 2-DAA's (ABT-450/r ±ABT-333±ABT-267 and all Phase 3 trials). The following trials were pooled for the analysis: M11-652 (all arms), M12-998, M12-746, M13-386, M11-646, M13-098, M13-389, M13-961, M14-002, M14-103, and M13-099

Source: Applicant's response to Labeling Comments submitted on August 29, 2014

Overall, 112/3039 (~3.7 %) subjects were using estrogen containing products. Out of the 112 subjects, 23 subjects (~21 %) were using ethinyl estradiol containing products and 89/112 subjects (~79 %) were using other estrogen containing products. Out of the 7 subjects who were on estrogen containing products and showed Grade 3+ ALT elevations, 6 subjects were using combined contraceptives [3 subjects were using Levonorgestrel 0.25 mg/0.03 mg EE; 1 subject was using desogestrel 0.15 mg +0.03 mg EE; 1 subject was using Nuvaring® (etonogestrel/ethinyl estradiol) and 1 subject was using estrogen NOS with testosterone] and 1 subject was using estradiol for post-menopausal use. Overall, the risk of post baseline serum ALT elevation appears to be higher in subjects taking estrogen containing products and the following recommendation is proposed:

Clinical Recommendation: Co-administration of VIEKIRA PAK™ with estrogen containing products is contraindicated. Progestin only contraceptives may be used with VIEKIRA PAK™.

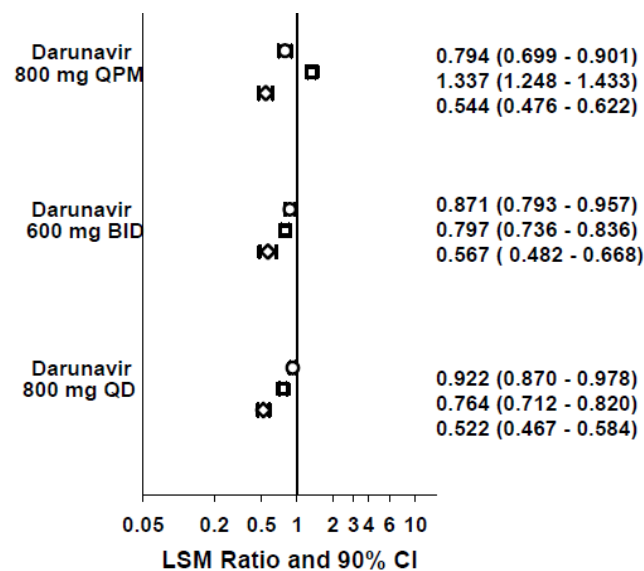
The final recommendation regarding the use of estrogen containing products with VIEKIRA PAK™ was under discussion with the applicant at the time of finalizing this review.

#### Co-Administration Not Recommended

##### *Darunavir*

**Figure 12** shows the least squares mean ratio and 90 % CI of darunavir administered once daily in the morning (without ritonavir), darunavir administered once daily in the evening (with ritonavir) and darunavir administered twice daily (evening dose of darunavir administered with ritonavir) with ABT-267/ABT-450/ritonavir and ABT-333 as compared with when given alone.

**Figure 12: Least squares mean ratio and 90 % CI of darunavir after the various aforementioned regimens**



Circle =  $C_{max}$ ; square = AUC; diamond =  $C_{trough}$

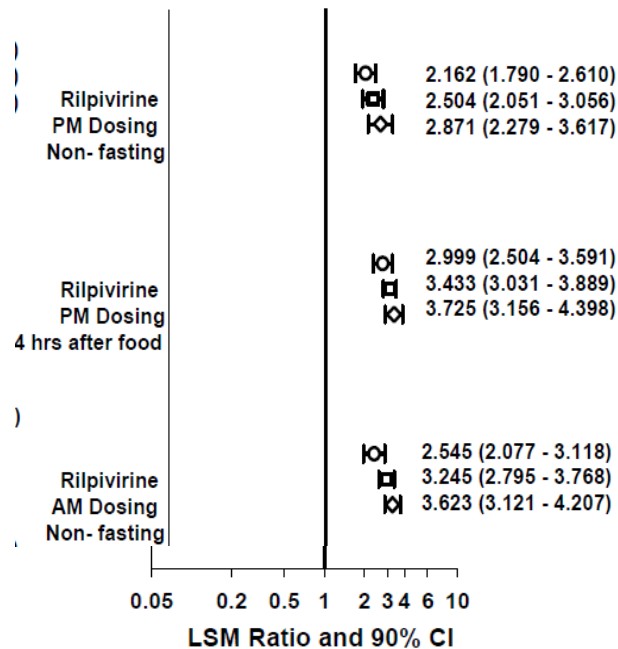
Source: Part of Fig 32 from Clinical Pharmacology Summary (Section 2.7.2), Page 194

Clinical Recommendation: Co-administration of VIEKIRA PAK<sup>TM</sup> with darunavir is not recommended due to the decrease in  $C_{trough}$  of darunavir after administration of various aforementioned darunavir regimens. Of note, decreases in darunavir  $C_{trough}$  of similar magnitude were previously observed when darunavir 600/100 mg twice daily was co-administered with telaprevir and boceprevir. The approved prescribing information of telaprevir and boceprevir does not recommend co-administration of darunavir/ritonavir with telaprevir and boceprevir, respectively.

### *Rilpivirine*

**Figure 13** shows the least squares mean ratio and 90 % CI of rilpivirine given in the morning under fed conditions, given in the evening under fed conditions and given under “semi fasting” conditions [3 hours after evening snack] with ABT-450/ritonavir, ABT-267 and ABT-333.

**Figure 13: least squares mean ratio and 90 % CI of rilpivirine after the various aforementioned regimens**



Circle =  $C_{max}$ ; square = AUC; diamond =  $C_{trough}$

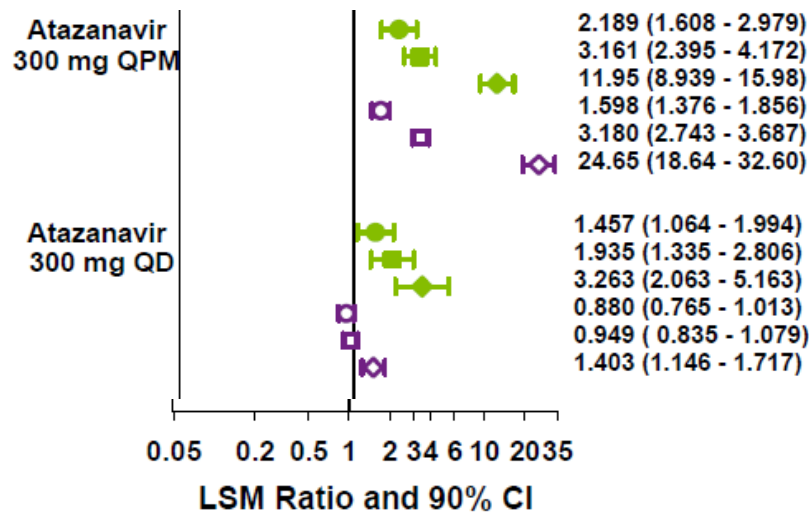
Source: Part of Fig 32 from Clinical Pharmacology Summary (Section 2.7.2), Page 194

**Clinical Recommendation:** Co-administration of VIEKIRA PAK<sup>TM</sup> with rilpivirine is not recommended based on concerns of QT prolongation which can be associated with increase in rilpivirine  $C_{max}$  observed after administration of various rilpivirine regimens.

#### *Atazanavir*

**Figure 14** shows the least squares mean ratio and 90 % CI of ABT-450 (solid symbol) and ritonavir (open symbol) after co-administration of ABT-450/ritonavir, ABT-267, ABT-333 with atazanavir given in the morning (300 mg once daily) and evening (300 mg with 100 mg ritonavir).

**Figure 14: Least squares mean ratio and 90 % CI of ABT-450 (solid symbol) and ritonavir (open symbol) after co-administration of ABT-450/ritonavir, ABT-267, ABT-333 with atazanavir given in the morning (300 mg once daily) and evening (300 mg with 100 mg ritonavir)**



Circle = C<sub>max</sub>; square = AUC; diamond = C<sub>trough</sub>

Source: Part of Fig 33 from Clinical Pharmacology Summary (Section 2.7.2), Page 196

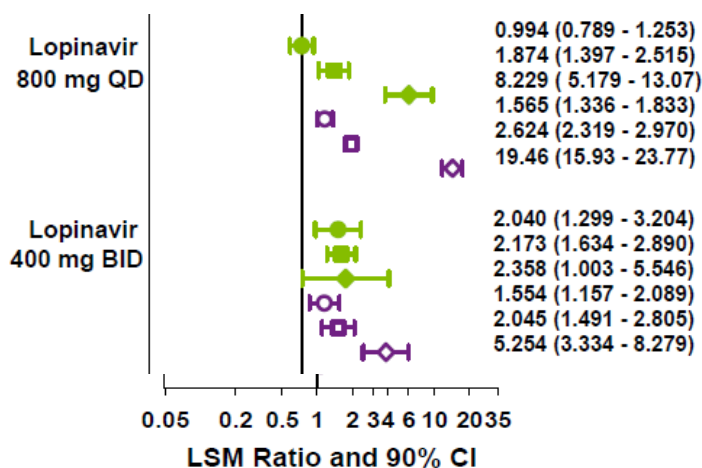
Clinical Recommendation: Co-administration of VIEKIRA PAK<sup>™</sup> with atazanavir (evening administration) is not recommended due to significant increase in the systemic exposure of ABT-450. Of note, VIEKIRA PAK<sup>™</sup> can be co-administered with atazanavir 300 mg once daily (morning administration) without any dose adjustments.

*Lopinavir/ritonavir (Kaletra<sup>®</sup>)*

**Figure 15** shows the least squares mean ratio and 90 % CI of ABT-450 (solid symbol) and ritonavir (open symbol) after co-administration of ABT-450/ritonavir, ABT-267, and ABT-333 with lopinavir/ritonavir 800 mg/100 mg once daily (administered in the evening) and 400/100 mg twice daily.



**Figure 15: Least squares mean ratio and 90 % CI of ABT-450 (solid symbol) and ritonavir (open symbol) after co-administration of ABT-450/ritonavir, ABT-267, and ABT-333 with lopinavir/ritonavir 800 mg/100 mg once daily (administered in the evening) and 400/100 mg twice daily**



Circle = C<sub>max</sub>; square = AUC; diamond = C<sub>trough</sub>

Source: Part of Fig 33 from Clinical Pharmacology Summary (Section 2.7.2), Page 196

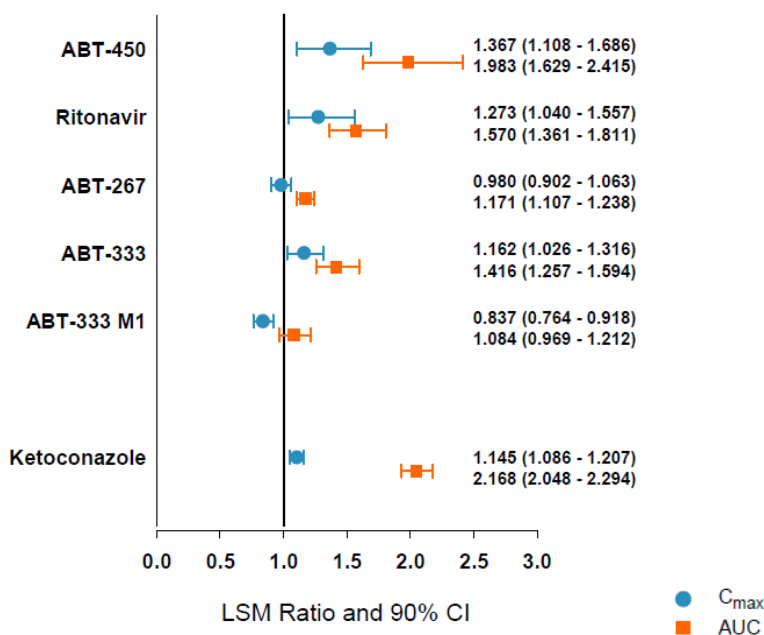
**Clinical Recommendation:** Co-administration of VIEKIRA PAK™ with lopinavir/ritonavir is not recommended due to significant increase in the systemic exposure of ABT-450 and due to the higher total daily dose of ritonavir (300 mg as compared with 100 mg when the 3-DAA regimen is given without lopinavir/ritonavir).

#### Dose Adjustment/Monitoring Recommended

*Ketoconazole (CYP3A and P-glycoprotein inhibitor)*

**Figure 16** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and ketoconazole after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with ketoconazole 400 mg once daily.

**Figure 16: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and ketoconazole after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with ketoconazole 400 mg once daily.**



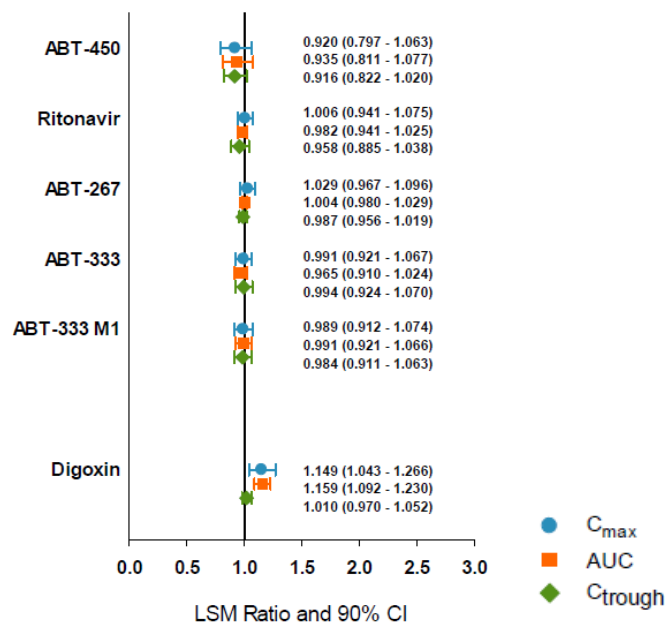
Source: Part of Fig 9 from Clinical Pharmacology Summary (Section 2.7.2), Page 61

**Clinical Recommendation:** Due to increase in the mean AUC of ketoconazole, when VIEKIRA PAK™ is co-administered with ketoconazole, the maximum dose of ketoconazole should be limited to 200 mg per day. Of note, the increase in mean ketoconazole AUC (~2.1 fold) is similar to the mean increase in ketoconazole AUC observed when ketoconazole is co-administered with protease inhibitors such as saquinavir/ritonavir (1000/100 mg) twice daily (~2.68 fold increase in mean AUC of ketoconazole) and fosamprenavir/ritonavir (700/100 mg) twice daily (~2.69 fold increase in mean AUC of ketoconazole). The approved prescribing information of saquinavir and fosamprenavir does not recommend doses of ketoconazole greater than 200 mg per day.

*Digoxin (P-glycoprotein substrate)*

**Figure 17** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and digoxin after co-administration of ABT-267, ABT-450, ritonavir, ABT-333 and digoxin.

**Figure 17: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and digoxin after co-administration of ABT-267, ABT-450, ritonavir, ABT-333 and digoxin**



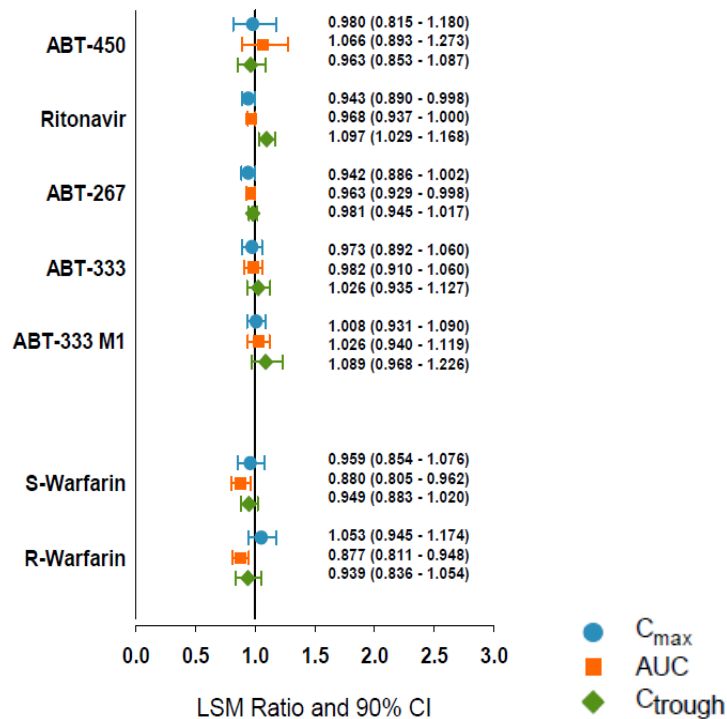
Source: Part of Fig 7 from Clinical Pharmacology Summary (Section 2.7.2), Page 66

Clinical Recommendation: When VIEKIRA PAK™ is co-administered with digoxin, no dose adjustment of digoxin is necessary; appropriate monitoring of serum digoxin levels is recommended.

*Warfarin (CYP2C9 substrate[S-Warfarin] and CYP3A4 substrate [R-Warfarin])*

Figure 18 shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, S-warfarin, and R-warfarin after co-administration of ABT-267, ABT-450, ritonavir, and ABT-333 with warfarin.

**Figure 18 : Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, S-warfarin, and R-warfarin after co-administration of ABT-267, ABT-450, ritonavir, and ABT-333 with warfarin**



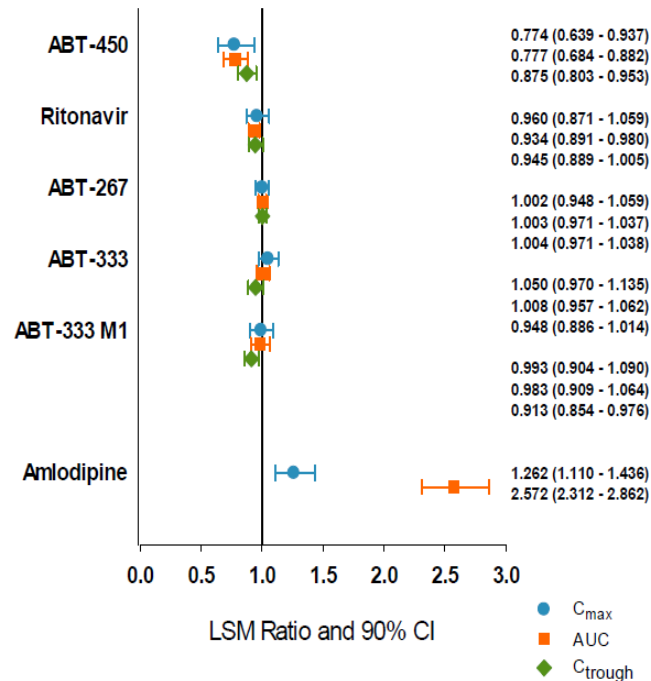
Source: Part of Fig 5 from Clinical Pharmacology Summary (Section 2.7.2), Page 57

**Clinical Recommendation:** When VIEKIRA PAK™ is co-administered with warfarin, no dose adjustment of warfarin is necessary; appropriate monitoring of international normalized ratio (INR) is recommended.

#### *Amlodipine (CYP3A Substrate)*

**Figure 19** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and amlodipine after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with amlodipine.

**Figure 19: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and amlodipine after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with amlodipine**



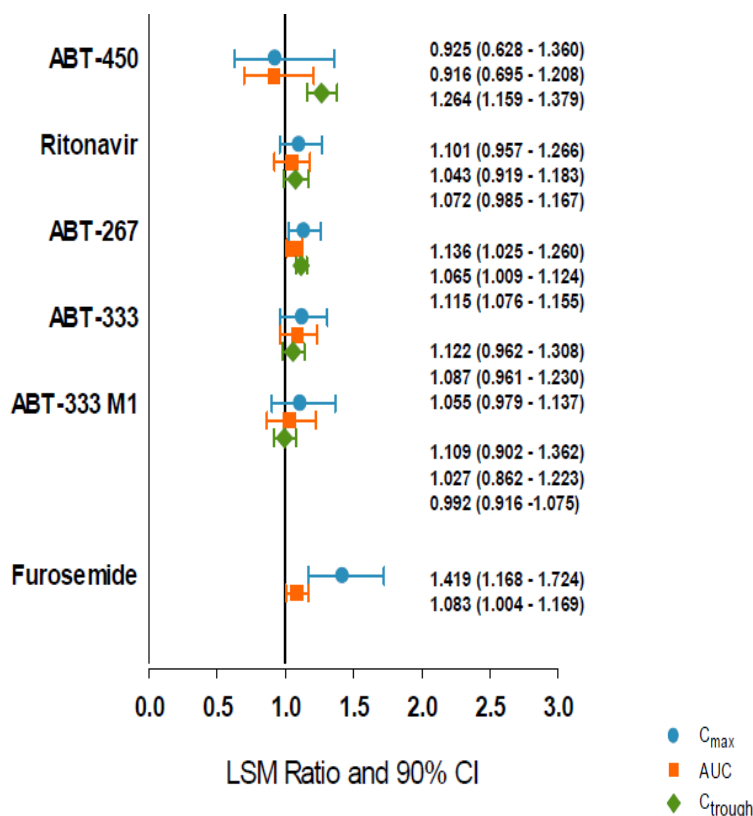
Source: Part of Fig 26 from Clinical Pharmacology Summary (Section 2.7.2), Page 119

**Clinical Recommendation:** Exposure to amlodipine was increased when amlodipine was co-administered with VIEKIRA PAK™. Caution should be used and dose reduction for amlodipine should be considered. Clinical monitoring is recommended”.

*Furosemide (UGT Substrate and Excreted through the Renal Route)*

**Figure 20** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and furosemide after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with furosemide.

**Figure 20: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and furosemide after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with furosemide**



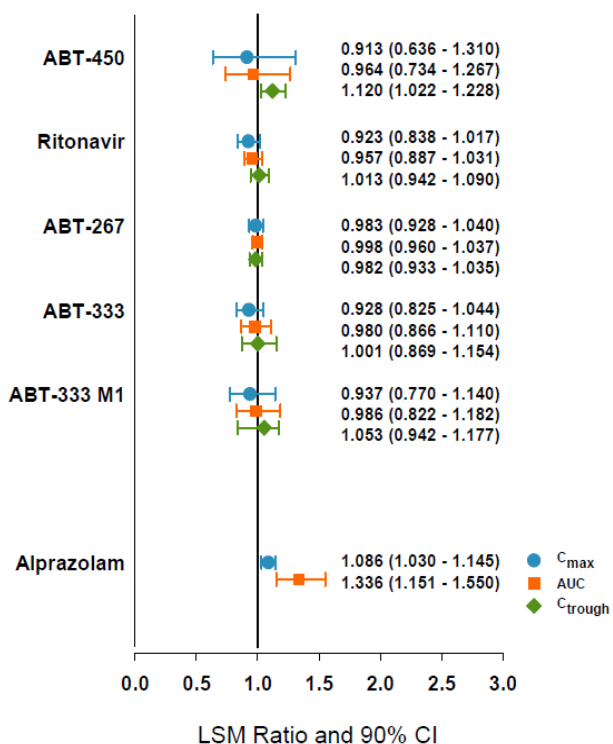
Source: Part of Fig 26 from Clinical Pharmacology Summary (Section 2.7.2), Page 119

**Clinical Recommendation:** When VIEKIRA PAK™ is co-administered with furosemide, clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.

*Alprazolam (CYP3A substrate)*

**Figure 21** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and alprazolam after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with alprazolam.

**Figure 21: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and alprazolam after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with alprazolam**



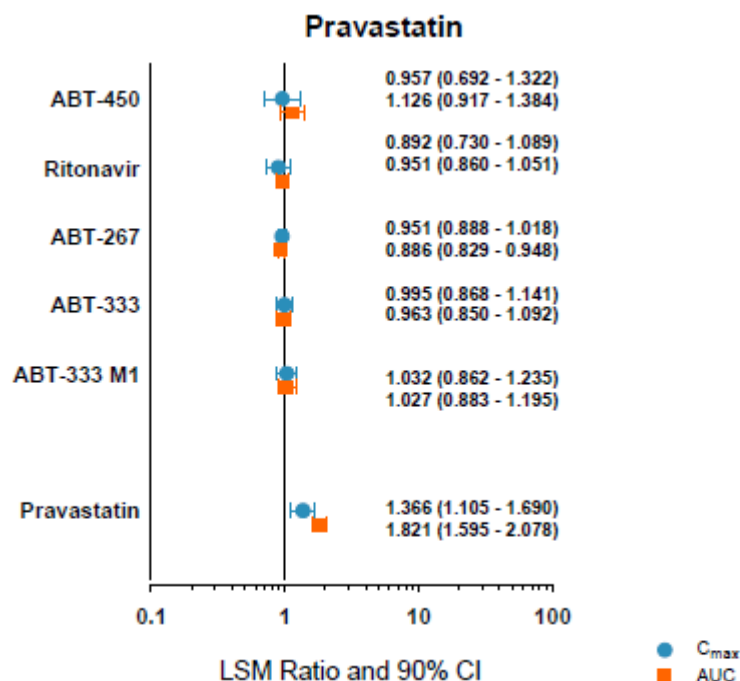
Source: Part of Fig 25 from Clinical Pharmacology Summary (Section 2.7.2), Page 117

**Clinical Recommendation:** When VIEKIRA PAK<sup>™</sup> is co-administered with alprazolam, clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.

*Pravastatin (OATP1B1 and OATP1B3 substrate) and Rosuvastatin (OATP1B1, OATP1B3, and BCRP substrate)*

**Figure 22** shows the least squares mean ratio and 90 % CI of pravastatin after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with pravastatin.

**Figure 22: Least squares mean ratio and 90 % CI of pravastatin after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with pravastatin**



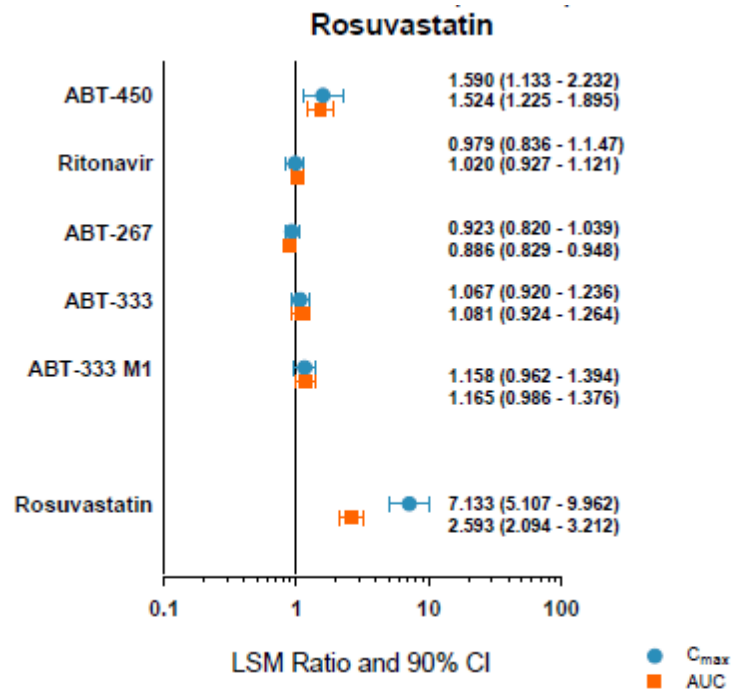
Source: Part of Fig 10 from Clinical Pharmacology Summary (Section 2.7.2), Page 69

**Clinical Recommendation:** When VIEKIRA PAK™ is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.



**Figure 23** shows the least squares mean ratio and 90 % CI of rosuvastatin after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with rosuvastatin.

**Figure 23: Least squares mean ratio and 90 % CI of rosuvastatin after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with rosuvastatin**



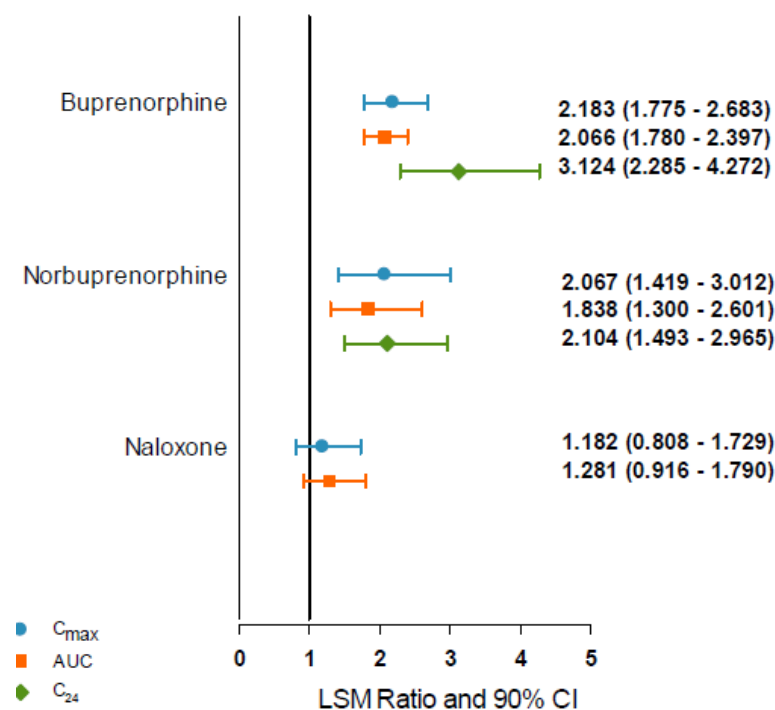
Source: Part of Fig 10 from Clinical Pharmacology Summary (Section 2.7.2), Page 69

Clinical Recommendation: When VIEKIRA PAK™ is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day.

*Buprenorphine/Naloxone (Buprenorphine is metabolized by various CYP enzymes such as CYP3A4, CYP2C8, CYP2C9, CYP2C19) and UGT enzymes (UGT1A1, UGT1A3, UGT2B7, and UGT2B17)*

**Figure 24** shows the least squares mean ratio and 90 % CI of buprenorphine, norbuprenorphine, and naloxone after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with buprenorphine/naloxone.

**Figure 24: Least squares mean ratio and 90 % CI of buprenorphine, norbuprenorphine, and naloxone after co-administration of ABT-267/ABT-450/ritonavir and ABT-333 with buprenorphine/naloxone**



Source: Part of Fig 22 from Clinical Pharmacology Summary (Section 2.7.2), Page 107

Clinical Recommendation: When VIEKIRA PAK™ is co-administered with buprenorphine/naloxone, clinical monitoring for sedation and cognitive effects is recommended and a dose reduction of buprenorphine may be considered.

*Cyclosporine and Tacrolimus (CYP3A and P-gp substrates)*

Cyclosporine

**Table 33** shows the point estimate and 90 % CI of the pharmacokinetic parameters of cyclosporine after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with cyclosporine.

**Table 33: Point estimate and 90 % CI of the pharmacokinetic parameters of cyclosporine after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with cyclosporine**

Cyclosporine Pharmacokinetic Parameter	Ratio of Central Values			
	Period 2/Day 1 <sup>a</sup> vs. Period 1/Day 1 <sup>b</sup>		Period 2/Day 15 <sup>c</sup> vs. Period 1/Day 1 <sup>b</sup>	
	Point Estimate	90% Confidence Interval	Point Estimate	90% Confidence Interval
<b>Arm 1 (2 DAAs)<sup>d</sup></b>				
C <sub>max</sub> /D (ng/mL/mg)	0.689	0.592 – 0.801	0.917	0.788 – 1.067
AUC <sub>r</sub> /D(ng•h/mL/mg)	2.635	2.275 – 3.051	3.864	3.337 – 4.475
C <sub>24</sub> /D (ng/mL/mg)	7.746	6.948 – 8.635	13.457	12.071 – 15.002
<b>Arm 2 (2 DAAs)<sup>e</sup></b>				
C <sub>max</sub> /D (ng/mL/mg)	0.669	0.587 – 0.762	0.825	0.724 – 0.940
AUC <sub>r</sub> /D(ng•h/mL/mg)	2.596	2.214 – 3.043	3.742	3.192 – 4.387
C <sub>24</sub> /D (ng/mL/mg)	6.717	5.548 – 8.133	12.845	10.609 – 15.553
<b>Arm 3 (3 DAAs)<sup>f</sup></b>				
C <sub>max</sub> /D (ng/mL/mg)	0.637	0.542 – 0.747	1.013	0.854 – 1.201
AUC <sub>r</sub> /D(ng•h/mL/mg)	2.784	2.313 – 3.350	5.687	4.667 – 6.929
C <sub>24</sub> /D (ng/mL/mg)	6.974	6.147 – 7.911	15.803	13.809 – 18.085

a. Period 2/Day 1: CsA + Day 1 dosing of DAAs.

b. Period 1/Day 1: CsA single dose.

c. Period 2/Day 15 CsA + steady-state DAAs.

d. CsA 100 mg (Period 1), 10 mg (Period 2), ABT-450/r (150/100 mg QD), ABT-333 (400 mg BID).

e. CsA 100 mg (Period 1), 10 mg (Period 2), ABT-450/r (150/100 mg QD), ABT-267 (25 mg QD).

f. CsA 100 mg (Period 1), 30 mg (Period 2), ABT-450/r (150/100 mg) QD, ABT-267 (25 mg QD), ABT-333 (400 mg BID).

Dose normalized AUC and C<sub>24</sub> of cyclosporine increased by ~6-fold and ~16-fold after co-administration of the 3-DAA regimen (Arm 3) as compared to administration of cyclosporine alone. Of note, the magnitude of increase in AUC (generally considered to be associated with efficacy) was lower than the magnitude of increase in C<sub>24</sub> (monitored in the clinical setting to adjust the dose of cyclosporine).

Clinical Recommendation: Under discussion at the time of completion of this review.

### *Tacrolimus*

**Table 34** shows the point estimate and 90 % CI of the pharmacokinetic parameters of tacrolimus after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with tacrolimus.

**Table 34: Point estimate and 90 % CI of the pharmacokinetic parameters of tacrolimus after co-administration of ABT-450, ritonavir, ABT-267, and ABT-333 with tacrolimus**

Tacrolimus Dose-Normalized Pharmacokinetic Parameter (Unit)	Ratio of Central Values (Period 2/Day 15 <sup>a</sup> vs. Period 1/Day 1 <sup>b</sup> )	
	Point Estimate	90% Confidence Interval
Arm 1 (2 DAAs) <sup>c</sup>		
C <sub>max</sub> /D (ng/mL/mg)	3.713	3.042 – 4.533
AUC <sub>∞</sub> /D(ng•h/mL/mg)	78.633	55.322 – 111.768
C <sub>24</sub> /D (ng/mL/mg)	25.129	17.561 – 35.958
Arm 2 (2 DAAs) <sup>d</sup>		
C <sub>max</sub> /D (ng/mL/mg)	4.267	3.491 – 5.216
AUC <sub>∞</sub> /D(ng•h/mL/mg)	85.813	67.875 – 108.491
C <sub>24</sub> /D (ng/mL/mg)	24.614	19.687 – 30.773
Arm 3 (3 DAAs) <sup>e</sup>		
C <sub>max</sub> /D (ng/mL/mg)	3.992	3.206 – 4.972
AUC <sub>∞</sub> /D(ng•h/mL/mg)	57.128	45.526 – 71.687
C <sub>24</sub> /D (ng/mL/mg)	16.562	12.967 – 21.155

a. Period 2/Day 15: Tacrolimus + steady-state DAAs.

b. Period 1/Day 1: Tacrolimus single dose.

c. Tacrolimus 2 mg (Period 1), 0.5 mg (Period 2), ABT-450/r (150/100 mg QD), ABT-333 (400 mg BID).

d. Tacrolimus 2 mg (Period 1), 0.5 mg (Period 2), ABT-450/r (150/100 mg QD), ABT-267 (25 mg QD).

e. Tacrolimus 2 mg (Period 1), 2 mg (Period 2), ABT-450/r (150/100 mg) QD, ABT-267 (25 mg QD), ABT-333 (400 mg BID).

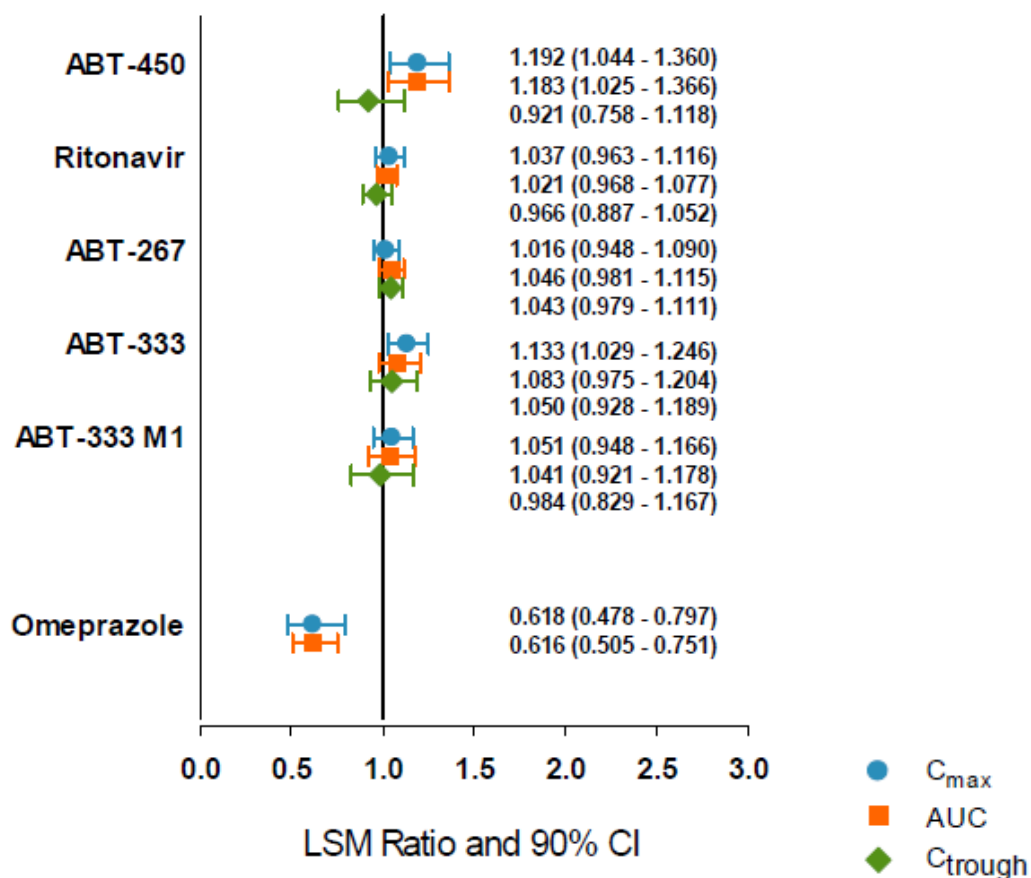
Dose normalized AUC and C<sub>24</sub> of tacrolimus increased by ~57-fold and ~17-fold after co-administration of the 3-DAA regimen (Arm 3) as compared to administration of tacrolimus alone. Of note, the magnitude of increase in AUC (generally considered to be associated with efficacy) was higher than the magnitude of increase in C<sub>24</sub> (monitored in the clinical setting to adjust the dose of tacrolimus).

Clinical Recommendation: Under discussion at the time of completion of this review.

*Omeprazole (CYP2C19 Substrate/Inhibitor and Gastric Acid Reducing Agent)*

**Figure 25** shows the least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and Omeprazole after co-administration of ABT-267/ABT-450/ritonavir and Omeprazole

**Figure 25: Least squares mean ratio and 90 % CI of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and Omeprazole after co-administration of ABT-267/ABT-450/ritonavir and Omeprazole**



AUC<sub>24</sub> and C<sub>24</sub>: ABT-450, ritonavir and ABT-267; AUC<sub>12</sub> and C<sub>12</sub>: ABT-333 and ABT-333 M1 metabolite.  
AUC<sub>t</sub>: Omeprazole

Clinical Recommendation: Under discussion at the time of completion of this review.

#### No Dose Adjustment Recommended

No dose adjustments are recommended when VIEKIRA PAK™ is co-administered with the following: Methadone, Progestin only contraceptives, Atazanavir (morning administration), Raltegravir, Emtricitabine/Tenofovir, Escitalopram, Duloxetine, and Zolpidam.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for pharmacodynamic drug-drug interactions with VIEKIRA PAK<sup>TM</sup>.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved issues related to metabolism, active metabolites, metabolic drug interactions, or protein binding.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The proposed total daily doses of ABT-267 (25 mg), ABT-450 (150 mg), ritonavir (100 mg) and ABT-333 (500 mg) are appropriate. The need for ribavirin in genotype 1a patients without cirrhosis and the duration of therapy in all genotype 1a patients with cirrhosis was under discussion at the time of finalizing this review.

## 2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Please refer to biopharmaceutics review.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The ABT-267/ABT-450/ritonavir coformulated tablet formulation used in all pivotal Phase 3 trials is identical in composition to the to-be-marketed ABT-267/ABT-450/ritonavir coformulated tablet; therefore, no relative bioavailability study was conducted. ABT-333 250 mg (b) (4) formulation used in all pivotal Phase 3 trials (manufactured at North Chicago, IL) is identical in composition to the to-be-marketed ABT-333 tablets (manufactured at Sligo, Ireland); however the applicant conducted a bioequivalence trial (M14-196) to compare the systemic exposures of ABT-333 manufactured at the two sites. Please refer to the biopharmaceutics review for further details.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

Not applicable to this NDA.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

**Table 35** shows the summary of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267 and ABT-333 after single dose administration of ABT-267/ABT-450/ritonavir coformulated tablets and ABT-333 tablets under moderate fat- and high-fat conditions.

**Table 35: Summary of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-67 and ABT-3333 after single dose administration of ABT-267/ABT-450/ritonavir coformulated tablets and ABT-333 tablets under moderate fat- and high-fat conditions**

Meal Type	PK Parameter	ABT-450*	Ritonavir*	ABT-267*	ABT-333**
Moderate Fat (617 Kcal; 29 % calories from fat) <sup>#</sup>	C <sub>max</sub>	4.67 [3.03-7.19]	1.63 [1.3-2.04]	2.27 [1.97-2.61]	1.52 [1.19-1.95]
	AUC <sub>∞</sub>	3.1 [2.16-4.46]	1.48 [1.23-1.79]	1.81 [1.6-2.05]	1.29 [1.08-1.55]
High Fat (917 Kcal; 60 % calories from fat) <sup>#</sup>	C <sub>max</sub>	4 [2.6-6.16]	1.5 [1.19-1.88]	2.06 [1.78-2.37]	1.41 [1.10-1.81]
	AUC <sub>∞</sub>	2.79 [1.94-4.01]	1.43 [1.19-1.73]	1.76 [1.55-1.98]	1.21 [1.01-1.45]

\*: Administered as a single dose of ABT-450/r/ABT-267 Co-formulated tablet

\*\* Administered as single dose of ABT-333 250 mg (b) (4) tablet

#: For ABT-333, moderate fat condition was 612 Kcal, 21 % fat and high-fat meal was 850 Kcal, 59 % fat  
Source: Generated by reviewer based on results of trial M11-389 (effect of food on the pharmacokinetics of ABT-267/ABT-450/ritonavir coformulated tablets) and M13-330 (effect of food on the pharmacokinetics of ABT-333 tablets)

ABT-267/ABT-450/ritonavir co-formulated tablets should always be taken with a meal. The differences in systemic exposure of ABT-450, ritonavir, and ABT-267 after administration of ABT-267/ABT-450/ritonavir co-formulated tablets under moderate fat and high fat conditions is not expected to be clinically relevant. ABT-333 tablets should be taken with food. The differences in systemic exposure of ABT-333 exposures under moderate fat and high fat conditions are not expected to be clinically relevant.

Of note, ABT-267/ABT-450/ritonavir co-formulated tablets and ABT-333 tablets were administered with food in the Phase 3 trials and drug-drug interaction trials.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable to this NDA.

## **2.6 Analytical section**

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moieties were identified in the plasma using validated LC/MS/MS methods.

2.6.2 Which metabolites have been selected for analysis and why?

The applicant only selected to analyze ABT-333 M1, an active metabolite of ABT-333. The  $C_{max}$  and AUC ratio of ABT-333 M1 metabolite: ABT-333 was 0.64 and 0.57, respectively, across healthy volunteer trials which evaluated the to-be-marketed regimen. The applicant selected to analyze ABT-333 M1 because it showed comparable anti HCV activity in cell culture based on a study conducted using HCV genotype 1a and 1b replicon systems. ABT-333 M1 was also assessed in drug-drug interaction trials and Phase 3 trials; however, ABT-333 M1 was not included in the population pharmacokinetic analysis. Please see the response to question 2.2.3 for additional information.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods measured the total concentrations, as was appropriate. The protein binding of ABT-450 (> 97 %), ABT-267 (>99 %), and ABT-333 (>99%) suggest that ABT-450, ABT-267, and ABT-333 are almost entirely bound to plasma proteins.

2.6.4 What bioanalytical methods are used to assess concentrations?

Please refer to individual trial reviews for detailed information related to calibration standards, quality control samples, precision and accuracy. Overall, the bioanalytical methods were found to be acceptable.

## **3 Labeling Recommendations**

Labeling recommendations were under discussion at the time of finalizing this review.



## **4 Appendices**

### **4.1 Individual Trial Reviews**

### **4.2 Pharmacometric Review (Page 407)**

**PK Assessment of ABT-450, with or without ritonavir**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M10-749**

**Title**

**A Double-Blind, Randomized, Placebo-Controlled, Nonfasting Study in Healthy Adults to Evaluate the Safety, Tolerability, and Pharmacokinetic Profiles of Single Doses of ABT-450 With and Without Ritonavir**

**Trial Period**

January 21, 2009 through July 20, 2009  
Final report date: July 20, 2010

**Trial Objectives**

The primary objectives of this study were:

- Assess the safety, tolerability, and pharmacokinetics of single, oral doses of ABT-450 under nonfasting conditions in healthy adult subjects in Substudy 1.
- Assess the safety, tolerability, and pharmacokinetics of escalating, single, oral doses of ABT-450 with ritonavir (ABT-450/r) under nonfasting conditions in healthy adult subjects in Substudy 2.

**Trial Design**

This was a Phase 1 study consisting of 2 substudies:

Substudy 1:

Single dose, double-blind, placebo-controlled, nonfasting study conducted according to a randomized, sequential design in 24 subjects. Subjects (8 subjects per group; 3 sequential groups) were randomized in a 3:1 ratio (active:placebo) to receive a single dose of ABT-450 or placebo. After assessment of ABT-450 safety, tolerability and pharmacokinetics in the first group, successive groups were enrolled to further characterize the pharmacokinetics of ABT-450.

Table 1 shows the ABT-450 doses used in substudy 1.

Group <sup>a</sup>	ABT-450 Dose	Number of Subjects ABT-450	Number of Subjects Placebo
1	300 mg	6	2
2	600 mg	6	2
3	900 mg	6	2

a. Subjects participated in one group only.

## Substudy 2:

Substudy 2 was to commence after completion of substudy 1. Substudy 2 was a double-blind, placebo-controlled, nonfasting single ascending dose (SAD) in the presence of ritonavir, study was conducted according to a randomized, sequential design. The study was conducted in 8 sequential groups, in which escalating doses of ABT-450/r were assessed. Of note, Group 8 was not dosed as planned in the protocol.

Table 2 shows the doses of ABT-450 and ritonavir used in substudy 2.

SAD Assessment in Healthy Subjects		
Group <sup>Y</sup>	ABT-450/r	Placebo/placebo
1	25 mg/100 mg n = 6	n = 2
2	300 mg/100 mg n = 6	n = 2
3a	100 mg/200 mg n = 6	n = 2
3b	100 mg/50 mg n = 6	n = 2
4	100 mg/100 mg n = 6	n = 2
5	400mg /100 mg n = 6	n = 2
6	200 mg/75 mg n = 6	n = 2
7	400 mg/50 mg n = 6	n = 2

Y. Subjects only participated in 1 group.

Dose escalation was to proceed after an evaluation of the safety and pharmacokinetic data obtained from the preceding group. Groups 3a, 3b and 4 were to be dosed in parallel with each other since the ABT-450 dose in each of these groups was lower than the dose in Group 2. The dose of ritonavir was  $\leq 200$  mg in substudy 2. The maximum dose of ABT-450/r to be administered in Substudy 2 was not to exceed 1000 mg/200 mg. The dose of ritonavir was  $\leq 200$  mg.

## Drug Administration

Study drug was administered on the morning of Study Day 1. Each dose was taken orally with approximately 240 mL of water, approximately 30 minutes after starting a breakfast containing approximately 30 % calories from fat. Each subject participated in only one group. An interval of at least 5 days separated the dose of a group from the next dose of any subsequent group.

## Identity of Investigational Products

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

Investigational Product	ABT-450		ABT-450 Placebo	Ritonavir		Ritonavir Placebo	
Mode of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Dosage Form	(b) (4)			SGC	SGC	SGC 25 mg placebo	SGC 100 mg placebo
Manufacturing Site	Abbott	Abbott	Abbott	(b) (4)			
Strength (mg)	5	50	0	25	100	0	0
Bulk Product Lot Number	08-019769	08-019770	08-019768	08-020467	09-021003	09-021004	09-021002
Finishing Lot Number	08-020912	08-020916	08-020914	09-021107	09-021109	09-021110	09-021111
Expiration/Retest Date	(b) (4)						
	(b) (4) SGC = soft gelatin capsule						
	† Abbott Formulation Development Center (AP39), Abbott Park, Illinois.						
	(b) (4)						

## Sample Collection

Blood samples for assay of ABT-450 and possible metabolites as well as ritonavir (sub-study 2 only) were collected prior to dosing (0 hour) and up to 72 hours after dosing on study day 1. Urine samples for assay of ABT-450 and possible metabolites as well as ritonavir (sub-study 2 only) were collected over the following intervals: 0-6, 6-12, 12-24, 24-48 and 48-72 hours after dosing.

## Pharmacokinetic Analysis

The pharmacokinetic parameters were computed using non-compartmental methods.

## Results

Table 4 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (µg/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.0239-1.99	0.0239	0.0276,0.197,1.64	2 % to	-2.5 % to 4.3

				7.4 %	%
ABT-450 (urine)	0.01-3.01	0.01	0.025,0.312,2.60	2.7 % to 3.7 %	-1 % to 4 %
Ritonavir	0.005-2.41	0.005	0.01,0.274,1.96	1.8 % to 2.8 %	2.6 % to 3.6 %

### *Subject Disposition and Demographics*

Table 4 shows the disposition of subjects in sub-study 1.

	Group 1 300 mg ABT-450		Group 2 600 mg ABT-450		Group 3 900 mg ABT-450	
	ABT-450	Placebo	ABT-450	Placebo	ABT-450	Placebo
Number of Subjects Planned	6	2	6	2	6	2
All Randomized Subjects	6	2	6	2	6	2
Completed Study	6	2	6	2	6	2
Prematurely Terminated	0	0	0	0	0	0

Table 5 shows the disposition of subjects in sub-study 2.

	Group 1 25/100 mg		Group 2 300/100 mg		Group 3a 100/200 mg		Group 3b 100/50 mg		Group 4 100/100 mg		Group 5 400/100 mg		Group 6 200/75 mg		Group 7 400/50 mg	
	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo	ABT-450/r	Pbo
Number of Subjects Planned	6	2	6	2	6	2	6	2	6	2	6	2	6	2	6	2
All Randomized Subjects	5	2	6	2	6	2	6	2	6	2	6	2	6	2	6	2
Completed Study	5	2	6	2	6	2	6	2	6	2	6	2	6	2	6	2
Prematurely Terminated	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pbo = placebo

Table 6 shows the demographic summaries of all randomized subjects.

	Mean $\pm$ SD	Min – Max
All Subjects in Substudy 1 (N = 24)		
Age (years)	33.1 $\pm$ 10.0	18 – 55
Weight (kg)	79.9 $\pm$ 9.1	59 – 92
Height (cm)	176.1 $\pm$ 9.2	153 – 189
Sex	3 Females (12%), 21 Males (88%)	
Race	17 White (71%), 6 Black (25%), 1 Asian (4%)	
All Subjects in Substudy 2 (N = 63)		
Age (years)	35.1 $\pm$ 10.6	18 – 55
Weight (kg)	75.7 $\pm$ 9.7	56 – 97
Height (cm)	173.2 $\pm$ 8.9	154 – 199
Sex	14 Females (22%), 49 Males (78%)	
Race	40 White (63%), 21 Black (33%), 1 Asian (2%), 1 American Indian (2%)	

SD = Standard Deviation.

## Pharmacokinetics

### Sub-study 1

Fig 1 shows the mean and standard deviation plasma concentration time profiles of ABT-450.

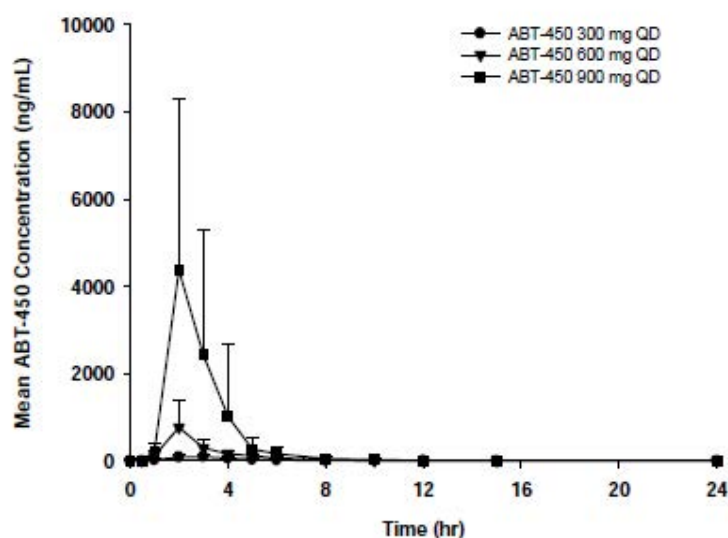


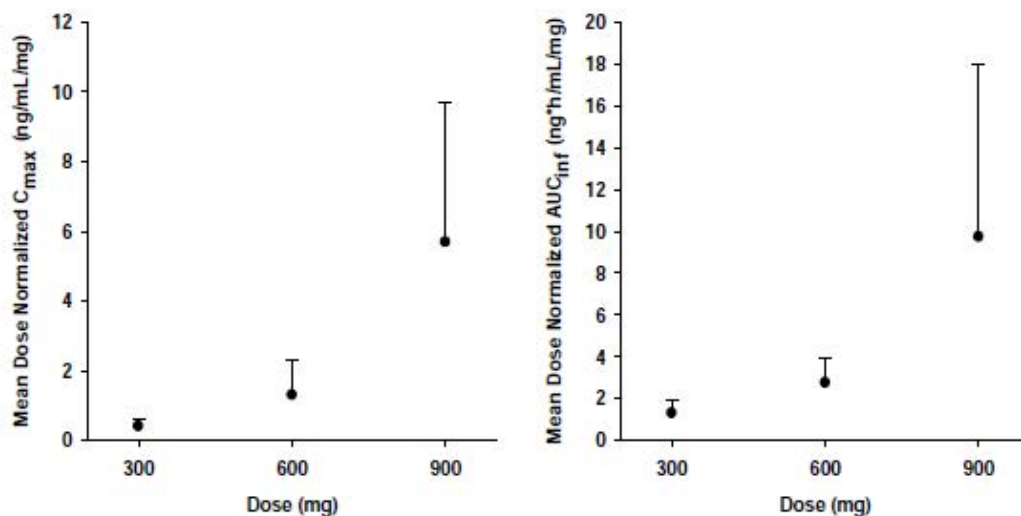
Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of the various ABT-450 doses in the trial

Pharmacokinetic Parameter	Group 1 300 mg ABT-450 (N = 6)	Group 2 600 mg ABT-450 (N = 6)	Group 3 900 mg ABT-450 (N = 6)
C <sub>max</sub> (ng/mL)	121 ± 68.2	780 ± 599	5120 ± 3581
C <sub>max</sub> /Dose (ng/mL/mg)	0.404 ± 0.227	1.30 ± 1.00	5.69 ± 3.98
C <sub>12</sub> (ng/mL)	3.63 ± 1.20	5.53 ± 2.21	13.0 ± 9.48
C <sub>24</sub> (ng/mL)	0.126 ± 0.308	0.447 ± 0.511	0.985 ± 0.880
T <sub>max</sub> (h)	2.3 ± 0.5	1.8 ± 0.4	2.2 ± 0.4
t <sub>1/2</sub> <sup>#</sup> (h)	2.67 ± 0.64	2.72 ± 1.17	3.05 ± 1.60
β (1/h)	0.260 ± 0.063	0.254 ± 0.103	0.227 ± 0.115
AUC <sub>t</sub> (ng•h/mL)	385 ± 190	1645 ± 729	8753 ± 7402
AUC <sub>t</sub> /Dose (ng•h/mL/mg)	1.29 ± 0.63	2.74 ± 1.21	9.73 ± 8.23
AUC <sub>∞</sub> (ng•h/mL)	391 ± 189	1651 ± 729	8758 ± 7401
AUC <sub>∞</sub> /Dose (ng•h/mL/mg)	1.30 ± 0.63	2.75 ± 1.21	9.73 ± 8.22
CL/F (L/h)	948 ± 502	434 ± 205	234 ± 242
Vdβ/F	3775 ± 2096	1745 ± 644	945 ± 612
f <sub>e</sub> (%)	0.009	0.021	0.096
CL <sub>R</sub> (L/h)	0.091	0.079	0.125

# Harmonic mean and pseudo SD.

After single dose administration of ABT-450 alone, the plasma concentrations reached peak levels within 2 hours. The mean terminal half-lives were approximately 3 hours. The mean fraction of the ABT-450 doses recovered in the urine were < 0.1 % for the 72 hour collection interval.

Fig 2 shows the mean + standard deviation dose normalized ABT-450 C<sub>max</sub> and AUC<sub>inf</sub> versus dose following single dose administration.



Dose-normalized ABT-450 C<sub>max</sub> and AUC<sub>∞</sub> values increased over the 300 to 900 mg dose range. The dose-normalized C<sub>max</sub> and AUC values for ABT-450 were statistically significantly ( $p \leq 0.021$ ) different across the doses of 300 mg to 900 mg.

## Sub-study 2



Fig 3 shows the mean (SD) plasma concentration time profiles of ABT-450 after administration of various doses of ABT-450/ritonavir (linear and log linear scale).

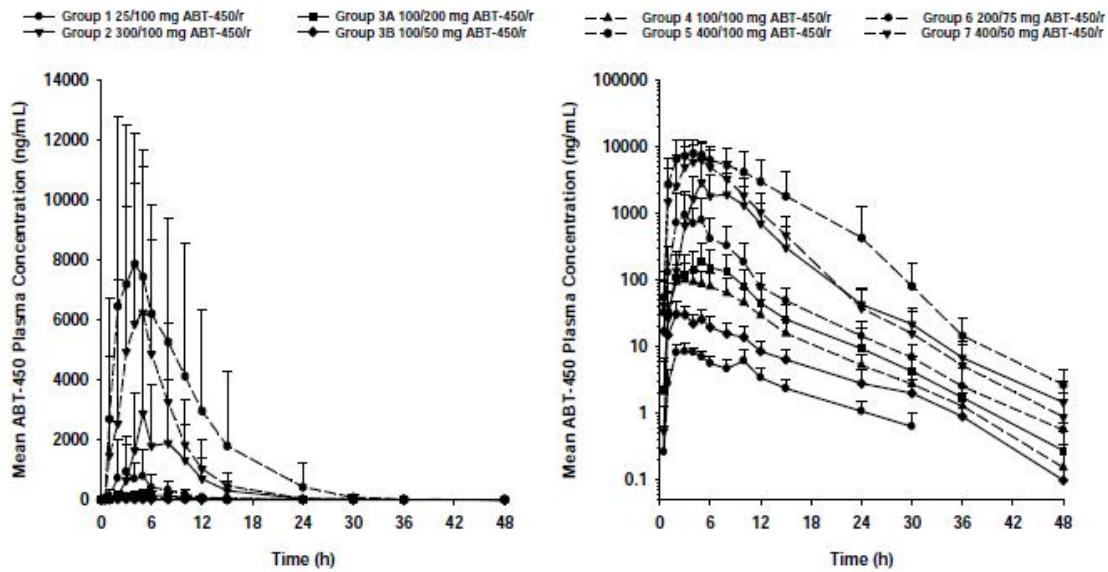


Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 after administration of single dose ABT-450 with ritonavir.

Pharmacokinetic Parameter	ABT-450/Ritonavir							
	Group 1 25/100 mg (N = 5)	Group 2 300/100 mg (N = 6)	Group 3a 100/200 mg (N = 6)	Group 3b 100/50 mg (N = 6)	Group 4 100/100 mg (N = 6)	Group 5 400/100 mg (N = 6)	Group 6 200/75 mg (N = 6)	Group 7 400/50 mg (N = 6)
$C_{max}$ (ng/mL)	10.4 $\pm$ 1.06	3397 $\pm$ 3297	223 $\pm$ 170	48.2 $\pm$ 28.7	115 $\pm$ 78.4	10267 $\pm$ 5122	1055 $\pm$ 1167	7079 $\pm$ 5445
$C_{max}/Dose$ (ng/mL/mg)	0.42 $\pm$ 0.04	11.3 $\pm$ 11.0	2.23 $\pm$ 1.70	0.48 $\pm$ 0.29	1.51 $\pm$ 0.78	25.7 $\pm$ 12.8	5.28 $\pm$ 5.83	17.7 $\pm$ 13.6
$C_{12}$ (ng/mL)	3.39 $\pm$ 1.39	698 $\pm$ 707	45.1 $\pm$ 36.7	8.44 $\pm$ 3.72	29.2 $\pm$ 19.3	2964 $\pm$ 3383	77.9 $\pm$ 46.9	1027 $\pm$ 952
$C_{24}$ (ng/mL)	1.07 $\pm$ 0.45	42.5 $\pm$ 26.9	9.29 $\pm$ 9.53	2.78 $\pm$ 1.71	5.20 $\pm$ 2.21	425 $\pm$ 810	14.2 $\pm$ 9.24	37.2 $\pm$ 36.4
$T_{max}$ (h)	4.0 $\pm$ 3.4	4.7 $\pm$ 2.1	5.2 $\pm$ 1.9	2.6 $\pm$ 1.5	4.2 $\pm$ 1.0	3.2 $\pm$ 1.2	3.5 $\pm$ 1.0	3.2 $\pm$ 1.7
$t_{1/2}^{\#}$ (h)	7.88 $\pm$ 1.16	4.61 $\pm$ 1.24	5.54 $\pm$ 0.80	6.41 $\pm$ 2.69	5.66 $\pm$ 0.99	4.89 $\pm$ 0.93	4.76 $\pm$ 0.66	4.02 $\pm$ 1.52
$\beta$ (1/h)	0.088 $\pm$ 0.013	0.150 $\pm$ 0.040	0.125 $\pm$ 0.018	0.108 $\pm$ 0.040	0.122 $\pm$ 0.022	0.142 $\pm$ 0.027	0.146 $\pm$ 0.020	0.172 $\pm$ 0.061
$AUC_t$ (ng•h/mL)	95.6 $\pm$ 16.6	18534 $\pm$ 17671	1612 $\pm$ 1240	310 $\pm$ 84.6	962 $\pm$ 540	81071 $\pm$ 61514	5520 $\pm$ 5734	43968 $\pm$ 35097
$AUC_t/Dose$ (ng•h/mL/mg)	3.83 $\pm$ 0.66	61.8 $\pm$ 58.9	16.1 $\pm$ 12.4	3.10 $\pm$ 0.85	9.62 $\pm$ 5.40	203 $\pm$ 154	27.6 $\pm$ 28.7	110 $\pm$ 87.7
$AUC_{\infty}$ (ng•h/mL)	104 $\pm$ 18.1	18543 $\pm$ 17672	1622 $\pm$ 1240	322 $\pm$ 85.0	970 $\pm$ 542	81078 $\pm$ 61512	5530 $\pm$ 5741	43974 $\pm$ 35098
$AUC_{\infty}/Dose$ (ng•h/mL/mg)	4.17 $\pm$ 0.72	61.8 $\pm$ 58.9	16.2 $\pm$ 12.4	3.22 $\pm$ 0.85	9.70 $\pm$ 5.42	203 $\pm$ 154	27.7 $\pm$ 28.7	110 $\pm$ 87.7
CL/F (L/h)	245 $\pm$ 39.2	67.3 $\pm$ 108	96.3 $\pm$ 67.0	329 $\pm$ 85.2	150 $\pm$ 121	20.3 $\pm$ 37.1	63.5 $\pm$ 35.0	96.5 $\pm$ 147
Vd $\beta$ /F	2825 $\pm$ 536	478 $\pm$ 790	835 $\pm$ 694	3172 $\pm$ 773	1307 $\pm$ 1148	175 $\pm$ 342	431 $\pm$ 238	720 $\pm$ 1141
$f_e$ (%)	0	0.356	0.048	0.009	0.048	1.169	0.213	0.727
CL <sub>R</sub> (L/h)	0	0.045	0.035	0.031	0.038	0.071	0.061	0.087

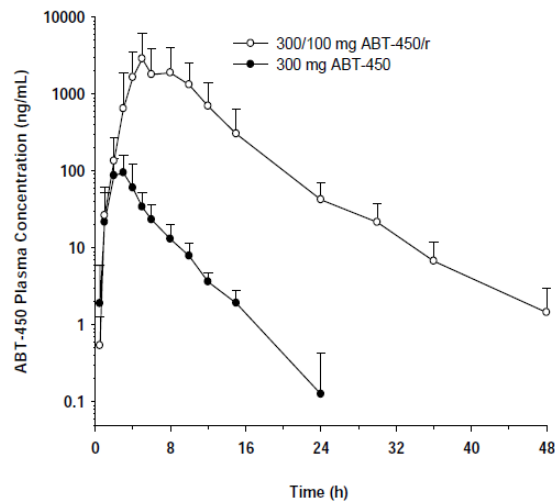
# Harmonic mean and pseudo SD.

Consistent with the nonlinearity observed in the  $C_{max}$  and AUC of ABT-450 alone, the pharmacokinetics of ABT-450 with ritonavir increased in a similar non-proportional manner. A 16-fold increase in ABT-450 dose (from 25 to 400 mg; both doses administered with 100 mg ritonavir) increased the mean dose normalized  $C_{max}$  and AUC values of ABT-450 by  $> 50$ -fold (from 4.17 ng•hr/mL/mg to 203 ng•hr/mL/mg).



### *Effect of Ritonavir on ABT-450 Pharmacokinetics*

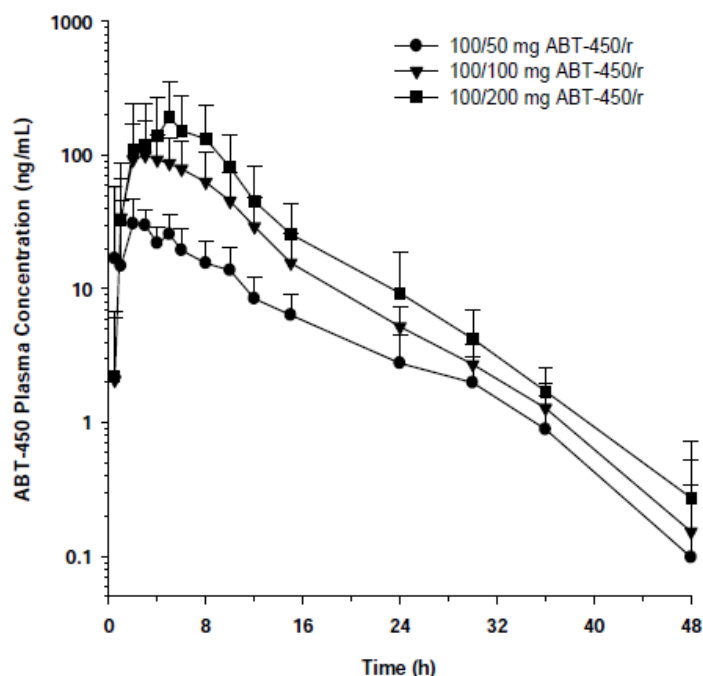
Fig 4 shows the mean (SD) plasma concentration-time profiles of ABT-450 300 mg given alone and with ritonavir 100 mg



The mean  $C_{\max}$  and AUC of ABT-450 at the 300/100 mg ABT-450/ritonavir dose increased by 28- and 48-fold, respectively as compared to administration of 300 mg ABT-450 alone. The mean  $t_{1/2}$  of ABT-450 increased from 3 to 5 hours when co-administered with ritonavir. with  $C_{12}$  value of ABT-450 300 mg dose when dosed with ritonavir 100 mg was approximately 6-fold higher than the mean  $C_{\max}$  of ABT-450 300 mg without ritonavir.

### *Effect of Different Doses of Ritonavir on the Pharmacokinetics of Same Dose of ABT-450*

Fig 5 shows the mean (SD) plasma concentration-time profiles of ABT-450 100 mg given with various doses of ritonavir (50 mg, 100 mg, and 200 mg).



Increasing the dose of ritonavir from 50 mg to 100 mg increased mean ABT-450  $C_{max}$  and AUC of ABT-450 by 2-3 fold. Increasing the ritonavir dose from 100 to 200 mg increased the mean  $C_{max}$  and AUC by 1.6 to 2-fold. At the 400 mg dose of ABT-450 (profile not shown in the figure above), changing the ritonavir dose from 50 to 100 mg led to a 1.5- to 2-fold increase in ABT-450  $C_{max}$  and AUC.

Mean  $t_{1/2}$  of ABT-450 did not appear to change with ritonavir dose. The mean  $t_{1/2}$  of ABT-450 100 mg when dosed with ritonavir 50 to 200 mg ranged from 5.5 to 6.4 hours and the mean  $t_{1/2}$  of ABT-450 400 mg when dosed with ritonavir 50 and 100 mg were 4.0 and 4.9 hours, respectively.

#### *Effect of Same Dose of Ritonavir on the Pharmacokinetics of Different Doses of ABT-450*

The pharmacokinetics of increasing ABT-450 dose when dosed with the same doses of ritonavir was evaluated by dosing ABT-450 25 to 400 mg with ritonavir 100 mg. Fig 6 shows the mean (SD) plasma concentration-time profiles and pharmacokinetic parameters of 25 to 400 mg ABT-450 dosed with ritonavir 100 mg.

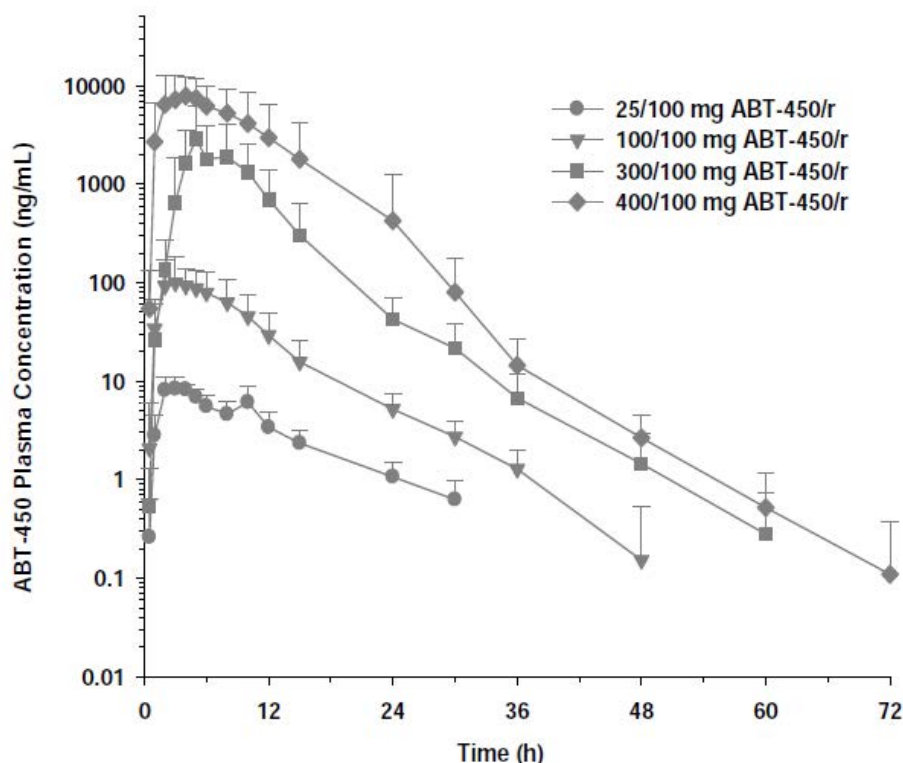
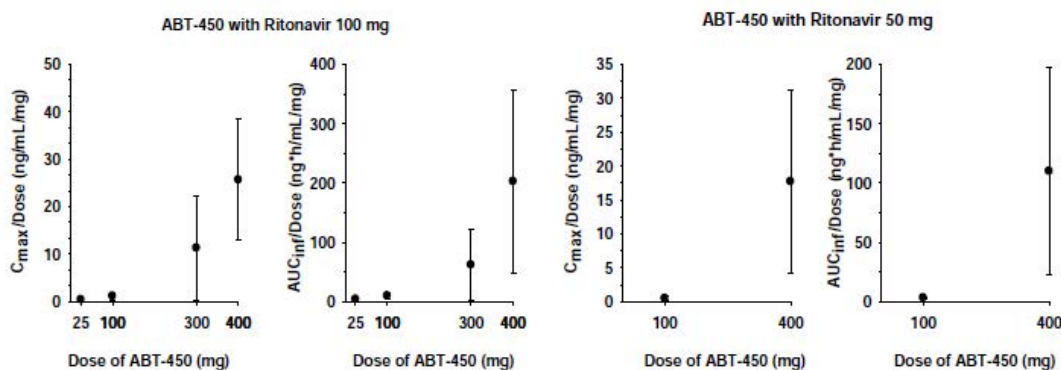


Fig 9 shows the mean  $\pm$  SD dose-normalized ABT-450  $C_{max}$  and  $AUC_{\infty}$  plotted vs ABT-450 coadministered with ritonavir 50 mg and 100 mg



At a 100 mg ritonavir dose, increasing ABT-450 dose from 25 to 400 mg increased the mean dose-normalized ABT-450  $C_{max}$  and AUC by approximately 60- and 50-fold, respectively. The dose-normalized  $C_{max}$  and AUC values for ABT-450 were statistically significantly ( $p \leq 0.001$ ) different across the doses of 25 mg to 400 mg.  $T_{max}$  values were not statistically significantly ( $p = 0.647$ ) across these doses.

### Pharmacokinetics of Ritonavir when Dosed with ABT-450

Fig 10 shows the mean (SD) plasma concentration-time profiles and pharmacokinetic parameters of ritonavir after co-administration of various doses of ABT-450 and ritonavir.

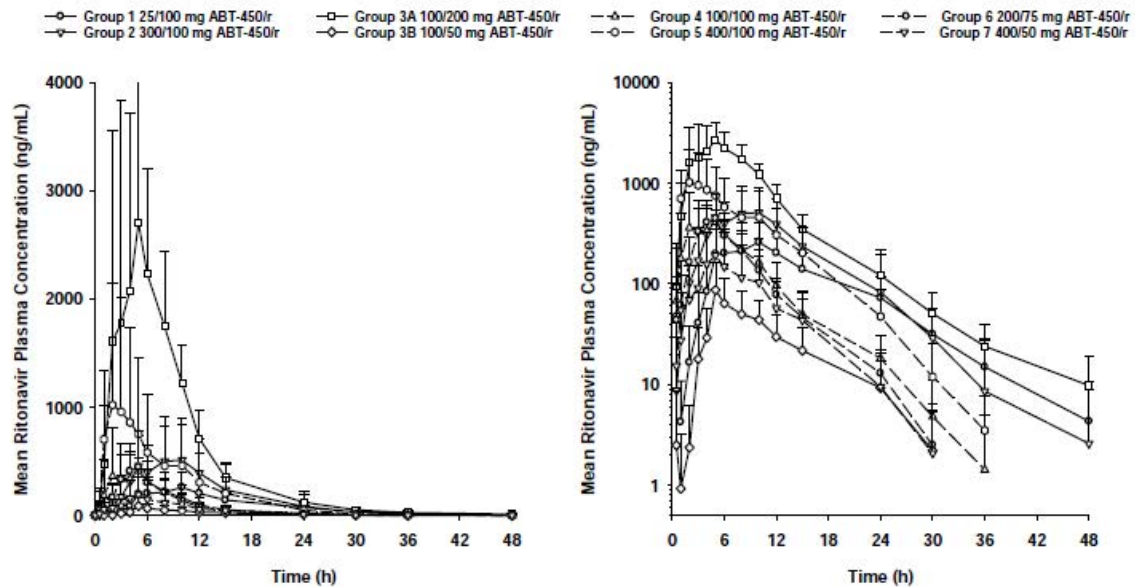


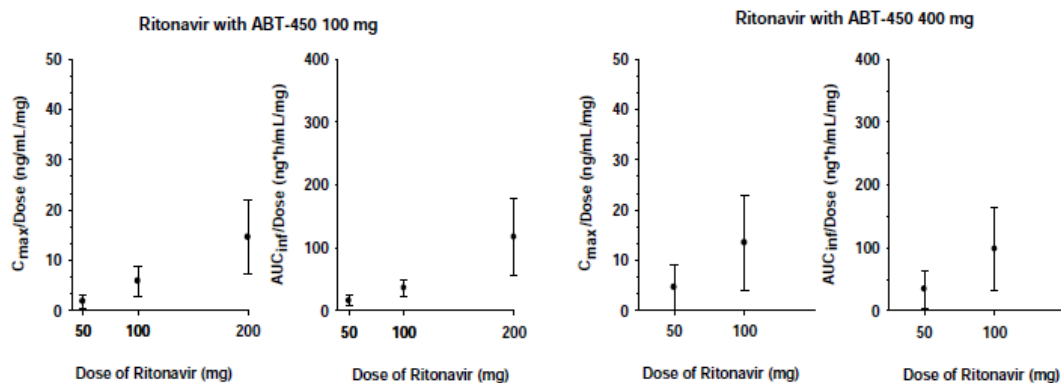
Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir after administration of single dose ABT-450 with ritonavir.

Pharmacokinetic Parameter	ABT-450/Ritonavir							
	Group 1 25/100 mg (N = 5)	Group 2 300/100 mg (N = 6)	Group 3a 100/200 mg (N = 6)	Group 3b 100/50 mg (N = 6)	Group 4 100/100 mg (N = 6)	Group 5 400/100 mg (N = 6)	Group 6 200/75 mg (N = 6)	Group 7 400/50 mg (N = 6)
$C_{max}$ (ng/mL)	301 $\pm$ 165	675 $\pm$ 331	2925 $\pm$ 1452	90.3 $\pm$ 70.3	586 $\pm$ 305	1350 $\pm$ 944	484 $\pm$ 332	230 $\pm$ 223
$C_{max}/Dose$ (ng/mL/mg)	3.01 $\pm$ 1.65	6.75 $\pm$ 3.31	14.6 $\pm$ 7.26	1.81 $\pm$ 1.41	5.86 $\pm$ 3.05	13.5 $\pm$ 9.44	6.46 $\pm$ 4.42	4.61 $\pm$ 4.47
$C_{12}$ (ng/mL)	203 $\pm$ 109	391 $\pm$ 316	709 $\pm$ 263	29.8 $\pm$ 18.7	95.9 $\pm$ 66.2	306 $\pm$ 264	77.8 $\pm$ 37.2	57.0 $\pm$ 48.3
$C_{24}$ (ng/mL)	72.7 $\pm$ 46.1	82.9 $\pm$ 133	121 $\pm$ 72.1	9.21 $\pm$ 8.10	18.2 $\pm$ 12.4	47.4 $\pm$ 39.0	12.9 $\pm$ 9.54	9.42 $\pm$ 11.1
$T_{max}$ (h)	7.8 $\pm$ 2.3	7.2 $\pm$ 3.4	5.7 $\pm$ 2.3	5.6 $\pm$ 3.7	4.0 $\pm$ 1.5	4.3 $\pm$ 4.4	4.2 $\pm$ 1.2	4.7 $\pm$ 3.1
$t_{1/2}$ (h)	5.55 $\pm$ 1.08	3.98 $\pm$ 0.88	5.38 $\pm$ 1.10	6.50 $\pm$ 2.90	4.96 $\pm$ 0.45	3.52 $\pm$ 0.60	4.01 $\pm$ 1.00	3.52 $\pm$ 1.25
$\beta$ (1/h)	0.125 $\pm$ 0.024	0.174 $\pm$ 0.039	0.129 $\pm$ 0.026	0.107 $\pm$ 0.046	0.140 $\pm$ 0.013	0.197 $\pm$ 0.033	0.173 $\pm$ 0.040	0.197 $\pm$ 0.067
$AUC_t$ (ng•h/mL)	3792 $\pm$ 1785	6921 $\pm$ 5789	23223 $\pm$ 12243	683 $\pm$ 445	3528 $\pm$ 1409	9240 $\pm$ 6639	3116 $\pm$ 1835	1670 $\pm$ 1498
$AUC_t/Dose$ (ng•h/mL/mg)	37.9 $\pm$ 17.8	69.2 $\pm$ 57.9	116 $\pm$ 61.2	13.7 $\pm$ 8.89	35.3 $\pm$ 14.1	92.4 $\pm$ 66.4	41.5 $\pm$ 24.5	33.4 $\pm$ 30.0
$AUC_{\infty}$ (ng•h/mL)	3896 $\pm$ 1797	6994 $\pm$ 5816	23301 $\pm$ 12270	779 $\pm$ 407	3589 $\pm$ 1414	9295 $\pm$ 6622	3175 $\pm$ 1832	1712 $\pm$ 1494
$AUC_{\infty}/Dose$ (ng•h/mL/mg)	39.0 $\pm$ 18.0	69.9 $\pm$ 58.2	117 $\pm$ 61.3	15.6 $\pm$ 8.14	35.9 $\pm$ 14.1	92.9 $\pm$ 66.2	42.3 $\pm$ 24.4	34.2 $\pm$ 29.9
CL/F (L/h)	31.0 $\pm$ 15.1	22.5 $\pm$ 14.5	11.8 $\pm$ 8.50	96.2 $\pm$ 82.1	31.7 $\pm$ 11.8	14.1 $\pm$ 6.18	29.9 $\pm$ 14.1	65.5 $\pm$ 81.7
Vd $\beta$ /F	247 $\pm$ 99.9	131 $\pm$ 92.0	86.9 $\pm$ 50.8	1574 $\pm$ 2556	230 $\pm$ 94.1	77.5 $\pm$ 44.9	169 $\pm$ 62.8	291 $\pm$ 240

# Harmonic mean and pseudo SD.

Ritonavir exposure increased more than proportionally with dose. This was expected as ritonavir in the dose range of 50 to 200 mg has been shown to have nonlinear increases in exposure.

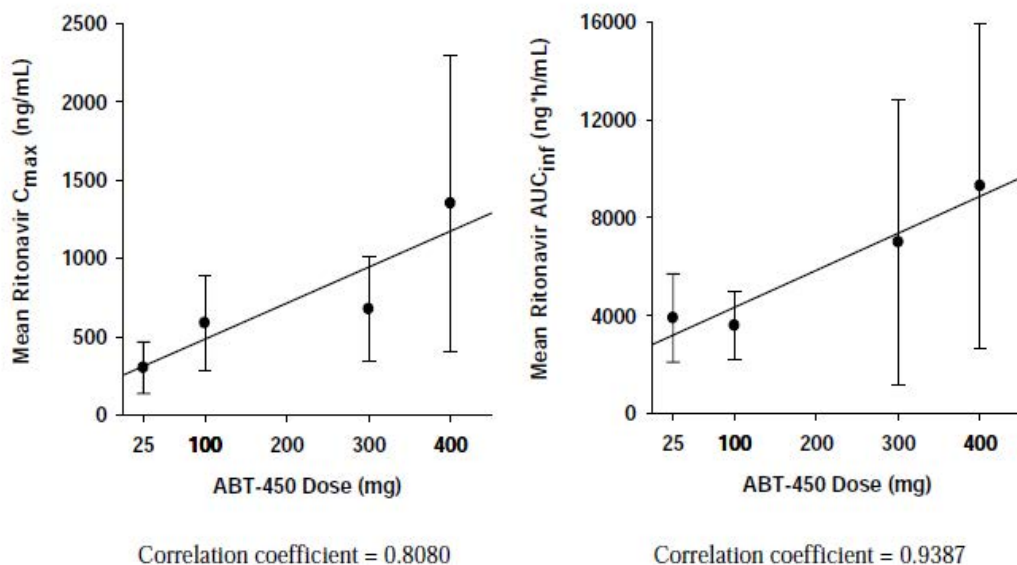
Fig 11 shows the mean  $\pm$  SD dose-normalized ritonavir  $C_{max}$  and  $AUC_{\infty}$  plotted versus ritonavir dose



Keeping the dose of ABT-450 constant and increasing ritonavir dose increased the exposure of ABT-450. Despite the nonlinear increase in ritonavir exposure from 50 to 200 mg, increasing ritonavir dose 4-fold from 50 to 200 mg increased the mean  $C_{max}$  and AUC of ABT-450 100 mg by approximately 5-fold which is proportional to the increase in ritonavir dose. Similarly, at an ABT-450 400 mg dose, increasing the ritonavir dose from 50 to 100 mg increased the  $C_{max}$  and AUC of ABT-450 by 1.5 to 2-fold which is proportional to the increase in ritonavir dose.

#### *Correlation Between $C_{max}$ and AUC of 100 mg Ritonavir with ABT-450 Dose*

Fig 12 shows the correlation between  $C_{max}$  and AUC of 100 mg ritonavir with ABT-450 dose.



#### Urinary Excretion of ABT-450

For Substudy 1, the mean fractions of ABT-450 doses recovered unchanged in urine ranged from 0.009% to 0.096% over the 72 hour collection period. When ABT-450 was dosed with ritonavir, the mean fractions of ABT-450 doses recovered unchanged in urine ranged from 0% at the 25/100 mg dose level to 1.17% at the 400/100 mg dose level.

### **Safety**

No subjects discontinued the study due to an adverse event, and no serious adverse events or deaths were reported. Transient increases in indirect bilirubin were observed at the highest doses of ABT-450/r. These asymptomatic elevations in indirect bilirubin returned to normal levels within approximately 2 days.

### **Conclusion**

- ABT-450 exhibited supraproportional increase in exposure with dose at ABT-450 doses of 300 to 900 mg without ritonavir and doses of 25 to 400 mg with ritonavir.
- Ritonavir co-administration significantly increased the  $C_{\max}$  and AUC of ABT-450.
- The mean percentages of the ABT-450 dose recovered in urine were less than 0.1% when ABT-450 was administered alone and less than 1.7% when ABT-450 was dosed with ritonavir, indicating that renal elimination is a minor elimination pathway.

## **Trial to Determine Absolute Bioavailability of ABT-333**

**Reviewer: Vikram Arya, Ph.D., FCP**

### **M11-030**

#### **Title**

**Evaluation of the intravenous pharmacokinetics of a microdose of ABT-333 and the absolute bioavailability of ABT-333 tablet in Healthy Subjects**

#### **Trial Period**

September 8, 2009 through October 14, 2009

Final report date: September 27, 2010

#### **Trial Objectives**

The objective of this study was to determine the absolute bioavailability of ABT-333 400 mg tablet formulation in healthy adults.

#### **Trial Design**

Phase 1, dual-dose, open-label study conducted in adult male subjects (N =8). The study drug was to be administered on Study Day 1 as one ABT-333 400 mg tablet, followed by a single dose of 100 µg <sup>14</sup>C-ABT-333 containing not more than 10 kBq (270 nCi) from an intravenous solution formulation over 15 minutes. The intravenous formulation was administered 2 hours 45 minutes after administration of the tablet.

#### **Rationale for Dose Selection**

The dose of ABT-333 used in the trial (400 mg) was the ABT-333 dose planned for the Phase 2b trials. The data from trial M13-331 established similarity of exposures between the ABT-333 400 mg dose and the to-be-marketed ABT-333 250 mg dose (administered as the 250 mg (b) (4) tablet formulation). Hence, the results from this trial are applicable to the clinically recommended dose and formulation.

Of note, the actual dose of <sup>14</sup>C-ABT-333 administered to each subject was slightly different than the nominal dose mentioned in the protocol and was calculated post-injection based on the dose volume, dose amount, and the radioactive dose. The actual single dose of <sup>14</sup>C-ABT-333 was 84 µg for Subjects 1605, 1611, and 1620 and 85 µg for Subjects 1609, 1610, 1615, 1617, and 1618. Though the planned dose in the study was 100 µg, the actual dose administered was lower than 100 µg because of specific activity of the starting material and the Administration of Radioactive Substances Advisory Committee (ARSAC) limits on the maximum amount of radioactivity that can be

administered. The actual dose administered to each subject was used for computation of the absolute bioavailability.

## Drug Administration

Subjects fasted from all food and drink (except water) on the day prior to dosing and remained fasted until approximately 07:30, when they were provided a standard moderate fat breakfast. The breakfast was to be consumed over a maximum period of 25 minutes, with dosing occurring 30 minutes after the start of breakfast.

## Identity of Investigational Products

ABT-333 400 mg tablets and  $^{14}\text{C}$ -ABT-333 were used in the trial. For ABT-333, the lot number was 09-021780 and for  $^{14}\text{C}$ -ABT-333, the nominal dose was 100  $\mu\text{g}$  (no more than 270 nCi).

## Sample Collection

Blood samples for ABT-333 and metabolite assay were collected at pre-dose and up to 72 hours after administration of the tablet. In addition, blood samples were collected for  $^{14}\text{C}$ -ABT-333 and the  $^{14}\text{C}$ -M1 metabolite at the following time points: -15 (just before the start of the infusion), -10, and -5 minutes during the infusion, 0 hour (end of infusion), and 5, 10, 20 minutes and up to 69 hours post-dose.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-333, the M1 metabolite,  $^{14}\text{C}$ -ABT-333, and the  $^{14}\text{C}$ -M1 metabolite were estimated using non-compartmental methods. The absolute bioavailability (F), ratio of  $\text{AUC}_{\infty}/\text{Dose}$  for tablet to  $\text{AUC}_{\infty}/\text{Dose}$  for IV, was estimated and a 95% confidence interval was computed.

## Results

### *Bioanalytical methods*

Table 1 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-333	1.04-531	1.04	2.95,36.9,461	3.9 % to 5.8 %	0.4 % to 3.8 %



ABT-333 M1	2.07-1060	2.07	5.81,72.6,908	2.6 % to 5.3 %	0.0 % to 2.3 %
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To determine the levels of [<sup>14</sup>C]-ABT-333 and [<sup>14</sup>C]-ABT-333-M1 in plasma, a protein precipitation method was developed in which (b) (4)



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

9 subjects were enrolled in the trial and 8 subjects completed the trial. One subject was removed from the study prior to dosing due to cold symptoms (subject took 1g paracetamol).

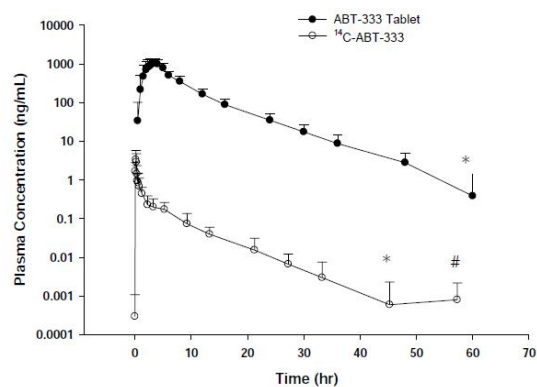
Table 2 shows the demographics of all subjects enrolled in the trial.

	Mean ± SD (N = 8)	Min – Max
Age (years)	30.5 ± 10.7	18 – 49
Weight (kg)	83.9 ± 13.6	67 – 103
Height (cm)	180.1 ± 4.7	174 – 186
Sex	8 Males (100%)	
Race	8 White (100%)	

### ***Pharmacokinetics***

#### ***ABT-333***

Fig 1 shows the mean (+SD) ABT-333 and <sup>14</sup>C-ABT-333 plasma concentration time profile (log-linear scale).



\* One observation was > LLOQ. Observations < LLOQ were set equal to zero.

# Two observations were > LLOQ. Observations < LLOQ were set equal to zero.

Table 3 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 and  $^{14}\text{C}$ -ABT-333.

Pharmacokinetic Parameter	Units	ABT-333 400 mg Tablet (N = 8)	85 $\mu\text{g}$ $^{14}\text{C}$ -ABT-333 (IV)* (N = 8)
$C_{\text{max}}$	(ng/mL)	$1141 \pm 356$	$3.7 \pm 2.3$
$C_{\text{max}}/\text{Dose}$	(ng/mL/mg)	$2.85 \pm 0.89$	$43.20 \pm 26.81$
$T_{\text{max}}$	(hr)	$3.1 \pm 0.9$	$0.2 \pm 0.1$
$\text{AUC}_t$	(ng•hr/mL)	$7092 \pm 2113$	$3.4 \pm 1.7$
$\text{AUC}_{\infty}$	(ng•hr/mL)	$7114 \pm 2118$	$3.4 \pm 1.7$
$\text{AUC}_{\infty}/\text{Dose}$	(ng•hr/mL/mg)	$17.78 \pm 5.29$	$40.35 \pm 19.52$
$\beta$	(1/hr)	$0.108 \pm 0.014$	$0.125 \pm 0.081$
$t_{1/2}^{\text{f}}$	(hr)	$6.4 \pm 0.9$	$5.6 \pm 3.9$
Vd	(L)	$566.20 \pm 152.87^{\text{§}}$	$400.60 \pm 397.28$
CL	(L/hr)	$60.96 \pm 18.33^{\text{€}}$	$29.25 \pm 11.02$
$\text{MRT}_t$	(hr)	$7.71 \pm 1.31$	$4.42 \pm 1.10$
$\text{MRT}_{\infty}$	(hr)	$7.87 \pm 1.36$	$5.76 \pm 1.91$

\* 84  $\mu\text{g}$  for Subjects 1605, 1611, and 1620.

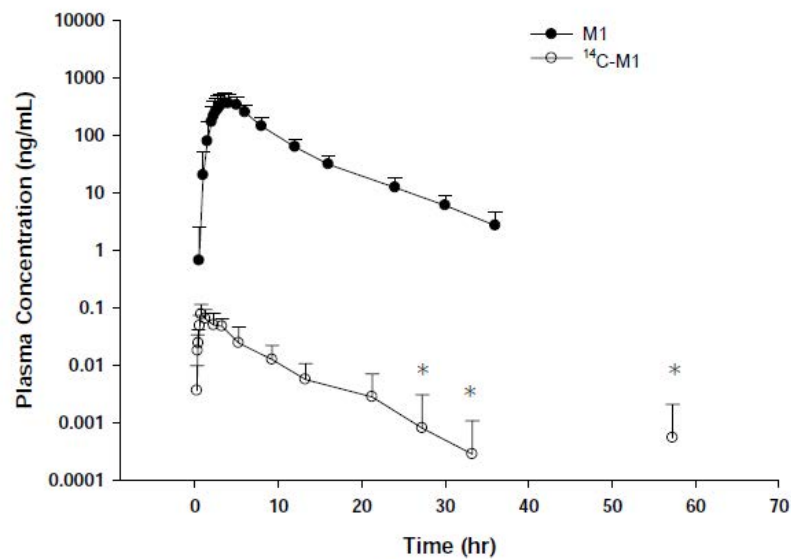
<sup>f</sup> Harmonic mean  $\pm$  pseudo-standard deviation.

<sup>§</sup> Denotes  $\text{Vd}_p/F$ .

<sup>€</sup> Denotes  $\text{CL}/F$ .

### M1 Metabolite

Fig 2 shows the mean ( $\pm$ SD) M1 and  $^{14}\text{C}$ -M1 metabolite plasma concentration time profile (log-linear scale).



\* One observation was > LLOQ. Observations < LLOQ were set equal to zero.

Table 4 shows the mean  $\pm$  SD pharmacokinetic parameters of M1 metabolite and  $^{14}\text{C}$ -M1 metabolite.

Pharmacokinetic Parameter	Units	M1 (N = 8)	$^{14}\text{C}$ -M1* (N = 8)
$C_{\max}$	(ng/mL)	404 $\pm$ 162	0.08 $\pm$ 0.03
$C_{\max}/\text{Dose}$	(ng/mL/mg)	1.01 $\pm$ 0.41	0.95 $\pm$ 0.40
$T_{\max}$	(hr)	4.3 $\pm$ 0.8	0.94 $\pm$ 0.26 <sup>#</sup>
$\text{AUC}_t$	(ng•hr/mL)	2589 $\pm$ 986	0.37 $\pm$ 0.19
$\text{AUC}_{\infty}$	(ng•hr/mL)	2617 $\pm$ 989	0.45 $\pm$ 0.22
$\text{AUC}_{\infty}/\text{Dose}$	(ng•hr/mL/mg)	6.54 $\pm$ 2.47	5.34 $\pm$ 2.64
$\beta$	(1/hr)	0.121 $\pm$ 0.016	0.133 $\pm$ 0.098
$t_{1/2}^{\text{£}}$	(hr)	5.8 $\pm$ 0.8	5.2 $\pm$ 4.5
Metabolite:Parent ( $C_{\max}$ )	--	0.35 $\pm$ 0.09	0.03 $\pm$ 0.03
Metabolite:Parent ( $\text{AUC}_{\infty}$ )	--	0.37 $\pm$ 0.09	0.16 $\pm$ 0.11

\* 84  $\mu\text{g}$  for Subjects 1605, 1611, and 1620.

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

<sup>#</sup>  $T_{\max}$  is relative to real time + 0.25 hour.

### *Assessment of Absolute Bioavailability*

Table 5 shows the assessment of absolute bioavailability, calculated using the ratio of observed dose normalized (non-logarithmically transformed)  $\text{AUC}_{\infty}$  for oral and intravenous formulations.

Subject ID	Oral AUC <sub>∞</sub> (ng•hr/mL)	IV AUC <sub>∞</sub> (ng•hr/mL)	F (AUC <sub>Oral</sub> /AUC <sub>IV</sub> ) Dose <sub>IV</sub> /Dose <sub>Oral</sub>
1605	9912	1.96	1.000 <sup>¥</sup>
1609	5695	2.37	0.511
1610	5379	6.68	0.171
1611	8899	2.61	0.716
1615	4980	2.17	0.487
1617	8502	4.58	0.394
1618	8849	4.50	0.418
1620	4693	2.49	0.396
Mean (SD, Range)	7114 (2118, 4693 – 9912)	3.42 (1.67, 1.96 – 6.68)	0.512 (0.249, 0.171 – 1.000)

¥ F (absolute bioavailability) should always be ≤ 1. The F value for Subject 1605 was > 1 (1.062), therefore, 1 was reported.

Note: Actual dose: 85 µg and for Subjects 1605, 1611, and 1620: 84 µg.

Table 6 shows the results of the paired t-test for ABT-333 beta (terminal phase elimination rate constant), logarithm transformed AUC<sub>t</sub>/Dose, AUC<sub>∞</sub>/Dose, and estimated absolute bioavailability (95 % confidence interval).

Formulation Test vs. Reference	Pharmacokinetic Parameter	Central Value*			Absolute Bioavailability	
		Test	Reference	p value <sup>#</sup>	Point Estimate	95% Confidence Interval
Tablet vs. IV	β	0.12	0.11	0.5409	--	--
	AUC <sub>t</sub> /Dose	17.03	35.97	0.0042	--	--
	AUC <sub>∞</sub> /Dose	17.08	36.88	0.0037	0.460	0.299 – 0.706

\* Geometric mean for AUC<sub>t</sub>/Dose and AUC<sub>∞</sub>/Dose.

# p value based on the paired t-test.

## Safety

No deaths, other serious adverse events, treatment emergent adverse events, or discontinuations due to adverse events occurred during the study.

## Results

- The mean absolute bioavailability of ABT-333 is approximately 46 %.
- The mean terminal half-life (5-6 hours) for ABT-333 was comparable after oral administration and intravenous administration, suggesting that terminal phase observed after oral administration represents the elimination phase.
- The mean systemic clearance of ABT-333 following IV dosing (~30 L/hr) was lower than the hepatic blood flow (~90 L/hr in a 70 kg individual) indicating that ABT-333 is not a high extraction ratio drug.

- The mean volume of distribution of ABT-333 following IV dosing (401 L) is greater than total body water (~0.5 L/kg or 35 L in a 70 kg individual), thus, suggesting tissue binding.
- The mean AUC ratio for the metabolite to parent (M1:ABT-333) was higher following oral administration (0.37) compared to IV administration (0.13). This suggests that more metabolite is formed after oral administration compared to IV administration and indicates the involvement of first pass metabolism in the disposition of ABT-333.

## **Conclusion**

The mean absolute bioavailability of ABT-333 is approximately 46 %. ABT-333 does not appear to be a high extraction drug. First pass metabolism is involved in the formation of M1, the major metabolite of ABT-333.

**Mass Balance Trial of ABT-450**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M10-798**

**Title**

**Absorption, Distribution, Metabolism and Excretion (ADME) Study of [<sup>14</sup>C] ABT-450/r in Healthy Male Subjects Following a Single Oral Dose Administration**

**Trial Period**

July 19, 2012 through August 16, 2012  
Final report date: June 28, 2013

**Trial Objectives**

The objective of this study was to evaluate the absorption, distribution, metabolism and excretion of [<sup>14</sup>C] ABT-450/r in healthy male subjects following a single oral dose.

**Trial Design**

Phase 1, single-dose, open-label, single center, ADME, mass balance study. Four adult male subjects (N = 4) were selected to participate in the study. On the morning of study Day 1, subjects received a single oral dose of [<sup>14</sup>C] ABT-450 and ritonavir under non-fasting conditions. The study drug, ABT-450 (200 mg active, 100 µCi [<sup>14</sup>C]) and ritonavir, 100 mg was administered as four (4 × 50 mg) (b) (4) ABT-450 and one 100 mg capsule of ritonavir. The single dose of study drug was taken orally in the morning on Study Day 1 and the total amount of liquid taken was approximately 240 mL, 30 minutes after starting a standardized breakfast (providing 40 % of the daily calories from fat and up to 45 % of the daily calories from carbohydrates; approximately 1900 calories/day). The radioactive dose level was approximately 100 µCi per subject.

Subjects were confined to the study site and supervised starting on the day prior to dosing (Study Day –1) and for a minimum of 120 hours, post-dose, or up to a maximum of 312 hours, post-dose. Excreta and blood for determination of the mass balance of [<sup>14</sup>C] ABT-450 were collected for up to a maximum of 312 hours after dose. Subjects were released from the study site at any time after 120 hours post-dose, if either of the following conditions were met: 1) greater than 90% of the total radioactivity had been recovered, or 2) less than 1% of the radioactive dose had been excreted in two consecutive 24-hour urine and fecal collection periods.

**Dose Selection**

The radioactive dose of 100  $\mu\text{Ci}$  was chosen so that the radiation burden for healthy volunteers remains below 2 mrem. An ABT-450 dose of 200 mg was chosen since this represented the higher end of doses that were being evaluated in the Phase 2 studies and provided the opportunity to characterize ABT-450 metabolites when dosed with 100 mg ritonavir as compared to lower doses.

The dose administered to each subject ranged from 205-207 mg (112-114  $\mu\text{Ci}$ ) and was close to the target dose of 200 mg (100  $\mu\text{Ci}$ ). The doses were calculated using the individual unit dose fill weights, the concentration of radioactivity in the dose formulation ( $7.81 \times 10^7$  dpm/g), and the specific activity of [ $^{14}\text{C}$ ] ABT-450 in the dose formulation (0.55  $\mu\text{Ci}/\text{mg}$ ).

## **Sample Collection**

### **Plasma Samples**

Two blood samples (approximately 10 mL each) for ABT-450/ritonavir assay, total radioactivity assay, metabolite identification, and metabolite profile were collected by venipuncture into potassium ( $\text{K}_2$ ) EDTA vacutainer collection tubes at the following times: 0 hour (pre-dose) and up to 312 hours after dosing of ABT-450/r on study day 1 or until 90 % of the administered radioactivity had been recovered or less than 1 % of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal sample collection periods.

For metabolite profiling, the plasma samples were pooled at the following times for the 4 subjects: (0, 1, 2, 4, 6, 8, 10, and 12 hours).

### **Urine Samples**

Subjects were instructed to collect their urine for pre-dose sampling starting approximately 12 hours prior to dosing and the entire sample was retained for baseline drug assay (pre-dosing sample). Thereafter, urine was collected during the following specified intervals: 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288 and 288 to 312 hours after dosing.

For metabolite profiling, the urine samples were pooled at the following times for the 4 subjects: (0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours).

### **Fecal Samples**

Fecal samples were collected pre-dose (upon check-in before dosing) and in the following dosing intervals: 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288 and 288 to 312 hours.

For metabolite profiling, the fecal samples were pooled at the following times for the 4 subjects: (0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours).

## Pharmacokinetic Analysis

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

## Results

### *Bioanalytical methods*

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-450	0.513-240	0.513	1.11, 29.6, 201	3 % to 6.5 %	-6.4 % to -0.2 %
Ritonavir	5.19-2430	5.19	10.9,290,1970	4.2 % to 5 %	-5.7 % to -1.1 %

For radioactivity analysis, all samples were analyzed by liquid scintillation counters. Each sample was homogenized or mixed before radioanalysis. If the results from same replicates (calculated as <sup>14</sup>C dpm/g sample) differed by more than 10 % from the mean value and sample aliquots had radioactivity greater than 200 dpm, the sample was rehomogenized and reanalyzed. The scintillation counting data (cpm) was automatically corrected for counting efficiency using the external standardization technique.

### *Subject Disposition and Demographics*

4 subjects were enrolled in the trial and 4 subjects completed the trial.

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

	Mean ± SD (N = 4)	Minimum (Min) – Maximum (Max)
Age (years)	32.8 ± 6.65	25 – 41
Weight (kg)	74.4 ± 5.89	67.5 – 81.3
Height (cm)	178 ± 8.38	167 – 186
Sex	4 Males (100%)	
Race	4 White (100%)	

SD = Standard Deviation



## Pharmacokinetics

### Pharmacokinetic Parameters of ABT-450 and Ritonavir

Table 2 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 and ritonavir.

Pharmacokinetic Parameters (units)		ABT-450 200 mg Dose	Ritonavir 100 mg Dose
$T_{\max}$	(h)	$3.0 \pm 1.2$	$4.5 \pm 1.9$
$C_{\max}$	(ng/mL)	$886 \pm 774$	$998 \pm 569$
$AUC_t$	(ng•h/mL)	$4610 \pm 3440$	$5460 \pm 1960$
$AUC_{\inf}$	(ng•h/mL)	$4630 \pm 3430$	$5580 \pm 1910$
$t_{1/2}^a$	(h)	$5.27 \pm 1.08$	$4.01 \pm 0.73$

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

The pharmacokinetic parameters of ABT-450 and ritonavir at the 200/100 mg dose were comparable to historical data.

### Total Radioactivity

Table 3 shows the summary of the pharmacokinetic parameters of total radioactivity in plasma following a 200/100 mg oral dose of [ $^{14}\text{C}$ ]ABT-450/ritonavir.

Subject	$T_{\max}$ (hr)	$C_{\max}$ (ng-eq/g)	$AUC_{0-t}$ (ng-eq•hr/g)	$AUC_{0-\infty}$ (ng-eq•hr/g)
201	4	1310	5042.5	5500.58
202	2	2020	9252	9601.25
203	6	89.3	440.9	-
204	2	1200	5104	5756.17
N	4	4	4	3
Mean	3.5	1154.8	4959.9	6952.7
SD	1.9	797.9	3599.6	2297.3
Min	2	89.3	440.9	5500.6
Median	3	1255.0	5073.3	5756.2
Max	6	2020.0	9252.0	9601.3
CV%	54.7	69.1	72.6	33.0
Harmonic Mean	2.8	301.0	1443.8	6526.3
Pseudo SD	1.4	1793.9	7229.3	1709.9
Geometric Mean	3.1	729.7	3201.0	6723.9
CV% Geometric Mean	58.6	254.7	228.4	31.7

- Subject 203  $AUC_{0-\infty}$  cannot be accurately calculated due to insufficient data points.

Table 4 shows the summary of the pharmacokinetic parameters of [ $^{14}\text{C}$ ]ABT-450/ritonavir and relative percent of metabolites in plasma.

Pharmacokinetic Parameters (units)		A-1043422	M2	M29	Total Radioactivity (Mean $\pm$ SD) (n=4)
$\lambda_z$	(1/hr)	0.29	0.48	0.18	
$T_{1/2\_}\lambda_z$	(hr)	2.36	1.46	3.92	
$T_{\max}$	(hr)	4	2	2	3.5 $\pm$ 1.9
$C_{\max}$	(ng-eq/g)	762.47	104.7	39.26	1154.8 $\pm$ 797.9
$AUC_{0-4}$	(ng-eq-hr/g)	4409.3	385.05	156.97	4959.9 $\pm$ 3599.6
$AUC_{0-\infty}$	(ng-eq-hr/g)	4681.72	391.25	174.71	6952.7 $\pm$ 2297.3 <sup>#</sup>
$AUC_{\text{extrap}}$	(%)	5.82	1.59	10.15	
% Total Drug ( $AUC_{0-\infty}$ )		67.3	5.6	2.5	
% Total Drug ( $AUC_{0-4}$ )		88.9	7.8	3.2	
% $C_{\max}$		-	13.7	5.2	

<sup>#</sup> - Subject 203 plasma radioactivity  $AUC_{0-\infty}$  was not included in the mean calculation.

### Recovery of Radioactivity in Urine and Feces

Fig 1 shows the cumulative percent of mean total radioactivity recovered in the urine and feces (linear scale).

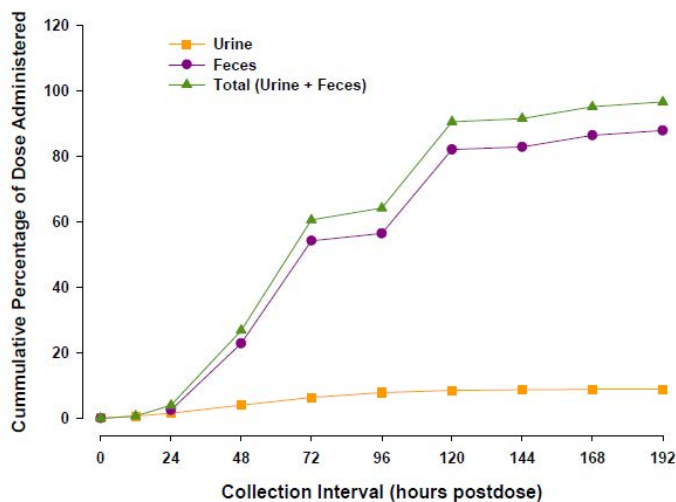


Table 5 shows the total percent recovery of radioactive dose for [ $^{14}\text{C}$ ] ABT-450 and metabolites in feces and urine.

	ABT-450	M29	M2	M6	M14	M17	M3/M18	M22/M23	M24	M13	Total Percent of Radioactive Dose Recovered
Feces <sup>a</sup>	1.10	59.9	8.55	0.78	1.12	1.08	7.47	2.78	3.32	1.67	87.8
Urine <sup>b</sup>	0.05	0.01	0.13	ND	ND	ND	ND	ND	ND	8.57	8.76
Total	1.15	59.9	8.68	0.78	1.12	1.08	7.47	2.78	3.32	10.2	96.5

ND = not detected

a. Sum of radioactivity dose recovery from 0 – 192 hours for pooled feces.

b. Sum of radioactivity dose recovery from 0 – 168 hours for pooled urine.

### Identification of ABT-450 Metabolites

Fig 2 shows the mean ABT-450 and metabolite concentration-time profiles in plasma (log-linear scale).

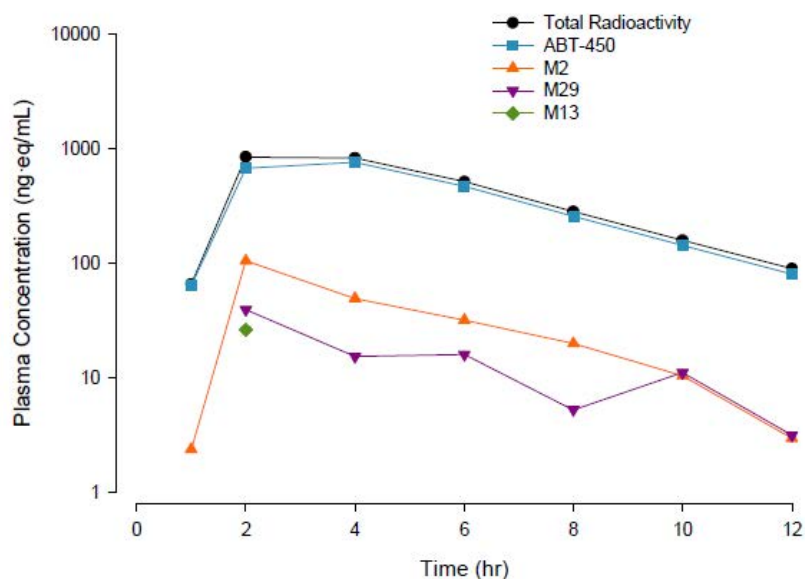
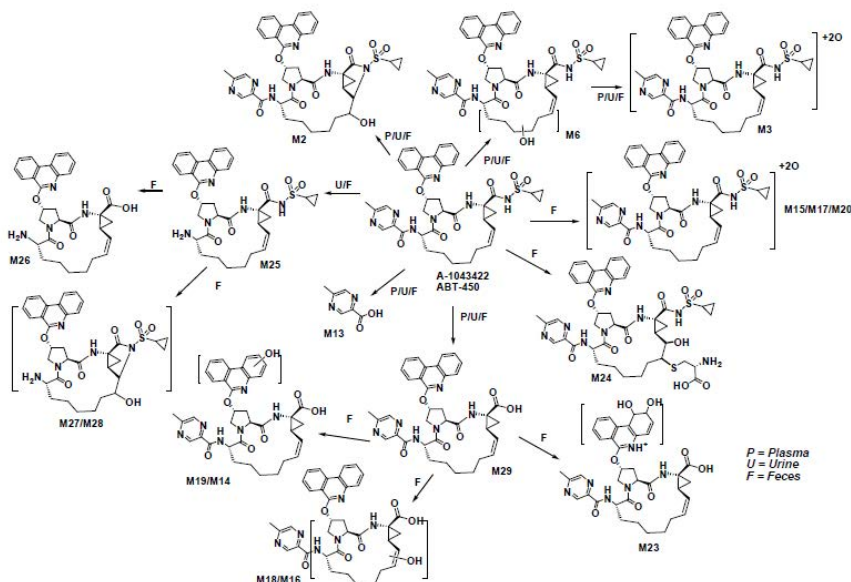


Table 6 shows the metabolites of ABT-450 (A-1043422) identified in plasma.

A-Compound	Identification
A-1043422	Parent
M2	Addition of one oxygen to the parent
M3	Addition of two oxygens to the parent
M6	Addition of one oxygen to the parent
M13	5-methylpyrazine-2-carboxylic acid
M29	hydrolytic product of A-1043422

Fig 3 shows the proposed metabolic pathway of ABT-450 in humans.



## Safety

No deaths, other serious adverse events, treatment emergent adverse events, or discontinuations due to adverse events occurred during the study. One treatment-emergent adverse event, constipation (reported by three subjects), was assessed by the Investigator as mild in severity, self-limited, and having a reasonable possibility of being related to the study drug.

## Conclusion

- Unchanged ABT-450 was the major component of drug-related radioactivity in plasma.
  - The plasma AUC of ABT-450 represented approximately 88.9 % of the drug related radioactivity in plasma.
- 87.8 % of the administered radioactive dose was recovered in feces and 8.76 % of the administered radioactive dose was recovered in the urine.
  - Unchanged ABT-450 recovered in the feces and urine represented 1.15 % of the administered radioactive dose.
- In plasma, 5 ABT-450 metabolites were identified, including M2, M29, and trace levels of M3, M13, and M6.
  - In urine, M13 was the major component (accounting for 8.57 % of the administered radioactive dose)
  - In feces, M29 was the major component (accounting for 59.9 % of the administered radioactive dose)

**Mass Balance Trial of ABT-267**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M12-186**

**Title**

**Absorption, Distribution, Metabolism and Excretion (ADME) Study of [<sup>14</sup>C] ABT-267 in Healthy Male Subjects Following a Single Oral Dose Administration**

**Trial Period**

October 11, 2012 through November 7, 2012  
Final report date: August 1, 2013

**Trial Objectives**

The objective of this study was to evaluate the absorption, distribution, metabolism and excretion of [14C] ABT-267 in healthy male subjects following a single oral dose.

**Trial Design**

Phase 1, single-dose, open-label, single center, ADME, mass balance study. Four adult male subjects (N = 4) were selected to participate in the study. On the morning of study Day 1, subjects received a single oral dose of [<sup>14</sup>C] ABT-267 under non-fasting conditions. The study drug, ABT-267 (25 mg active, 100 µCi [<sup>14</sup>C]) was administered as a single liquid filled capsule. ABT-267 was taken with approximately 240 mL, 30 minutes after starting a standardized breakfast. The radioactive dose level was approximately 100 µCi per subject.

**Rationale for Dose Selection**

The radioactive dose of 100 µCi was chosen so that the radiation burden for healthy volunteers remains below 2 mRem. An ABT-267 dose of 25 mg was used as 25 mg once daily dose was being tested in Phase 2 trials and was the dose selected for Phase 3 evaluation.

**Sample Collection**

**Plasma Samples**

Two blood samples (approximately 10 mL each) for ABT-267 assay, total radioactivity assay, metabolite identification, and metabolite profile were collected by venipuncture into potassium (K<sub>2</sub>) EDTA vacutainer collection tubes at 0 hour (pre-dose) and up to 312

hours after dosing of ABT-267 on study day 1 or until either 90 % of the radioactivity had been recovered or less than 1 % of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods.

For metabolite profiling, the plasma samples were pooled from 0-192 hours for the 4 subjects. Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

### Urine Samples

Subjects were instructed to collect their urine for pre-dose sampling starting approximately 12 hours prior to dosing, thereafter, urine was collected during the specified intervals following dosing. Urine was collected at the following time intervals: 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288, 288 to 312, 312 to 366, and 336-360 hours after dosing or until either 90 % of the administered radioactivity had been recovered or until less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods. To ensure complete urine collection, subjects were instructed to void into a container at the conclusion of each collection interval.

For metabolite profiling, three representative urine samples (12-24, 48-72, and 168-192 hours) across the entire time profile of urine were selected to evaluate the metabolite profile in urine. Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

### Fecal Samples

Fecal samples were collected pre-dose (upon check-in before dosing) and quantitatively for the following intervals after dosing: 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288 and 288 to 312, 312 to 336, and 336 to 360 hours or until either 90% of the administered radioactivity had been recovered or until less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods. All feces collected during a collection interval were kept frozen until the end of the interval.

For metabolite profiling, the fecal samples were pooled from 0-192 hours for the 4 subjects. Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

### Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-267 and metabolites were determined using non-compartmental methods.

## Results

### *Bioanalytical methods*

Table 1 provides the summary of the bioanalytical assay parameters.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-267	0.126-134	0.126	0.248, 3.97, 103	4.2 % to 5.1 %	-1.5 % to 4 %

For radioactivity analysis, all samples were analyzed by liquid scintillation counters. Each sample was homogenized or mixed before radioanalysis. If the results from same replicates (calculated as  $^{14}\text{C}$  dpm/g sample) differed by more than 10 % from the mean value and sample aliquots had radioactivity greater than 200 dpm, the sample was rehomogenized and reanalyzed. The scintillation counting data (cpm) was automatically corrected for counting efficiency using the external standardization technique.

### *Subject Disposition and Demographics*

4 subjects were enrolled in the trial and 4 subjects completed the trial. Table 2 shows the demographics of all subjects enrolled in the trial.

	Mean $\pm$ SD (N = 4)	Min – Max
Age (years)	37.8 $\pm$ 10.53	28.0 – 52.0
Weight (kg)	71.6 $\pm$ 5.85	65.9 – 79.6
Height (cm)	172 $\pm$ 4.02	167 – 176
Sex	4 Males (100%)	
Race	2 White (50%), 2 Black (50%)	

### *Pharmacokinetics*

#### *Pharmacokinetic Parameters of ABT-267*

Table 3 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-67.

Pharmacokinetic Parameters (Units)		ABT-267 25 mg Dose
T <sub>max</sub>	(h)	4.0 ± 0.00
C <sub>max</sub>	(ng/mL)	27.8 ± 6.08
AUC <sub>t</sub>	(ng•h/mL)	359 ± 63.9
AUC <sub>inf</sub>	(ng•h/mL)	366 ± 63.1
t <sub>1/2</sub> <sup>a</sup>	(h)	30.3 ± 9.80

a. Harmonic mean ± pseudo-standard deviation.

### Total Radioactivity

Table 4 shows the summary of the pharmacokinetic parameters of total radioactivity in plasma following a 25 mg (100 µCi) oral dose of [<sup>14</sup>C]ABT-267

Subject	T <sub>max</sub> (hr)	C <sub>max</sub> (ng-eq/g)	AUC <sub>0-192h</sub> (hr•ng-eq/g)	AUC <sub>0-∞</sub> (hr•ng-eq/g)
301	24	160	19168.1	38664.8
302	24	144	18290.4	32220.4
303	24	141	16922.4	27706.4
304	24	125	15262.6	23288.7
N	4	4	4	4
Mean	24	142.5	17410.9	30470.1
SD	0	14.3	1704.4	6568.3
Min	24	125	15262.6	23288.7
Median	24	142.5	17606.4	29963.4
Max	24	160	19168.1	38664.8
CV%	0	10.1	9.8	21.6
Harmonic Mean	24	141.4	17281.9	29426.6
Pseudo SD	0	14.5	1773.6	6425.4
Geometric Mean	24	142.0	17346.9	29942.9
CV% Geometric Mean	0	10.2	10.0	21.9

Table 5 shows the summary of the pharmacokinetic parameters of [<sup>14</sup>C]ABT-267 and relative percent of metabolites in plasma.



Pharmacokinetic Parameters (units) <sup>a</sup>		ABT-267	M5	M23	M25	M26	M29	M34	M36	M37	Total Radioactivity (Mean ± SD) <sup>b</sup>
T <sub>max</sub>	(h)	6.0	6.0	48.0	72	24.0	48.0	96.0	48.0	72.0	24.0 ± 0.0
C <sub>max</sub>	(ng q/g)	51.4	5.36	29.8	7.79	7.70	37.9	4.38	23.0	17.6	143 ± 14.3
AUC <sub>t</sub>	(ng eq•h/g)	1540	29.2	2610	682	680	5430	151	3730	2430	17400 ± 1700
AUC <sub>∞</sub>	(ng eq•h/g)	1830	--	3810	2180	1410	7310	--	7350	--	30500 ± 6570
% AUC <sub>ext</sub>		16.0	--	31.6	68.7	51.9	25.8	--	49.3	--	41.8 ± 6.80
% of Total Radioactivity (AUC <sub>t</sub> )		8.85	0.168	15.0	3.92	3.91	31.2	0.868	21.4	13.9	--
% of ABT-267 (AUC <sub>t</sub> )		--	1.90	169	44.3	44.2	353	9.81	242	158	--

a. Calculated from pooled samples (pooled for each time point across subjects so that one concentration time profile was obtained for parent and each metabolite in this study).

b. 4 subjects.

### Recovery of Radioactivity in Urine and Feces

Fig 1 shows the cumulative percent of mean total radioactivity recovered in the urine and feces (linear scale).

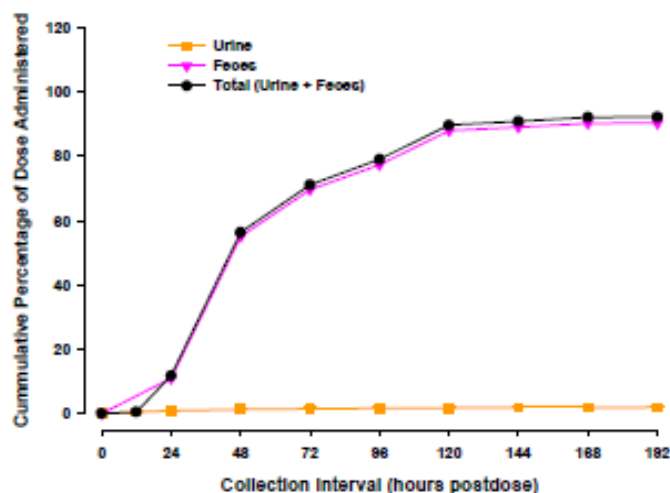


Table 6 shows the total percent recovery of radioactive dose for [<sup>14</sup>C] ABT-267 and metabolites in feces and urine.

	ABT-267	M2	M3	M5	M6	M9	Uf1-3 <sup>c</sup>	Mu1-5 <sup>d</sup>	Total Percent of Drug Recovered
Feces	87.8	0.2	0.6	0.2	0.2	0.7	0.6	ND	90.3 <sup>a</sup>
Urine	0.03	ND	ND	ND	ND	ND	ND	0.57	0.6 <sup>b</sup>
Total	87.83	0.2	0.6	0.2	0.2	0.7	0.6	0.57	90.9

ND = not detected

a. Sum of radioactivity dose recovery from 0 – 192 hours pooled feces.

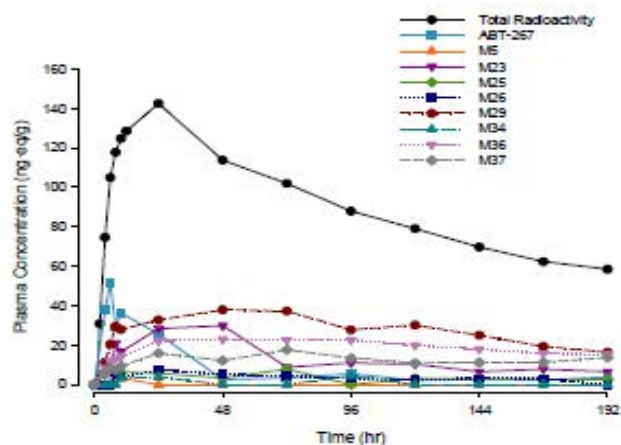
b. Sum of radioactivity dose recovery from 12 – 24 hours, 48 – 72 hours, and 168 – 192 hours pooled urine.

c. Uf = unknown metabolites in feces. Uf1-3 is the combined radioactivity dose recovery for Uf1, Uf2, and Uf3.

d. Mu = unknown metabolites in urine. MU1-5 is the combined radioactivity dose recovery for Mu1, Mu2, Mu3, Mu4, and Mu5.

### Identification of ABT-267 Metabolites

Fig 2 shows the mean ABT-267 and metabolite concentration-time profiles in plasma (linear scale).



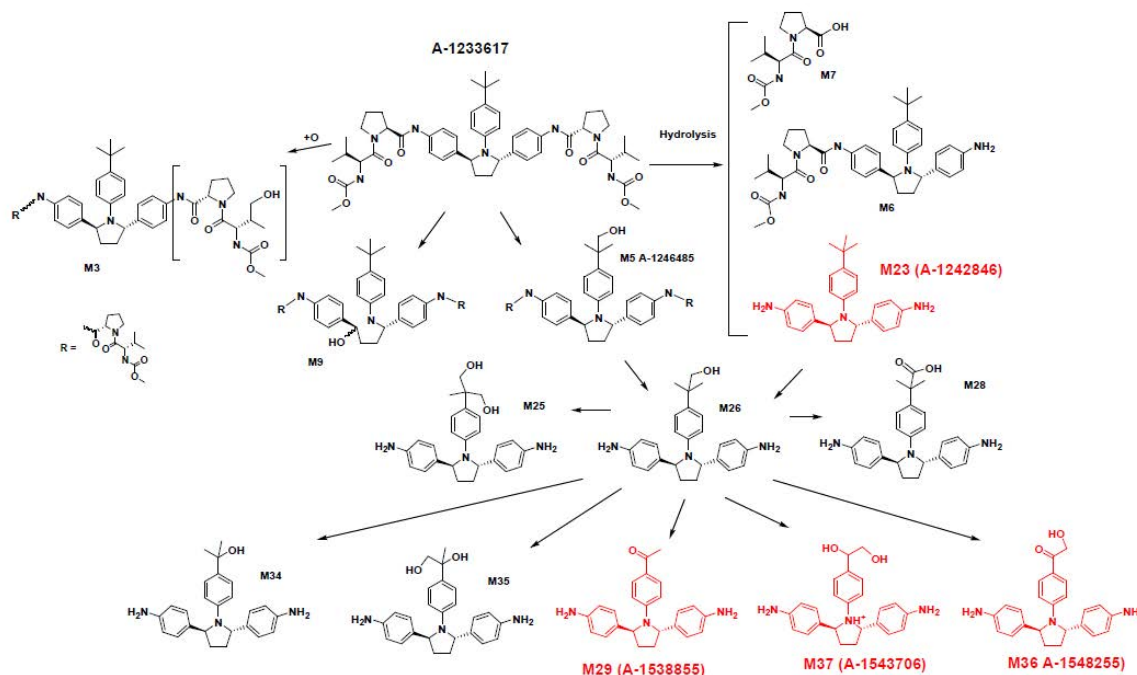
Determined from pooled samples (pooled for each time point across subjects so that one concentration time profile was obtained for parent and each metabolite in this study).

Table 7 shows the metabolites of ABT-450 (A-1043422) identified in plasma.

A-Compound	Identification
A-1233617	Parent
M5 <sup>a</sup>	hydroxylation metabolite of A-1233617
M6 <sup>a</sup>	partial hydrolysis product of A-1233617 (mono-aniline)
M7	A-1241411
M9 <sup>a</sup>	hydration metabolite of A-1233617
M23	A-1242846, di-aniline
M25	tert-butyl di-hydroxyl metabolite of M23
M26	tert-butyl hydroxyl metabolite of M23
M28	tert-butyl carboxylic acid metabolite of M23
M29	2,5-bis(4-aminophenyl)pyrrolidin-1-yl)phenyl)ethanone
M34	tert-butyl demethylation and hydroxylation metabolite of M23
M35	tert-butyl demethylation and di-hydroxylation metabolite of M23
M36	hydroxylated metabolite of M29
M37	di-hydroxylated 4-ethylphenyl-pyrrolidine-2,5-diyl-dianiline

a. Observed in fecal samples only.

Fig 3 shows the proposed metabolic pathway of ABT-267 in humans.



## Safety

No deaths, other serious adverse events, or discontinuations due to adverse events occurred during the study. The treatment-emergent adverse event of skin irritation was assessed by the investigator as mild in severity and having no reasonable probability of being related to the study drug.

## Conclusion

- Unchanged ABT-267 accounted for 8.85 % of the total radioactivity in plasma.
- 90.2 % of the administered radioactive dose was recovered in the feces with limited radioactivity (1.91 %) found in urine.
  - About 87.8 % of the administered radioactive dose was excreted in feces as unchanged ABT-267, indicating that ABT-267 was mainly eliminated as unchanged parent drug in the feces.
- In plasma, 13 metabolites were identified: M23, M29, M36, and M37 were present as major circulating metabolites.

**Mass Balance Trial of ABT-333**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M13-329**

**Title**

**Absorption, Distribution, Metabolism and Excretion (ADME) Study of [<sup>14</sup>C] ABT-333 in Healthy Male Subjects Following a Single Oral Dose Administration**

**Trial Period**

April 12, 2012 through May 20, 2012  
Final report date: May 28, 2013

**Trial Objectives**

The objective of this study was to evaluate the absorption, distribution, metabolism and excretion of [<sup>14</sup>C] ABT-333 in healthy male subjects following a single oral dose.

**Trial Design**

Phase 1, single-dose, open-label, single center, ADME, mass balance study. Four adult male subjects (N = 4) were selected to participate in the study. On the morning of study Day 1, subjects received a single oral dose of [<sup>14</sup>C] ABT-333 under non-fasting conditions. The study drug, ABT-333 (400 mg active, 100 µCi [<sup>14</sup>C]) was administered as a liquid suspension. The total amount of liquid taken, which included the [<sup>14</sup>C] ABT-333 oral suspension was approximately 240 mL, 30 minutes after starting a standardized breakfast. The radioactive dose level was approximately 100 µCi per subject.

**Rationale for Dose Selection**

The radioactive dose of 100 µCi was chosen so that the radiation burden for healthy Volunteers remains below 2 mRem. An ABT-333 dose of 400 mg was used as 400 mg twice daily dose was being evaluated in Phase 2 trials and an equivalent ABT-333 dose of 250 mg (in terms of ABT-333 systemic exposures) was evaluated in Phase 3 trials.

**Sample Collection**

**Plasma Samples**

Two blood samples (approximately 10 mL each) for total radioactivity assay, ABT-333 assay, M1 assay, other metabolic assay, and metabolite profile or identification were collected at 0 hour (pre-dose and up to 312 hours after dosing of ABT-333 on study day 1

or until either 90 % of the radioactivity had been recovered or less than 1 % of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods.

For metabolite profiling, the plasma samples were pooled from 0-12 hours for the 4 subjects. Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

### Urine Samples

Subjects were instructed to collect their urine for pre-dose sampling starting approximately 12 hours prior to dosing, thereafter, urine was collected during the specified intervals following dosing. Urine was collected at the following time intervals: 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288 and 288 to 312 hours after dosing or until either 90 % of the administered radioactivity had been recovered or until less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods. To ensure complete urine collection, subjects were instructed to void into a container at the conclusion of each collection interval.

For metabolite profiling, urine samples were pooled at the following time points for the 4 subjects: (0-12 and 12-24 hours). Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

### Fecal Samples

Fecal samples were collected pre-dose (upon check-in before dosing) and quantitatively for the following intervals after dosing: 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, 168 to 192, 192 to 216, 216 to 240, 240 to 264, 264 to 288 and 288 to 312 hours or until either 90% of the administered radioactivity had been recovered or until less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods. All feces collected during a collection interval were kept frozen until the end of the interval.

For metabolite profiling, fecal samples were pooled at the following time points for the 4 subjects: (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, and 192-216 hours). Samples at these time points from the 4 subjects were pooled to obtain one sample per time point and used for metabolite profiling.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-333 and metabolites were determined using non-compartmental methods.

## Results

### ***Bioanalytical methods***

Table 1 provides the summary of the bioanalytical assay parameters.

For radioactivity analysis, all samples were analyzed by liquid scintillation counters. Each sample was homogenized or mixed before radioanalysis. If the results from same replicates (calculated as 14C dpm/g sample) differed by more than 10 % from the mean value and sample aliquots had radioactivity greater than 200 dpm, the sample was rehomogenized and reanalyzed. The scintillation counting data (cpm) was automatically corrected for counting efficiency using the external standardization technique.

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-333	1.06-523	1.06	2.73,34.2, 427	3.8 % to 5.8 %	1.3 % to 2.7 %
ABT-333 M1	2.14-1060	2.14	5.46,68.2,853	3 % to 7.3 %	0.7 % to 4.6 %

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

4 subjects were enrolled in the trial and 4 subjects completed the trial. Table 2 shows the demographics of all subjects enrolled in the trial.

**Table 4. Demographic Summary for All Subjects**

	Mean $\pm$ SD (N = 4)	Minimum (Min) – Maximum (Max)
Age (years)	27.8 $\pm$ 4.03	23 – 32
Weight (kg)	82.2 $\pm$ 16.9	67.5 – 105
Height (cm)	184 $\pm$ 11.0	177 – 200
Sex	4 Males (100%)	
Race	3 White (75%), 1 Multi-race (25%)	

SD = Standard Deviation

### ***Pharmacokinetics***

#### ***Pharmacokinetic Parameters of ABT-333 and ABT-333 M1***

Table 3 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 and ABT-333 M1.

Pharmacokinetic Parameters (units)		ABT-333 400 mg dose	ABT-333 M1	Metabolite/Parent Ratio
T <sub>max</sub>	(h)	3.0 ± 1.2	4.0 ± 0.0	--
C <sub>max</sub>	(ng/mL)	658 ± 252	267 ± 116	0.400 ± 0.072
AUC <sub>t</sub>	(ng•h/mL)	6260 ± 1930	2230 ± 948	0.358 ± 0.058
AUC <sub>inf</sub>	(ng•h/mL)	6290 ± 1930	2280 ± 934	0.355 ± 0.054
t <sub>1/2</sub> <sup>a</sup>	(h)	8.35 ± 3.19	6.17 ± 1.34	--

a. Harmonic mean ± pseudo-standard deviation.

### Total Radioactivity

Table 4 shows the summary of the pharmacokinetic parameters of total radioactivity in plasma following a 400 mg oral dose of [<sup>14</sup>C]ABT-333

Parameter	101	102	103	104	Mean ± SD	CV%
T <sub>max</sub> (hours)	4	4	4	4	4 ± 0	0
C <sub>max</sub> (ng-eq/g)	1150	1200	2120	731	1300 ± 586	45
AUC <sub>0-last</sub> (ng-eq•hr/g)	8332	7809	12225	4640	8251 ± 3111	37.7
AUC <sub>0-∞</sub> (ng-eq•hr/g)	9769	9733	14338	5996	9959 ± 3414	34.3
% AUC <sub>ext</sub>	14.7	19.8	14.7	22.6	18.0 ± 3.9	21.8

Table 5 shows the summary of the pharmacokinetic parameters of [<sup>14</sup>C]ABT-333 and relative percent of metabolites in plasma.

Pharmacokinetic Parameters (units) <sup>a</sup>		A-998821	M1 <sup>b</sup>	M2	M3	M4	M5 <sup>c</sup>	M6	M11	U1	Total Radioactivity (Mean ± SD) <sup>d</sup>
T <sub>max</sub>	(h)	2.0	4.0	4.0	4.0	2.0	4.0	4.0	6.0	6.0	4.0 ± 0.0
C <sub>max</sub>	(ng-eq/g)	710	286	110	59.7	33.7	59.7	69.1	22.7	59.1	1300 ± 586
AUC <sub>t</sub>	(ng-eq•hr/g)	4890	1880	392	244	165	140	210	22.7	194	8250 ± 3110
AUC <sub>∞</sub>	(ng-eq•hr/g)	5950	2220	--	--	--	--	--	--	--	9960 ± 3410
% AUC <sub>ext</sub>		18	17	46	--	66	--	--	--	--	18.0 ± 3.92
t <sub>1/2</sub>	(h)	4.42	3.88	--	--	--	--	--	--	--	4.10 ± 0.28 <sup>e</sup>
% of Total Drug (AUC <sub>∞</sub> )		59.7	22.3	--	--	--	--	--	--	--	--
% of Total Drug (AUC <sub>t</sub> )		59.3	22.8	4.75	2.96	2.00	1.70	2.55	0.28	2.35	--
% of A-998821 (C <sub>max</sub> )		--	40.3	15.5	8.41	4.75	8.41	9.73	3.20	5.23	--

a. Calculated from pooled samples

b. M1 is A-1041392

c. M5 is A-1039710

d. 4 subjects

e. Harmonic mean ± pseudo-standard deviation

## Recovery of Radioactivity in Urine and Feces

Fig 1 shows the cumulative percent of mean total radioactivity recovered in the urine and feces (linear scale).

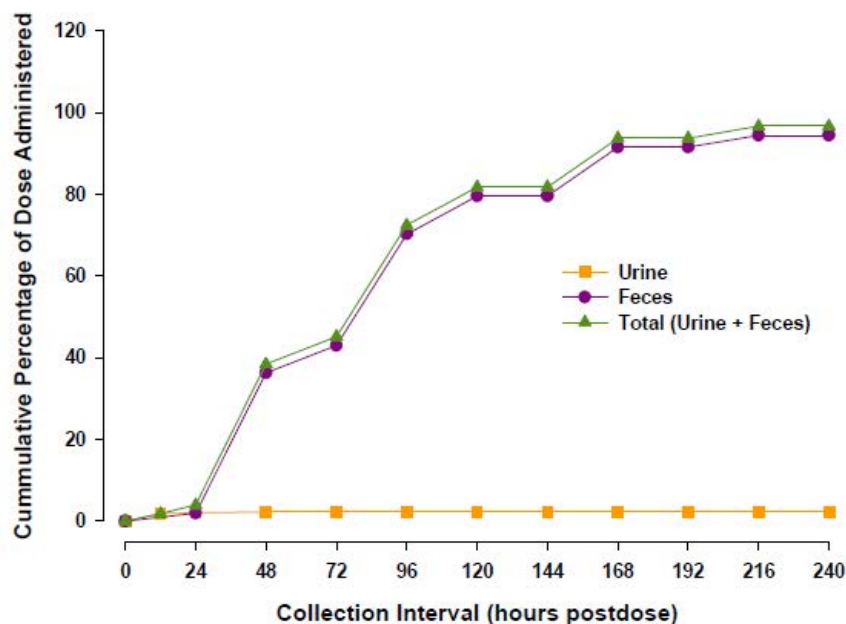


Table 6 shows the total percent recovery of radioactive dose for [ $^{14}\text{C}$ ] ABT-333 and metabolites in feces and urine.

	ABT-333	M1 <sup>c</sup>	M2	M3	M4	M5 <sup>d</sup>	M6	M7	M8	M9	M10	M11	Unknowns	Total Percent of Drug Recovered
Feces <sup>a</sup>	26.2	31.52	15.17	ND	ND	11.13	ND	ND	2.05	4.91	3.37	ND	ND	94.35
Urine <sup>b</sup>	0.03	0.85	0.30	0.19	0.12	0.12	0.02	0.38	ND	ND	ND	0.03	0.01	2.05
Total	26.23	32.37	15.47	0.19	0.12	11.25	0.02	0.38	2.05	4.91	3.37	0.03	0.01	96.40

ND = not detected

a. Sum of radioactivity dose recovery from 0-216 hours for pooled feces.

b. Sum of radioactivity dose recovery from 0-24 hours for pooled urine.

c. M1 is A-1041392.

d. M5 is A-1039710.

## Identification of ABT-333 Metabolites

Fig 2 shows the mean ABT-333 and metabolite concentration-time profiles in plasma (linear scale).



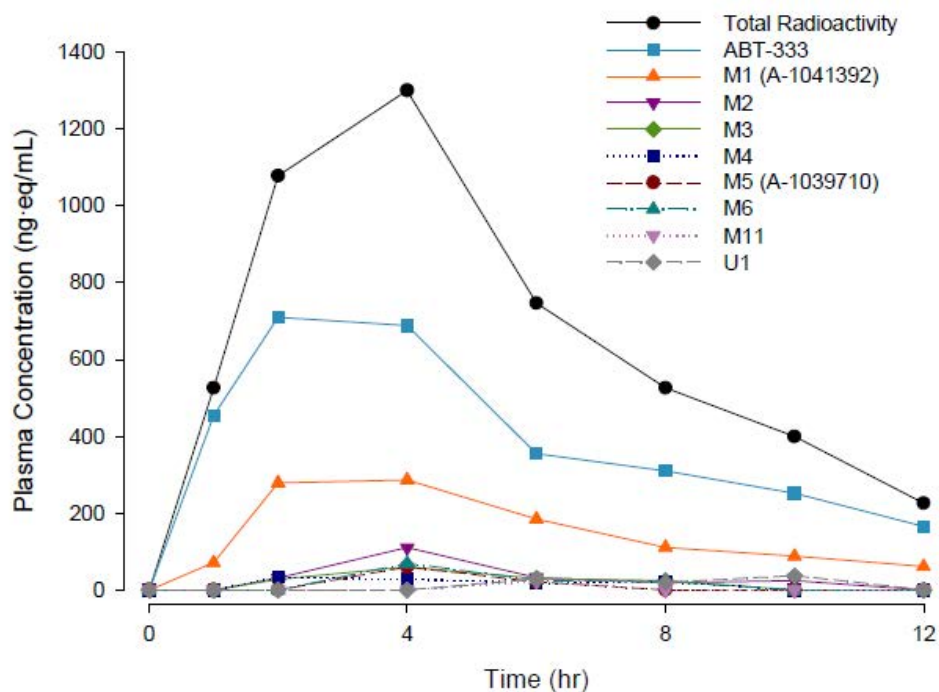
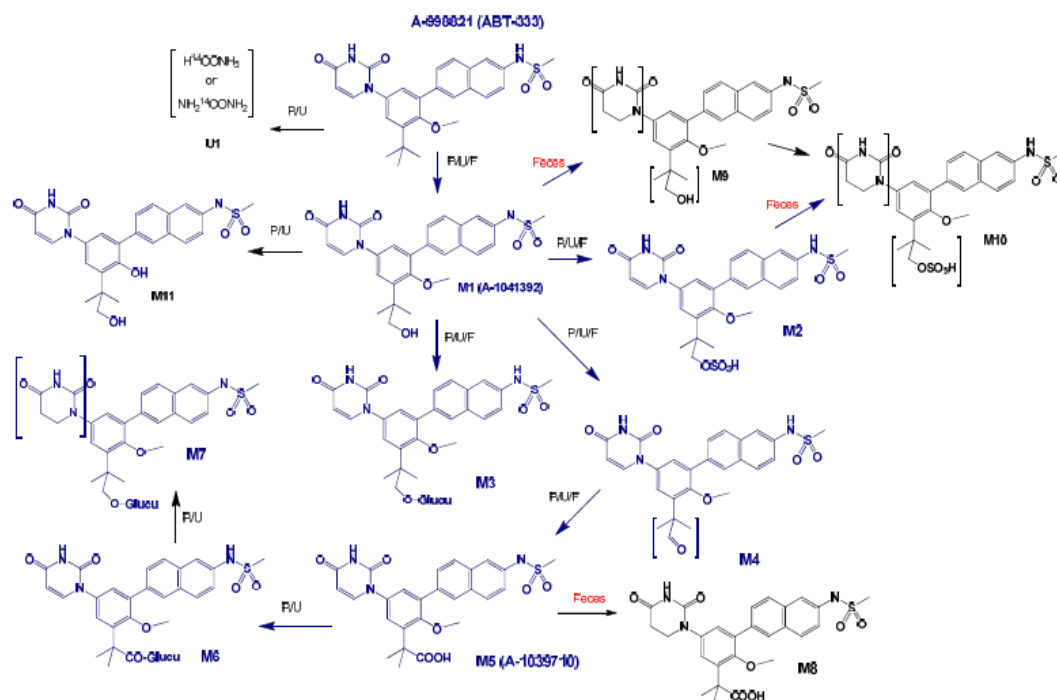


Table 7 shows the metabolites of ABT-333 identified in plasma.

A-Compound	Identification
A-998821 (ABT-333)	Parent
M1	Addition of one oxygen to the parent
M2	Sulfate conjugate of M1
M3	Glucuronide conjugate of M1
M4	Dehydrogenation product of M1
M5	Acid metabolite at the <i>tert</i> -butyl group
M6	Glucuronide conjugate of M5
M7	Dihydro metabolite of M6
M8 <sup>a</sup>	Reduced metabolite of M5
M9 <sup>a</sup>	Reduced metabolite of M9
M10 <sup>a</sup>	Reduced metabolite of M2
M11	Desmethyl metabolite of M1
Unknown	Degradation product of the pyrimidine-2,4(1H,3H)-dione moiety

Fig 3 shows the proposed metabolic pathway of ABT-333 in humans.



## Safety

No deaths, other serious adverse events, or discontinuations due to adverse events occurred during the study. One treatment emergent adverse event, headache, was assessed by the investigator as having a reasonable possibility of being related to the study drug and was mild in severity.

## Conclusion

- Unchanged ABT-333 accounted for approximately 60 % of the two total radioactivities in plasma.
- Seven metabolites (M1, M2, M3, M4, M5, M6, and M11) were observed in plasma
  - AUC<sub>0-∞</sub> of M1 was about 22 % of total drug related material in plasma (or 37 % of the unchanged parent drug).
- 94.4 % of the administered radioactive dose was recovered in the feces with limited radioactivity (2.02%) found in urine.
  - M1 was the major component in the feces with a mean of ~32 % of the administered radioactive dose, followed by unchanged parent drug (26 %), M2 (15 %), and M5 (11 %).
  - M1 was the major component in the urine (0.85 %).

HEPATIC IMPAIRMENT STUDY REVIEW																								
Study #	Protocol M12-215	Study Period	06/29/2011-10/05/2012	Reviewer: Islam Younis																				
Title	Evaluation of the Pharmacokinetics and Safety of Co-administered ABT-267, ABT-333, and ABT-450 plus Ritonavir (ABT-450/r) as a Single Dose in Subjects with Normal Hepatic Function and in Subjects with Mild, Moderate, and Severe Hepatic Impairment																							
<b>STUDY DESIGN</b>																								
A Phase 1, multicenter, single-dose, non-fasting, open-label study. This study was conducted in a sequential manner where subjects with normal and mildly impaired liver function were first enrolled followed by subjects with moderate liver impairment and lastly subjects with severe liver impairment. Cohorts were enrolled after evaluating the available pharmacokinetics and safety in the previous cohort.																								
Treatments	1. ABT-450 200 mg tablet. 2. ABT-267 25 mg tablet. 3. ABT-333 400 mg tablet. 4. Ritonavir 100 mg capsule																							
Dose Selection Rationale	Doses of ABT-450 and ABT-333 used are different from the label recommended doses of 150 mg QD and 250 mg BID for ABT-450 and ABT-333, respectively. No rationale was provided in the study report for using these doses.																							
Administration	<input type="checkbox"/> Fasted <input checked="" type="checkbox"/> Fed Meals with approximately 1900 Kcal. The composition (protein, fat, carbohydrate, and total calories) of the meals was determined by a dietician.																							
Formulation	<table border="1"> <thead> <tr> <th>Drug</th> <th>ABT-450</th> <th>ABT-267</th> <th>ABT-333</th> <th>Ritonavir</th> </tr> </thead> <tbody> <tr> <td>Dosage Form/Strength</td> <td>Tablet (25 mg)</td> <td>Table (50 mg)</td> <td>Capsule (100 mg)</td> <td>Tablet (400 mg)</td> </tr> <tr> <td>Bulk Product Lot Number</td> <td>10-003507</td> <td>10-003611</td> <td>10-002930 and 11-003207</td> <td>11-000511</td> </tr> <tr> <td>Finishing Lot Number</td> <td>11-001511</td> <td>11-001510</td> <td>11-001513 and 12-000141</td> <td>11-001512</td> </tr> </tbody> </table>				Drug	ABT-450	ABT-267	ABT-333	Ritonavir	Dosage Form/Strength	Tablet (25 mg)	Table (50 mg)	Capsule (100 mg)	Tablet (400 mg)	Bulk Product Lot Number	10-003507	10-003611	10-002930 and 11-003207	11-000511	Finishing Lot Number	11-001511	11-001510	11-001513 and 12-000141	11-001512
Drug	ABT-450	ABT-267	ABT-333	Ritonavir																				
Dosage Form/Strength	Tablet (25 mg)	Table (50 mg)	Capsule (100 mg)	Tablet (400 mg)																				
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Finishing Lot Number	11-001511	11-001510	11-001513 and 12-000141	11-001512																				
Interfering Substances Excluded	Grapefruit, star fruit, Seville oranges, or products containing any of these Alcohol Caffeine																							
Groups matching	Subjects with mild hepatic impairment were matched to subjects with normal hepatic function in terms of age, weight, sex, and race. Subjects with moderate and severe hepatic impairment were similar to subjects with normal hepatic function in terms of age, weight, and race though not matched. The subjects with moderate and severe hepatic impairment were all males.																							
Hepatic Function Assessment	Hepatic function was assessed using Child-Pugh Score. Scores were assessed at baseline and at screening.																							
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 of AUC and C <sub>max</sub> , and V <sub>β</sub> /F, as well as T <sub>max</sub> and β. Unbound C <sub>max</sub> and AUC were also determined.																							
Is the study design acceptable? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No																								
<b>STUDY CONDUCT</b>																								
<b>Bioanalytical Method:</b>																								
<table border="1"> <thead> <tr> <th>Method Type</th> <th>LC-MS/MS</th> <th>Matrix</th> <th>Plasma</th> </tr> </thead> <tbody> <tr> <td>Analytes</td> <td>ABT-450</td> <td>ABT-267</td> <td>ABT-333</td> </tr> </tbody> </table>					Method Type	LC-MS/MS	Matrix	Plasma	Analytes	ABT-450	ABT-267	ABT-333												
Method Type	LC-MS/MS	Matrix	Plasma																					
Analytes	ABT-450	ABT-267	ABT-333																					

Range (ng/mL)			0.492 - 251	0.126-132	1.01 - 518
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 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
Inspection	Will the bioanalytical site be inspected	<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

## STUDY RESULTS

### Study Population

Randomized	24
Treated	24
Completed	24
Discontinued Due to AE	0
PK Population/Safety Population	24
Age [Mean (range)]	52.3 [40-64]
Male/Female	18/6
Race (Caucasian/Black/Asian/Other)	12/2/0/1

### Distribution of Child-Pugh Scores

Score	5	6	7	8	9	10	11	12	13	14	15
N-Screening	4	2	1	4	1	2	2	1	0	0	0
N-Baseline	4	2	0	4	2	2	2	1	0	0	0

### Etiology of Liver Disease

	HCV	Alcohol Cirrhosis	Cirrhosis	Other	None
Mild	3	1	0	1-enlarged liver	1
Moderate	1	5	0	0	0
Severe	0	4	1	0	0

### Notes:

- No females were enrolled in the moderate and severe hepatic impairment groups.
- None of the subjects switched categories between screening (Day -28) and baseline (Day -1), although 2 subjects in moderate impairment category had different scores at screening and baseline.
- All subjects in moderate group had either ascites or encephalopathy or both which can be an indication of decompensated liver.

**Pharmacokinetics:** Table of AUC and Cmax LS means ratio and 90%CI for the hepatic impairment groups relative to the control group.

Drug	Group	Total Concentrations		Unbound Fraction	
		Cmax	AUC	Cmax	AUC
ABT-450	Mild	0.519 (0.213 – 1.266)	0.708 (0.273 – 1.839)	0.362 (0.143 – 0.920)	0.494 (0.189 – 1.297)
	Moderate	1.261 (0.511 – 3.111)	1.616 (0.615 – 4.244)	0.845 (0.329 – 2.171)	1.083 (0.408 – 2.873)

	<b>Severe</b>	4.247 (1.660 – 10.868)	<b>10.456</b> ( 3.828 – 28.559)	4.560 (1.709 – 12.17)	<b>11.228</b> ( 4.068 – 30.988)
<b>Ritonavir</b>	<b>Mild</b>	0.596(0.328 – 1.083)	<b>0.659</b> (0.356 – 1.218)	0.469(0.260 – 0.848)	<b>0.520</b> (0.282 – 0.959)
	<b>Moderate</b>	0.671(0.367 – 1.227)	<b>0.700</b> (0.378 – 1.294)	0.591(0.325 – 1.075)	<b>0.642</b> (0.348 – 1.183)
	<b>Severe</b>	0.647 (0.345 – 1.212)	<b>1.129</b> (0.591 – 2.156)	0.708 (0.380 – 1.320)	<b>1.223</b> (0.642 – 2.329)
<b>ABT-267</b>	<b>Mild</b>	1.002 (0.769 – 1.306)	<b>0.921</b> (0.669 – 1.269)	1.261 (0.800 – 1.987)	<b>1.246</b> (0.775 – 2.004)
	<b>Moderate</b>	0.708 (0.542 – 0.926)	<b>0.699</b> (0.505 – 0.966)	0.772 (0.490 – 1.217)	<b>0.783</b> (0.487 – 1.259)
	<b>Severe</b>	0.317 (0.240 – 0.419)	<b>0.456</b> (0.325 – 0.638)	0.807 (0.512 – 1.271)	<b>1.193</b> (0.742 – 1.918)
<b>ABT-333</b>	<b>Mild</b>	1.241 (0.795 - 1.937)	<b>1.172</b> (0.732 - 1.877)	0.827 (0.385 – 1.776)	<b>0.740</b> (0.367 – 1.492)
	<b>Moderate</b>	0.608 (0.388 - 0.955)	<b>0.836</b> (0.519 - 1.346)	0.429 (0.210 – 0.880)	<b>0.564</b> (0.290 – 1.096)
	<b>Severe</b>	1.336 (0.836 - 2.136)	<b>4.250</b> (2.589 - 6.978)	1.187 (0.579 – 2.431)	<b>3.520</b> (1.831 – 6.768)

Percent mean fraction unbound is shown in the table below.

<b>Hepatic Function Group</b>	<b>Normal</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>ABT-450</b>	1.13	0.779	0.754	1.19
<b>Ritonavir</b>	0.634	0.524	0.599	0.687
<b>ABT-267</b>	0.021	0.023	0.020	0.047
<b>ABT-333</b>	0.612	0.293	0.281	0.423

**Notes:**

Variability in AUC was high (CV% >100%) for ABT-450 in all subjects except for ABT-450 in severe hepatic impairment group (~50%). Ritonavir, ABT-267, aBT-333 AUC variability was ~35-50%.

- Were there any outliers or excluded data from analysis? ☐ Yes ☒ No ☐ NA
- Are the study results acceptable? ☒ Yes ☐ No

**Safety**

Was there any death or serious adverse events? ☐ Yes ☒ No

Two subjects experienced mild treatment-emergent adverse events

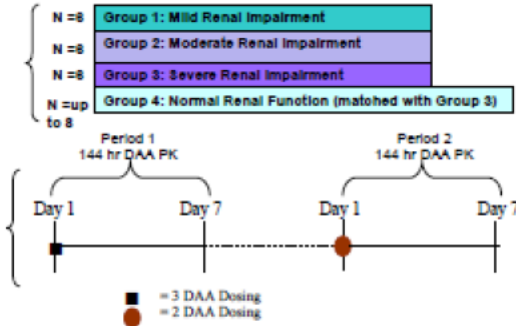
**CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS**

**CONCLUSIONS**

Based on the available exposure data:

1. No dose adjustment is necessary in subjects with mild and moderate hepatic impairment.
2. The combination should be contraindicated in patients with severe hepatic impairment due to the large increase in ABT-450 exposure. ABT-450 exposure at the 200 mg dose was associated with higher incidence of ALT and bilirubin elevations compared to the 150 mg dose. The expected average exposure of ABT-450 in patients with severe hepatic impairment is 10 times that of patients with normal renal function and is expected to produce more significant increase in ALT and bilirubin; therefore, it is more advisable to contraindicate the combination in this patient group given the potential greater risk.



RENAL IMPAIRMENT STUDY REVIEW																				
Study #	Protocol M12-193	Study Period	12/14/2012 -10/04/2013	Reviewer: Islam Younis																
Title	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. 3. ABT-333: 400 mg tablet.																			
Dose Selection Rationale	ABT-333 dose (400 mg QD) used was lower than the label recommended doses of 250 BID. No rationale was provided in the study report. 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><tr><td>Drug</td><td>ABT-450/r</td><td>ABT-267</td><td>ABT-333</td></tr><tr><td>Dosage Form/ Strength</td><td>Tablet (75/50 mg)</td><td>Table (25 mg)</td><td>Tablet (400 mg)</td></tr><tr><td>Bulk Product Lot Number</td><td>11-002033 11-</td><td>002720 12-</td><td>002722</td></tr><tr><td>Finishing Lot Number</td><td>12-004915</td><td>12-004917</td><td>12-007176</td></tr></table>				Drug	ABT-450/r	ABT-267	ABT-333	Dosage Form/ Strength	Tablet (75/50 mg)	Table (25 mg)	Tablet (400 mg)	Bulk Product Lot Number	11-002033 11-	002720 12-	002722	Finishing Lot Number	12-004915	12-004917	12-007176
Drug	ABT-450/r	ABT-267	ABT-333																	
Dosage Form/ Strength	Tablet (75/50 mg)	Table (25 mg)	Tablet (400 mg)																	
Bulk Product Lot Number	11-002033 11-	002720 12-	002722																	
Finishing Lot Number	12-004915	12-004917	12-007176																	
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			
<b>STUDY CONDUCT</b>			
<b>Bioanalytical Method:</b>			
	Method Type	LC-MS/MS	Matrix
	Analytes	ABT-450	ABT-267
	Range	0.6 - 431	0.4 - 299
	Plasma	ABT-333	
	Range	0.6 - 431	4.4 - 3150

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 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <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.

<b>STUDY RESULTS</b>	
<b>Study Population</b>	
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 Cmax LS means ratio and 90%CI for the renal impairment groups relative to the control group in part 1 of the study (3DAAs) 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)	1.002 (0.656 – 1.532)	1.004 (0.495 – 2.037)	1.005 (0.401 – 2.521)
AUC <sub>∞</sub> (ng•h/mL)	1.188 (0.855 – 1.651)	1.333 (0.770 – 2.305)	1.453 (0.712 – 2.962)
<b>Ritonavir</b>			
C <sub>max</sub> (ng/mL)	1.262 (1.003 – 1.588)	1.475 (1.006 – 2.163)	1.657 (1.007 – 2.726)
AUC <sub>∞</sub> (ng•h/mL)	1.422 (1.122 – 1.801)	1.798 (1.212 – 2.666)	2.144 (1.284 – 3.579)
<b>ABT-267</b>			
C <sub>max</sub> (ng/mL)	0.925 (0.836 – 1.024)	0.878 (0.742 – 1.040)	0.845 (0.678 – 1.052)
AUC <sub>∞</sub> (ng•h/mL)	1.002 (0.885 – 1.133)	1.003 (0.816 – 1.232)	1.004 (0.768 – 1.312)
<b>ABT-333</b>			
C <sub>max</sub> (ng/mL)	1.054 (0.881 – 1.260)	1.091 (0.810 – 1.470)	1.120 (0.760 – 1.651)
AUC <sub>∞</sub> (ng•h/mL)	1.206 (0.969 – 1.501)	1.367 (0.949 – 1.967)	1.501 (0.935 – 2.410)
<b>ABT-333 MI Metabolite</b>			
C <sub>max</sub> (ng/mL)	0.729 (0.558 – 0.950)	0.590 (0.379 – 0.919)	0.503 (0.283 – 0.896)
AUC <sub>∞</sub> (ng•h/mL)	0.936 (0.739 – 1.187)	0.896 (0.604 – 1.330)	0.867 (0.519 – 1.449)

Percent mean fraction unbound is shown in the table below (Period 1 and 2 combined).

Renal Function Group	Normal	Mild	Moderate	Severe
<b>ABT-450</b>	0.777	0.782	0.891	0.859
<b>Ritonavir</b>	0.535	0.496	0.557	0.553
<b>ABT-267</b>	0.014	0.016	0.019	0.014
<b>ABT-333</b>	5.64	5.23	5.96	6.23

**Notes:**

Variability in AUC was high (CV% 64-93%) for ABT-450 in all subjects and was higher in moderate and severe groups compared to normal and mild groups. Ritonavir and ABT-333 AUC variability was ~29-64%. ABT-267 variability was 12%-36%

- Were there any outliers or excluded data from analysis? ☐ Yes ☒ No ☐ NA
- Are the study results acceptable? ☒ Yes ☐ No

**Safety**

Was there any death or serious adverse events? ☐ Yes ☒ No

Only two subjects in the moderate group experienced treatment-emergent AEs in period 1 and were considered mild to moderate in nature.

**CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS**

**CONCLUSIONS**

Based on the available exposure data; no dose adjustment is necessary in subjects with mild and moderate hepatic impairment.



## RACE EFFECT STUDY REVIEW

<b>Study #</b>	Protocol M12-221	<b>Study Period</b>	05/23/2011 – 09/07/2011	Reviewer: Islam Younis
<b>Title</b>	Assessment of Multiple-Dose Pharmacokinetics and Safety of the Co-administration of ABT-267 plus ABT 450 with Ritonavir (ABT-450/r) and ABT-333 in Healthy Han Chinese, Japanese, and Caucasian Subjects			

### STUDY DESIGN

A Phase 1, single-center, multiple-dose, open-label, three-arms study

**Table 2. Dosing Scheme**

Arm <sup>a</sup>	Cohort <sup>a</sup>	Subject Numbers	Treatment
1	1	1101, 1102, 1103, 1105, 1110, 1112 (Han-Chinese), 1201, 1202, 1204, 1205, 1207, 1208 (Japanese), and 1301, 1303, 1308, 1309, 1311, 1312 (Caucasian)	ABT-267 25 mg QD (b) (4) + ABT-450/r 250/100 mg QD
1	2	1104, 1106, 1107, 1108, 1109, 1111 (Han-Chinese), 1203, 1206, 1209, 1210, 1211, 1212 (Japanese), and 1302, 1304, 1305, 1306, 1307, 1310 (Caucasian)	ABT-267 25 mg QD (b) (4) + ABT-450/r 250/100 mg QD
2	1	2102, 2103, 2104, 2106, 2110, 2112 (Han-Chinese), 2201, 2205, 2206, 2208, 2211, 2212 (Japanese), and 2301, 2302, 2305, 2306, 2308, 2310 (Caucasian)	ABT-267 25 mg QD (b) (4) + ABT-450/r 200/100 mg QD
2	2	2101, 2105, 2107, 2108, 2109, 2111 (Han-Chinese), 2202, 2203, 2204, 2207, 2209, 2210 (Japanese), and 2303, 2304, 2307, 2309, 2311, 2312 (Caucasian)	ABT-267 25 mg QD (b) (4) + ABT-450/r 200/100 mg QD
3	--	3101, 3102, 3103, 3104, 3105, 3106 (Han-Chinese), 3201, 3202, 3203, 324, 3205, 3206 (Japanese), and 3301, 3302, 3303, 3304, 3305, 3306 (Caucasian)	ABT-267 25 mg QD (b) (4) + ABT-450/r 150/100 mg QD + ABT-333 400 mg BID

**This review will focus on arm 3 as it is the most relevant to the current application**

Treatments	All drugs were co-administered for 21 days. ABT-267 and ABT-450/r were dosed QD and ABT-333 was dosed BID (see study design for doses).
Dose Selection Rationale	ABT-333 dose used was higher than the label recommended doses of 250 mg BID. No rationale was provided in the study report. ABT-450 and ABT-267 doses are the recommended daily dose.
Administration	<input type="checkbox"/> Fasted <input checked="" type="checkbox"/> Fed All doses of study drug were taken orally with approximately 240 mL of water approximately 30 minutes after starting a standardized breakfast (QD and BID) or evening snack (BID only). Standardized diet, providing approximately 30% of the daily calories from fat and up to 50% of the daily calories from carbohydrates and approximately 20% of the daily calories from protein (approximately 2000 to 2200 calories/day).

Formulation	Drug	ABT-450/r	Ritonavir	ABT-267	ABT-333																																																																																																																	
	Dosage Form/ Strength	Tablet 50 mg	Capsule 100 mg	(b) (4) Tablet 25 mg	Tablet 400 mg																																																																																																																	
	Bulk Product Lot Number	10-003507	10-002930	10-004949	11-000511																																																																																																																	
	Finishing Lot Number	11-001500	11-001502	11-001499	11-001501																																																																																																																	
Interfering Substances Excluded	Grapefruit, star fruit, Seville oranges, or products containing any of these Alcohol Caffeine																																																																																																																					
Sampling Times	<table border="1"> <thead> <tr> <th rowspan="2">Activity</th> <th rowspan="2">SCR<sup>a</sup></th> <th colspan="28">Study Day</th> </tr> <tr> <th>-1</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th><th>9</th><th>10</th><th>11</th><th>12</th><th>13</th><th>14</th><th>15</th><th>16</th><th>17</th><th>18</th><th>19</th><th>20</th><th>21</th><th>22</th><th>23</th><th>24<sup>f</sup></th><th>30<sup>g</sup></th> </tr> </thead> <tbody> <tr> <td>Blood Samples for Drug Assay – Intensive Sampling<sup>c</sup></td> <td></td> <td></td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>X</td><td></td> </tr> <tr> <td>Blood Samples for Drug Assay – Trough Concentrations<sup>c</sup></td> <td></td> <td></td><td></td><td></td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td>X<sup>k</sup></td> </tr> </tbody> </table>					Activity	SCR <sup>a</sup>	Study Day																												-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24 <sup>f</sup>	30 <sup>g</sup>	Blood Samples for Drug Assay – Intensive Sampling <sup>c</sup>			X	X																				X	X	X	X		Blood Samples for Drug Assay – Trough Concentrations <sup>c</sup>						X		X		X		X		X		X		X		X	X	X					X <sup>k</sup>
Activity	SCR <sup>a</sup>	Study Day																																																																																																																				
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24 <sup>f</sup>	30 <sup>g</sup>																																																																																											
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PK Parameters	AUC, AUC <sub>t</sub> , C <sub>max</sub> , T <sub>max</sub> , t <sub>1/2</sub> , CL/F, V <sub>B</sub> /F.																																																																																																																					
PK Analysis	Non-Compartmental PK analysis.																																																																																																																					
Statistical Analysis	Arm 3: A repeated measures analysis was to be used to assess the steady-state of ABT-267, ABT-450, ritonavir, ABT-333, and ABT-333 M1 Ctrough (prior to the morning dose) utilizing corresponding data from Study Days 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 19, 20, 21, and 22. The model had day as a fixed effect and subject as a random effect.																																																																																																																					
Is the study design acceptable? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No																																																																																																																						
<b>STUDY CONDUCT</b>																																																																																																																						
<b>Bioanalytical Method:</b>																																																																																																																						
		Method Type	LC-MS/MS	Matrix	Plasma																																																																																																																	
		Analytes	ABT-450	ABT-267	ABT-333																																																																																																																	
		Range (ng/mL)	0.49 - 251	0.132 - 132	1.04 - 530																																																																																																																	
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 <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No																																																																																																																	
Inspection	Will the bioanalytical site be inspected				<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No																																																																																																																	
<b>Protocol Deviations</b>																																																																																																																						
<ul style="list-style-type: none"> <li>Are there any protocol deviations listed in the study report? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</li> <li>Do any of the listed deviations affect the integrity of the study? <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> NA</li> </ul>																																																																																																																						
<b>STUDY RESULTS</b>																																																																																																																						
<b>Study Population (arm 3)</b>																																																																																																																						
		Randomized	18																																																																																																																			
		Treated	18																																																																																																																			
		Completed	18																																																																																																																			
		Discontinued Due to AE	0																																																																																																																			
		PK Population/Safety Population	18/18																																																																																																																			

Age [Mean (range)]	35.2 [21-55]
Male/Female	1/17
Race (Caucasian/Asian)	6/12
Ethnicity (Hispanic/ Han Chinese/Japanese/None)	2/6/6/4

**Pharmacokinetics:** In general exposure of all 3 DAAs was higher in Chinese and Japanese subjects relative to Caucasians. The effect is more pronounced for ABT-450. Study Day 21 ratios (90% confidence intervals) are listed in the Table below. Note AUCt is AUC<sub>24</sub> for all compounds except ABT-333 where it is AUC<sub>12</sub>.

	Chinese/Caucasian		Japanese/Caucasian	
	Cmax	AUCt	Cmax	AUCt
ABT-450	3.17 (1.54 – 6.53)	2.45 (1.24 – 4.85)	3.69 (1.63 – 8.36)	2.91 (1.41 – 6.02)
Ritonavir	1.28 (0.916 – 1.78)	1.24 (0.977 – 1.57)	1.21 (0.852 – 1.73)	1.06 (0.819 – 1.36)
ABT-267	1.05 (0.857 – 1.30)	1.01 (0.840 – 1.22)	1.31 (1.12 – 1.53)	1.30 (1.09 – 1.55)
ABT-333	1.08 (0.716 – 1.62)	1.11 (0.761 – 1.60)	1.40 (0.931 – 2.11)	1.29 (0.887 – 1.87)

**Notes:**

Variability in AUC was high (CV% 38-94%) for ABT-450 irrespective of race. Ritonavir, ABT-267 and ABT-333 AUC variability was < 46%.

- Were there any outliers or excluded data from analysis? ☐ Yes ☒ No ☐ NA
- Are the study results acceptable? ☒ Yes ☐ No

**Safety**

Was there any death or serious adverse events? ☐ Yes ☒ No

**CONCLUSIONS/COMMENTS/LABEL RECOMMENDATIONS**

**CONCLUSIONS**

At steady state, when co-administered with 25 mg ABT-267 and 400 mg BID ABT-333 for 21 days, ABT-450 Cmax and AUC in Chinese and Japanese subjects were 2.5- to 3.2-fold and 2.9- to 3.7-fold of exposures in Caucasian subjects. This increase is not caused by an increase in ritonavir exposure. The clinical significance of this increase in terms of safety should be evaluated in clinical trials.

ABT-267 and ABT-333 are slightly higher in Asians compared to Caucasians.

## Effect of Food on ABT-450/r/ABT-267 Coformulated Tablets

Reviewer: Vikram Arya, Ph.D., FCP

### M11-389

#### Title

**A Pharmacokinetic Study to Evaluate the Effect of Food on the Oral Bioavailability of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) Co-formulated Tablets**

#### Trial Period

Feb 26, 2013 through April 12, 2013

Final report date: November 6, 2013

#### Trial Objectives

The objective of this study was to determine the effect of food on the bioavailability of ABT-450, ritonavir, and ABT-267 from the ABT-450/r/ABT-267 co-formulated tablet formulation.

#### Trial Design

This was a Phase 1, single-dose, open-label, randomized, three-period, crossover study designed to evaluate the effect of moderate-fat and high-fat meals on the bioavailability of ABT-450/r/ABT-267 co-formulated tablets.

Adult male and female subjects (N = 21) were randomly assigned in equal numbers to receive one of the three sequences of Regimens A, B, and C as shown in Table 1 below.

Sequence Number	Subject Number	Regimens		
		Period 1	Period 2	Period 3
I	102, 105, 108, 110, 114, 116, and 120 <sup>a</sup>	A	B	C
II	103, 104, 109, 111, 115, <sup>a</sup> 118, and 121	B	C	A
III	101, 106, 107, 112, <sup>a</sup> 113, 117, and 119	C	A	B

a. Subjects 112, 115, and 120 prematurely discontinued from the study after Period 1.

The study drug was administered in the morning on study day 1 of each period as follows:

**Regimen A:** Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

**Regimen B:** Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

**Regimen C:** Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

Table 2 shows the meal content for day 1 of each period.

Meal	Approximate Time	Menu	Meal Composition
No Breakfast (Regimen A)	NA	NA	NA
Moderate-fat Breakfast (Regimen B)	0830	1 cinnamon raisin bagel, 1 oz. cream cheese 1 box Cheerios 1 tsp. sugar, 6 fl. oz. orange juice 8 fl. oz. 1% milk	617 Kcal; 28.9% calories from fat, 58.4% calories from carbohydrates, and 12.8% calories from protein
High-fat Breakfast (Regimen C)	0830	2 fried eggs, 2 strips bacon, 4 oz. fried hash browns, 2 slices toast, 6 tsp. butter, 8 fl. oz. whole milk	917 Kcal; 59.6% calories from fat, 27.7% calories from carbohydrates, and 12.6% calories from protein
Lunch	1300	1 beef patty, 1 hamburger bun, ¼ cup shredded lettuce, 2 slices tomato, 1 fresh onion ring, 1 pkt. ketchup, 1 pkt. mustard, 1 pkt. light mayonnaise, ¼ cup creamy coleslaw, 1 bag potato chips, 2 oz. carrot sticks, 2 oz. celery sticks 4 fl. oz. fruit punch with ice	910 Kcal; 43.4% calories from fat, 43.3% calories from carbohydrates, and 13.3% calories from protein
Dinner	1800	3 oz. roast beef, ½ cup mashed potatoes, ½ cup iceberg lettuce salad, 1 pkt. Ranch dressing, 1 peanut butter cookie, 8 fl. oz. whole milk	681 Kcal; 49.2% calories from fat, 29.0% calories from carbohydrates, and 21.8% calories from protein
Snack	2100	5 vanilla wafers, 1 cup diced peaches, 12 fl. oz. 7-Up with ice	287 Kcal; 11.3% calories from fat, 86.9% calories from carbohydrates, and 1.8% calories from protein

## Rationale for Dose Selection

The dose of ABT-450 (150 mg), ritonavir (100 mg) and ABT-267 (25 mg) evaluated in the trial is identical to the dose of ABT-450, ritonavir, and ABT-267 doses used in the pivotal Phase 3 trials.

## Drug Administration

For Regimen A, each dose of study drug was taken orally with approximately 240 mL of water after a 10-hour fast and approximately 4 hours before lunch. For Regimens B and C, each dose of study drug was taken orally approximately 30 minutes after starting a moderate-fat or a high-fat breakfast, respectively.



On Days 2 through 4 of each period, breakfast was served following collection of the morning blood sample, lunch approximately 4 hours after breakfast, dinner approximately 6 hours after lunch and a snack approximately 4 hours after dinner. Meals were served at approximately the same time each day and the subjects abstained from all other food and beverage.

A washout interval of at least 7 days separated the doses of the three study periods. Subjects were confined to the study site and supervised for approximately 5 days in each period. Confinement in each period began on Day –1 (1 day prior to dosing) and ended after the collection of the 72-hour blood samples and completion of all scheduled procedures on Day 4.

### **Identity of Investigational Products**

ABT-450/ritonavir/ABT-267 75 mg/50 mg/12.5 mg co-formulated tablets were used in the trial. The lot number is 12-006414 and the expiration date is March 31, 2014.

### **Sample Collection**

Blood samples for assay of ABT-450, ritonavir, and ABT-267 were collected by venipuncture prior to dosing (0 hour) and up to 72 hours after dosing on Day 1 in each period or upon subject discontinuation due to an adverse event.

### **Pharmacokinetic Analysis**

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

### **Trial 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	1.4 % to 5.9 %	5.7 % to 8.9 %
Ritonavir	4.71-3380	4.71	12.7,211,2640	3.5 % to 4.4 %	3.3 % to 6.4 %
ABT-267	0.417-299	0.417	1.09, 18.1, and 227	2.9 % to 4.1 %	3.5 % to 6.1 %

## ***Trial Population***

### **Subject Disposition and Demographics**

21 subjects were enrolled in the trial and 18 subjects completed the trial. 3 subjects were discontinued due to the following reasons:

- Subject 112, a 42-year-old White female, was discontinued from the study due to a positive pregnancy result on Day 7 (Day –1, Period 2), and therefore, did not receive Regimen A (fasting) and Regimen B (moderate-fat breakfast).
- Subject 115, a 46-year-old White male, was discontinued from the study due to Applicant's discretion at Period 2 check-in (Day –1), and therefore, did not receive Regimen A (fasting) and Regimen C (high-fat breakfast).
- Subject 120, a 32-year-old White female, was discontinued from the study due to out of range labs (positive cotinine) at Period 2 check-in (Day –1), and therefore, did not receive Regimen B (moderate-fat breakfast) and Regimen C (high-fat breakfast).

Table 4 shows the subject inclusion by regimen and analyses.

<b>Regimen</b>	<b>Safety N<sup>a</sup></b>	<b>Pharmacokinetic N<sup>b</sup></b>	<b>Statistical Analyses<sup>c</sup></b>
A	19	19	18
B	19	19	18
C	19	19	18

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

a. Number of subjects included in the safety analyses for each regimen.

b. Number of subjects included in the pharmacokinetic parameter summary statistics for each regimen.

c. Number of subjects included in the statistical analyses of the pharmacokinetic parameters for each regimen.

Table 5 shows the demographics of all subjects enrolled in the trial.

	<b>Mean ± SD (N = 21)</b>	<b>Min – Max</b>
Age (years)	34.4 ± 8.7	21 – 48
Weight (kg)	74.3 ± 14.3	47 – 105
Height (cm)	167 ± 11.4	145 – 187
Sex	9 Males (43%), 12 Females (57%)	
Race	16 White (76%), 5 Black or African American (24%)	

## Pharmacokinetics

### ABT-450

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 after administration of various regimens.

Pharmacokinetic Parameters	(Units)	Regimen A Fasting (N = 19)	Regimen B Moderate-Fat Breakfast (N = 19)	Regimen C High-Fat Breakfast (N = 19)
$C_{max}$	(ng/mL)	529 $\pm$ 937	1580 $\pm$ 1710 <sup>c</sup>	1410 $\pm$ 1880 <sup>c</sup>
$T_{max}$	(h)	4.2 $\pm$ 1.8	4.9 $\pm$ 1.3	5.8 $\pm$ 2.5 <sup>c</sup>
$t_{1/2}$ <sup>a,b</sup>	(h)	5.97 $\pm$ 1.94	5.20 $\pm$ 1.33	5.41 $\pm$ 1.46
$\beta$	(1/h)	0.116 $\pm$ 0.037	0.133 $\pm$ 0.034 <sup>c</sup>	0.128 $\pm$ 0.034 <sup>c</sup>
$AUC_t$	(ng•h/mL)	2990 $\pm$ 4240	7640 $\pm$ 8190 <sup>c</sup>	7070 $\pm$ 8810 <sup>c</sup>
$AUC_{\infty}$	(ng•h/mL)	3020 $\pm$ 4300	7660 $\pm$ 8190 <sup>c</sup>	7100 $\pm$ 8810 <sup>c</sup>
$CL/F$ <sup>b</sup>	(L/h)	129 $\pm$ 103	43.2 $\pm$ 43.7	46.9 $\pm$ 41.7
$Vd_F/F$ <sup>b</sup>	(L)	1430 $\pm$ 1550	400 $\pm$ 538	431 $\pm$ 492

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

a. Harmonic mean  $\pm$  pseudo-standard deviation; see the corresponding statistical significance (table note c) for  $\beta$  regarding regimen group comparisons of  $t_{1/2}$ .

b. Parameter was not tested statistically.

c. Statistically significantly different from reference regimen (Regimen A, ANOVA,  $p < 0.05$ ).

Table 7 shows the statistical comparison of the pharmacokinetic parameters of ABT-450 after the various regimens.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability (N = 18)			
		Central Value <sup>a</sup>		Point Estimate <sup>b</sup>	90% Confidence Interval
		Test	Reference		
B vs. A	$C_{max}$	960	205	4.674	3.036 – 7.195
	$AUC_t$	5215	1660	3.142	2.184 – 4.521
	$AUC_{\infty}$	5242	1687	3.108	2.164 – 4.463
C vs. A	$C_{max}$	822	205	4.003	2.600 – 6.161
	$AUC_t$	4689	1660	2.825	1.963 – 4.065
	$AUC_{\infty}$	4720	1687	2.798	1.948 – 4.018

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.



## Ritonavir

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir after administration of the various regimens.

Pharmacokinetic Parameters	(Units)	Regimen A	Regimen B	Regimen C
		Fasting (N = 19)	Moderate-Fat Breakfast (N = 19)	High-Fat Breakfast (N = 19)
$C_{max}$	(ng/mL)	1070 $\pm$ 746	1510 $\pm$ 667 <sup>c</sup>	1360 $\pm$ 668 <sup>c</sup>
$T_{max}$	(h)	3.5 $\pm$ 0.90	4.4 $\pm$ 1.3 <sup>c</sup>	5.2 $\pm$ 2.0 <sup>c</sup>
$t_{1/2}$ <sup>a,b</sup>	(h)	4.63 $\pm$ 1.43	4.41 $\pm$ 0.78	4.24 $\pm$ 0.70
$\beta$	(1/h)	0.150 $\pm$ 0.045	0.157 $\pm$ 0.028 <sup>c</sup>	0.164 $\pm$ 0.027 <sup>c</sup>
$AUC_t$	(ng•h/mL)	6230 $\pm$ 3800	9150 $\pm$ 5090 <sup>c</sup>	8960 $\pm$ 5630 <sup>c</sup>
$AUC_{\infty}$	(ng•h/mL)	6320 $\pm$ 3840	9210 $\pm$ 5090 <sup>c</sup>	9010 $\pm$ 5630 <sup>c</sup>
$CL/F$ <sup>b</sup>	(L/h)	23.1 $\pm$ 14.0	14.6 $\pm$ 9.99	15.0 $\pm$ 8.95
$Vd_F$ <sup>b</sup>	(L)	166 $\pm$ 117	97.3 $\pm$ 72.7	95.1 $\pm$ 66.8

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

- Harmonic mean  $\pm$  pseudo-standard deviation; see the corresponding statistical significance (table note c) for  $t_{1/2}$  regarding regimen group comparisons of  $t_{1/2}$ .
- Parameter was not tested statistically.
- Statistically significantly different from reference regimen (Regimen A, ANOVA,  $p < 0.05$ ).

Table 9 shows the statistical comparison of the pharmacokinetic parameters of ritonavir after the various regimens.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability (N = 18)			
		Central Value <sup>a</sup>		Point Estimate <sup>b</sup>	90% Confidence Interval
		Test	Reference		
B vs. A	$C_{max}$	1341	822	1.632	1.300 – 2.048
	$AUC_t$	7970	5313	1.500	1.243 – 1.810
	$AUC_{\infty}$	8041	5409	1.486	1.232 – 1.793
C vs. A	$C_{max}$	1234	822	1.502	1.197 – 1.886
	$AUC_t$	7717	5313	1.453	1.204 – 1.753
	$AUC_{\infty}$	7773	5409	1.437	1.191 – 1.733

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

- Antilogarithm of the least squares means for logarithms.
- Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

## ABT-267

Table 10 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 after administration of the various regimens.

Pharmacokinetic Parameters	(Units)	Regimen A	Regimen B	Regimen C
		Fasting (N = 19)	Moderate-Fat Breakfast (N = 19)	High-Fat Breakfast (N = 19)
C <sub>max</sub>	(ng/mL)	58.2 ± 20.7	127 ± 35.9 <sup>c</sup>	114 ± 31.0 <sup>c</sup>
T <sub>max</sub>	(h)	4.8 ± 0.63	5.2 ± 0.50	5.9 ± 1.2 <sup>c</sup>
t <sub>1/2</sub> <sup>a,b</sup>	(h)	28.6 ± 11.5	29.0 ± 9.71	28.0 ± 9.25
β	(1/h)	0.024 ± 0.009	0.024 ± 0.008	0.025 ± 0.008
AUC <sub>t</sub>	(ng•h/mL)	844 ± 354	1480 ± 383 <sup>c</sup>	1430 ± 315 <sup>c</sup>
AUC <sub>∞</sub>	(ng•h/mL)	969 ± 397	1670 ± 470 <sup>c</sup>	1630 ± 373 <sup>c</sup>
CL/F <sup>b</sup>	(L/h)	29.5 ± 10.1	16.3 ± 5.17	16.3 ± 4.34
Vd <sub>p</sub> /F <sup>b</sup>	(L)	1350 ± 555	717 ± 292	699 ± 238

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions.

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

- Harmonic mean ± pseudo-standard deviation; see the corresponding statistical significance (table note c) for β regarding regimen group comparisons of t<sub>1/2</sub>.
- Parameter was not tested statistically.
- Statistically significantly different from reference regimen (Regimen A, ANOVA, p < 0.05).

Table 11 shows the statistical comparison of the pharmacokinetic parameters of ABT-267 after the various regimens.

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability (N = 18)			
		Central Value <sup>a</sup>		Point Estimate <sup>b</sup>	90% Confidence Interval
		Test	Reference		
B vs. A	C <sub>max</sub>	124	54	2.273	1.974 – 2.618
	AUC <sub>t</sub>	1447	781	1.852	1.628 – 2.107
	AUC <sub>∞</sub>	1630	897	1.817	1.608 – 2.053
C vs. A	C <sub>max</sub>	112	54	2.061	1.789 – 2.373
	AUC <sub>t</sub>	1397	781	1.788	1.571 – 2.034
	AUC <sub>∞</sub>	1578	897	1.760	1.557 – 1.988

Regimen A: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under fasting conditions

Regimen B: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a moderate-fat breakfast.

Regimen C: Two ABT-450/r/ABT-267 75/50/12.5 mg co-formulated tablets (total dose of 150/100/25 mg) administered under non-fasting conditions with a high-fat breakfast.

- Antilogarithm of the least squares means for logarithms.
- Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

## Safety

No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study.

## Results

Relative to single dose administration of ABT-450/r/ABT-267 co-formulated tablet formulation under fasting conditions:

- Administration of ABT-450/r/ABT-267 co-formulated tablet formulation under moderate fat conditions increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ABT-450 by 367 % and 210 %, respectively, increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ritonavir by 63 % and 48 %, respectively, and increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ABT-267 by 127 % and 81 %, respectively.
- Administration of ABT-450/r/ABT-267 co-formulated tablet formulation under high fat conditions increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ABT-450 by 300 % and 179 %, respectively, increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ritonavir by 50 % and 43 %, and increased the mean  $C_{\max}$  and  $AUC_{\infty}$  of ABT-267 by 106 % and 76 %, respectively.

## Conclusion

ABT-450/r/ABT-267 co-formulated tablet formulation should be taken with food. The differences in systemic exposure of ABT-450, ritonavir, and ABT-267 after administration of ABT-450/r/ABT-267 co-formulated tablet formulation under moderate fat and high fat conditions is not expected to be clinically relevant.

Of note, ABT-450/r/ABT-267 co-formulated tablet formulation were administered with food in the pivotal Phase III trials in which the safety and efficacy of ABT-450, ritonavir, ABT-267 (and the other drugs of the proposed regimen) was evaluated.

**Effect of Food on ABT-333 (b) (4) Tablets**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M13-330**

**Title**

**A Pharmacokinetic Study to Evaluate the Effect of Food on the Oral Bioavailability of ABT-333 (b) (4) Tablets**

**Trial Period**

November 28, 2012 through January 21, 2013  
Final report date: May 8, 2013

**Trial Objectives**

The objective of this study was to determine the effect of food on the bioavailability of ABT-333 (b) (4) Phase 3 tablet formulation.

**Trial Design**

Phase 1, single-dose, open-label, randomized, three-period, crossover study. Adult male and female subjects (N = 18) were selected to participate in the study and were randomly assigned in equal numbers to receive one of the three sequences of Regimens A, B, and C as shown in Table 1 below.

Sequence Group	Subject Numbers	N	Regimens		
			Period 1	Period 2	Period 3
I	103, 106, 109, 111, 117, 118	6	A	B	C
II	101, 105, 110, 112, 114, 115 <sup>a</sup>	6	B	C	A
III	102, 104, 107, 108, 113, 116	6	C	A	B

Regimen A = One 250 mg ABT-333 (b) (4) tablet administered under fasting conditions.  
Regimen B = One 250 mg ABT-333 (b) (4) tablet administered with a moderate-fat breakfast.  
Regimen C = One 250 mg ABT-333 (b) (4) tablet administered with a high-fat breakfast.

a. Subject was discontinued from the study due to a positive urine drug screen result on Day -1 of Period 3.

The study drug was administered in the morning on study day 1 of each period as follows:

**Regimen A:** One 250 mg ABT-333 (b) (4) tablet administered under fasting conditions.

**Regimen B:** One 250 mg ABT-333 (b) (4) tablet administered under non-fasting conditions with a moderate-fat breakfast.

**Regimen C:** One 250 mg ABT-333 (b) (4) tablet administered under non-fasting conditions with a high-fat breakfast.

Table 2 shows the meal content for day 1 of each period.

Meal	Approximate Time	Menu	Meal Composition
No Breakfast (Regimen A)	NA	NA	NA
Moderate-fat Breakfast (Regimen B)	0830	1 cinnamon raisin bagel, 1 oz. cream cheese 17 g. cereal (Cheerios) 1 tsp. sugar, 6 oz. orange juice	612.4 Kcal; 21.2% calories from fat, 65.0% calories from carbohydrates, and 13.8% calories from protein
High-fat Breakfast (Regimen C)	0830	1 fried egg, 2 pieces bacon, 4 oz. hash browns, 2 slices white bread, 6 tsp. butter, 8 fl. oz. whole milk	849.9 Kcal; 58.5% calories from fat, 26.7% calories from carbohydrates, and 14.8% calories from protein
Lunch	1300	3 oz. hamburger patty on bun, 1 slice lettuce, 2 slices tomato, 1 piece white onion, 1 pkt. ketchup, 1 pkt. mustard, 1 pkt. mayonnaise, 0.5 cup coleslaw, 1 pkg. Lays potato chips, 2 oz. carrots, 2 oz. celery 4 fl. oz. fruit punch	908.6 Kcal; 43.4% calories from fat, 43.3% calories from carbohydrates, and 13.3% calories from protein
Dinner	1800	3 oz. roast beef, 1 serving mashed potatoes, ½ cup lettuce, 1 pkt. fat-free Ranch salad dressing, 1 peanut butter cookie, 8 fl. oz. whole milk	680.5 Kcal; 49.2% calories from fat, 29.0% calories from carbohydrates, and 21.8% calories from protein
Snack	2100	5 vanilla wafers, 4 oz. peaches with juice, 12 fl. oz. soda	287.4 Kcal; 11.3% calories from fat, 86.9% calories from carbohydrates, and 1.8% calories from protein

## Rationale for Dose Selection

The dose of ABT-333 (250 mg) is the dose used in the Phase 3 trials.

## Drug Administration

For Regimen A, each dose of study drug was taken orally with approximately 240 mL of water after a 10-hour fast and approximately 4 hours before lunch. For Regimens B and C, each dose of study drug was taken orally approximately 30 minutes after starting a moderate-fat or a high-fat breakfast, respectively.

On Days 2 and 3 of each period, breakfast was served following collection of the morning blood sample, lunch at approximately 4 hours after breakfast, dinner at approximately 6 hours after lunch, and a snack at approximately 4 hours after dinner. Meals were served at approximately the same time each day and the subjects abstained from all other food and beverage.

A washout interval of at least 7 days separated the doses of the three study periods. Subjects were confined to the study site and supervised for approximately 4 days in each period.

### **Identity of Investigational Products**

ABT-333 250 mg (b) (4) tablets were used in the trial. The lot number is 12-003123.

### **Sample Collection**

Blood samples for assay of ABT-333 and the ABT-333 M1 metabolite were collected by venipuncture prior to dosing (0 hour) and up to 48 hours after dosing on Day 1 in each period.

### **Pharmacokinetic Analysis**

The pharmacokinetic parameters 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-333	1.06-523	1.06	2.73,34.2, 427	3.9 % to 5.1 %	-7.4 % to -1.8 %
ABT-333 M1	2.14-1060	2.14	5.46,68.2, 853	2.3 % to 4.4 %	-8.3 % to -1.9 %

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

18 subjects were enrolled in the trial and 17 subjects completed the trial. One subject, randomized to sequence group II, was discontinued from the study due to a positive urine drug screen result on Day -1 of Period 3, hence, the subject did not receive Regimen A (250 mg ABT-333 (b) (4) tablet administered under fasting conditions). The subject was excluded from the pharmacokinetic analysis as the subject did not receive the reference regimen.

Table 4 shows the demographics of all subjects enrolled in the trial.

	Mean $\pm$ SD (N = 18)	Min – Max
Age (years)	32.1 $\pm$ 9.2	20 – 49
Weight (kg)	72.2 $\pm$ 12.5	50 – 95
Height (cm)	169 $\pm$ 10.1	155 – 187
Sex	7 Males (39%), 11 Females (61%)	
Race	13 White (72%), 5 Black (28%)	

### Pharmacokinetics

Table 5 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 metabolite for the various regimens.

Pharmacokinetic Parameters	(Units)	Regimen A Fasting (N = 17)	Regimen B Moderate-Fat Breakfast (N = 17)	Regimen C High-Fat Breakfast (N = 17)
<b>ABT-333</b>				
C <sub>max</sub>	(ng/mL)	482 $\pm$ 156	741 $\pm$ 284*	721 $\pm$ 334*
T <sub>max</sub>	(h)	2.7 $\pm$ 1.0	3.2 $\pm$ 1.0	3.8 $\pm$ 1.6*
t <sub>1/2</sub> <sup>a</sup>	(h)	14.1 $\pm$ 5.7	8.4 $\pm$ 3.3	7.0 $\pm$ 2.0
$\beta$	(1/h)	0.049 $\pm$ 0.020	0.082 $\pm$ 0.032*	0.099 $\pm$ 0.027*
AUC <sub>t</sub>	(ng•h/mL)	3720 $\pm$ 1270	5340 $\pm$ 2890*	5040 $\pm$ 2520*
AUC <sub>∞</sub>	(ng•h/mL)	4070 $\pm$ 1670	5440 $\pm$ 2960*	5090 $\pm$ 2580
CL/F <sup>b</sup>	(L/h)	69.4 $\pm$ 23.2	55.3 $\pm$ 23.1	58.2 $\pm$ 22.4
<b>ABT-333 M1 Metabolite</b>				
C <sub>max</sub>	(ng/mL)	173 $\pm$ 79.8	250 $\pm$ 94.2*	197 $\pm$ 65.0
T <sub>max</sub>	(h)	3.8 $\pm$ 1.0	3.8 $\pm$ 0.8	4.5 $\pm$ 1.5*
t <sub>1/2</sub> <sup>a</sup>	(h)	10.8 $\pm$ 4.7	6.7 $\pm$ 1.7	5.5 $\pm$ 0.8
$\beta$	(1/h)	0.064 $\pm$ 0.027	0.104 $\pm$ 0.027*	0.126 $\pm$ 0.018*
AUC <sub>t</sub>	(ng•h/mL)	1310 $\pm$ 510	1760 $\pm$ 634 <sup>b</sup>	1480 $\pm$ 502
AUC <sub>∞</sub>	(ng•h/mL)	1390 $\pm$ 531	1790 $\pm$ 640 <sup>b</sup>	1510 $\pm$ 509
CL/F <sup>b</sup>	(L/h)	208 $\pm$ 84.4	161 $\pm$ 71.5	185 $\pm$ 64.5

Regimen A = One 250 mg ABT-333 (b) (4) tablet administered under fasting conditions.

Regimen B = One 250 mg ABT-333 (b) (4) tablet administered with a moderate-fat breakfast.

Regimen C = One 250 mg ABT-333 (b) (4) tablet administered with a high-fat breakfast.

\* Statistically significantly different from reference regimen (Regimen A, ANOVA,  $p < 0.05$ ).

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

b. Parameter was not tested statistically.

### Relative Bioavailability Assessments:

Table 6 shows the relative bioavailability and 90 % confidence intervals for ABT-333 and ABT-333 M1 metabolite for the various regimens.



Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Relative Bioavailability	
		Test	Reference	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-333					
B vs. A	C <sub>max</sub>	701	459	1.527	1.190 – 1.959
	AUC <sub>t</sub>	4846	3536	1.370	1.136 – 1.653
	AUC <sub>∞</sub>	4939	3815	1.295	1.080 – 1.552
C vs. A	C <sub>max</sub>	650	459	1.416	1.104 – 1.817
	AUC <sub>t</sub>	4602	3536	1.301	1.079 – 1.570
	AUC <sub>∞</sub>	4635	3815	1.215	1.013 – 1.457
ABT-333 M1 Metabolite					
B vs. A	C <sub>max</sub>	236	158	1.497	1.189 – 1.886
	AUC <sub>t</sub>	1637	1217	1.345	1.115 – 1.622
	AUC <sub>∞</sub>	1673	1286	1.301	1.085 – 1.560
C vs. A	C <sub>max</sub>	185	158	1.172	0.931 – 1.476
	AUC <sub>t</sub>	1393	1217	1.144	0.948 – 1.380
	AUC <sub>∞</sub>	1422	1286	1.106	0.922 – 1.326

Regimen A = One 250 mg ABT-333 (b) (4) tablet administered under fasting conditions.

Regimen B = One 250 mg ABT-333 (b) (4) tablet administered with a moderate-fat breakfast.

Regimen C = One 250 mg ABT-333 (b) (4) tablet administered with a high-fat breakfast.

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

## Safety

No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study.

## Results

Relative to administration of ABT-333 250 mg (b) (4) tablet under fasting conditions:

- Administration of ABT-333 250 mg (b) (4) tablet with a moderate-fat breakfast increased the mean C<sub>max</sub> and AUC of ABT-333 by 53 % and 30 %, respectively, and the mean C<sub>max</sub> and AUC of ABT-333 M1 metabolite by 50 % and 30 %, respectively.
- Administration of ABT-333 250 mg (b) (4) tablet with a high-fat breakfast increased the mean C<sub>max</sub> and AUC of ABT-333 by 42 % and 22 %, respectively, and the mean C<sub>max</sub> and AUC of ABT-333 M1 metabolite by 17 % and 10 %, respectively.

## Conclusion

ABT-333 250 mg (b) (4) tablets should be taken with food. The differences in systemic exposure of ABT-333 after administration of ABT-333 250 mg (b) (4) formulation under moderate fat and high fat conditions is not expected to be clinically relevant.

Of note, ABT-333 250 mg (b) (4) tablets were administered with food in the pivotal Phase III trials in which the safety and efficacy of ABT-333 (and the other drugs of the proposed regimen) was evaluated.



**Drug-Drug Interaction Trial with Carbamazepine**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M14-027**

**Title**

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

**Trial Period**

March 27 2013 to July 3, 2013

Final report date: Jan 27, 2014

**Trial Design**

Phase 1, single-center, multiple-dose, sequential, open-label study.

Arm 1: ABT-450/r/ABT-267 and ABT-333 with carbamazepine.

Arm 2: ABT-450/r/ABT-267 with carbamazepine.

After meeting the selection criteria, subjects were sequentially enrolled as shown in table 1 below.

	Subjects	Regimens	
		Period 1	Period 2
Arm 1	101 – 112	A	B
Arm 2 <sup>a</sup>	12 subjects planned	C	D

a. Arm 2 was not conducted. Regimens C and D were not administered.

Regimen A: Single dose of ABT-450/r/ABT-267 150/100/25 mg +ABT-333 250 mg on Day 1, Period 1, followed by a washout of 7 days.

Regimen B: Carbamazepine 200 mg once daily from day 1 to day 3 in Period 2, carbamazepine 200 mg twice daily from day 4 to day 24 in period 2 + single dose of ABT-450/r/ABT-267 150/100/25 mg +ABT-333 250 mg on day 22 in Period 2.

Regimen C: Single dose of ABT-450/r/ABT-267 150/100/25 mg on Day 1, Period 1 followed by a washout interval of at least 7 days.

Regimen D: Carbamazepine 200 mg once daily from day 1 to day 3 in Period 2, carbamazepine 200 mg twice daily from day 4 to day 24 in period 2 + single dose of ABT-450/r/ABT-267 150/100/25 mg on day 22 in Period 2.

Carbamazepine induces its own metabolism and hence the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. The initial half life of carbamazepine ranges from 25 to 65 hours and decreases to 12 to 17 hours after repeated doses. Carbamazepine is anticipated to take about 21 days to reach steady-state; hence, the DAAs were added on Day 22 after carbamazepine reached steady state. The label recommends starting carbamazepine treatment at a low initial daily dosage with a gradual increase. Thus, in Period 2, carbamazepine was dosed as 200 mg QD for Days 1 to 3, followed by 200 mg BID doses from Days 4 to 25. Carbamazepine dosing on day 23 and 24 maintained the enzyme induction and allowed determination of the half-lives and concentrations of the DAAs in the presence of the carbamazepine. CYP3A4 was identified as the major isoform responsible for the formation of the active metabolite, carbamazepine-10,11-epoxide (CBZE), from carbamazepine. CBZE exposures were expected to increase in the presence of a CYP3A4 inhibitor like ritonavir and hence, plasma samples were also analyzed for CBZE.

**Of note, Arm 2 was not conducted and regimen C and regimen D were not administered because per the sponsor's assessment, the pharmacokinetic data collected from arm 1 was adequate for assessing the extent of the drug-drug interaction expected between 2 DAAs and carbamazepine.**

Carbamazepine, ABT-450/r/ABT-267 and ABT-333 were taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast in the morning. In the evening, carbamazepine was taken orally with approximately 240 mL of water approximately 30 minutes after the start of the evening snack.

Subjects received a standardized diet, providing approximately 40% of the daily calories from fat and up to 45 % of daily calories from carbohydrates at each meal during confinement (approximately 2200 calories/day). The meal content was identical on the pharmacokinetic sampling days (Period 1, Day 1 and Period 2, Days 21 and 22).

*Reviewer's Note:*

*The carbamazepine (Tegretol®) label recommends administration of carbamazepine doses with meals. The DAAs were given with food in Phase 2- and Phase 3 studies. Additionally, all Phase 1 studies have evaluated the pharmacokinetics of DAAs when administered with food. Hence, in the current study DAAs and carbamazepine were given with food.*

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

ABT-450, ABT-333 and ABT-267 have been shown to be *in vitro* substrates of CYP3A

and ritonavir is a CYP3A4 substrate and inhibitor. Carbamazepine, an anticonvulsant, is a CYP3A4 substrate as well as a potent inducer of CYP3A4 and other oxidative enzyme systems in the liver, and it may also increase glucuronyltransferase activity. Hence, the study was designed to evaluate the effect of CYP3A induction on the disposition of the DAAs. In addition, the study also evaluated the effect of a single dose of DAAs on carbamazepine steady state pharmacokinetics.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), ABT-267 (25 mg) and ABT-333 (250 mg) were the doses evaluated in the Phase 3 trials.

## Identity of Investigational Products

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

	ABT-450/Ritonavir/ABT-267	ABT-333	Carbamazepine
Dosage Form	Tablet	Tablet	Tablet
Strength (mg)	75/50/12.5 mg	250 mg	200 mg
Bulk Product Lot Number	12-008149	12-007842	13-000872 (Vendor Lot F0315)
Potency	(b) (4)		N/A
Manufacturing Site	AbbVie North Chicago, IL	AbbVie North Chicago, IL	Novartis East Hanover, NJ
Finishing Lot Number	13-001258	13-001263	13-001264 (b) (4)
Expiration Date	(b) (4)		

N/A = Not available

## Sample Collection

Blood samples for measurement of the concentrations of ABT-450, ritonavir, ABT-333, ABT-333 M1, and ABT-267 were collected by venipuncture on the following days:

Arm 1, Period 1, Day 1: Prior to dosing (0 hour) and up to 72 hours after dosing on day 1  
 Arm 1, Period 2, Day 22: Prior to dosing (0 hour) and up to 72 hours after dosing on day 22.

Blood samples for measurement of the concentrations of carbamazepine and its metabolite CBZE were collected on the following days in period 2:

Day 21: Prior to morning dosing (0 hour) and up to 16 hours after dosing on Day 1.  
 Day 22: Prior to morning dosing (0 hour) and up to 72 hours after dosing on day 22.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, carbamazepine, and CBZE 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	5.3 % to 12.7 %	6.4 % to 8.7%
Ritonavir	4.71-3380	4.71	12.7, 211, 2640	2.8 % to 9.9 %	3.4 % to 4.3 %.
ABT-267	0.417-299	0.417	1.09, 18.1, 227	4.1 % to 13.6 %	4 % to 8.3 %
ABT-333	4.39-3150	4.39	11.7, 195, 2430	4.4 % to 11.1 %	0.9 % to 4.1 %
ABT-333 M1	4.58-3290	4.58	12, 199, 2490	4.2 % to 11.8 %	1.7 % to 5.5 %
Carbamazepine*	0.05-50	0.05	0.15, 0.4, 1.5, 6, 37.5	3.2 % to 5.17 %	-2.7 % to 4.5 %
CBZE*	0.05-50	0.05	0.15, 0.4, 1.5, 6, 37.5	1.5 % to 5.9 %	2.1 % to 6.1 %

\*: Concentrations shown are in µg/mL.

### *Subject Disposition and Demographics*

Adult male and female subjects (N = 12) were enrolled in the study for Arm 1. All subjects completed the study.

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

	Arm 1	
	Mean ± SD (N = 12)	Min – Max
Age (years)	35.7 ± 8.11	23 – 49
Weight (kg)	74.2 ± 14.8	51 – 97
Height (cm)	172 ± 11.6	149 – 194
Sex	9 Males (75%), 3 Females (25%)	
Race	6 White (50%), 6 Black (50%)	

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

## Pharmacokinetics

### ABT-450

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 1.

Parameter (Unit)	Day 1, Period 1	Day 22, Period 2
	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg + Carbamazepine 200 mg
N	12	12
C <sub>max</sub> (ng/mL)	1866 ± 1899	815 ± 1115
T <sub>max</sub> (h)	4.2 ± 1.1	4.0 ± 1.1
t <sub>1/2</sub> <sup>a</sup> (h)	5.5 ± 1.2	3.4 ± 0.8
AUC <sub>t</sub> (ng•h/mL)	11536 ± 14126	3398 ± 3966
AUC <sub>∞</sub> (ng•h/mL)	11589 ± 14105	3446 ± 3991
CL/F <sup>b</sup> (L/h)	30.1 ± 22.1	106 ± 81
V <sub>db</sub> /F <sup>b</sup> (L)	263 ± 192	532 ± 386

a. Harmonic mean ± pseudo-standard deviation.

b. Parameter was not tested statistically.

### Ritonavir

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

Parameter (Unit)	Day 1, Period 1	Day 22, Period 2
	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg + Carbamazepine 200 mg
N	12	12
C <sub>max</sub> (ng/mL)	1992 ± 1129	483 ± 555
T <sub>max</sub> (h)	4.0 ± 1.0	3.8 ± 1.0
t <sub>1/2</sub> <sup>a</sup> (h)	3.8 ± 0.5	2.3 ± 0.6
AUC <sub>t</sub> (ng•h/mL)	10826 ± 6963	1953 ± 2249
AUC <sub>∞</sub> (ng•h/mL)	11075 ± 7266	1990 ± 2259
CL/F <sup>b</sup> (L/h)	11.8 ± 5.5	124 ± 105
Vdb/F <sup>b</sup> (L)	64.5 ± 28.3	424 ± 318

a. Harmonic mean ± pseudo-standard deviation.

b. Parameter was not tested statistically.

## ABT-267

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

Parameter (Unit)	Day 1, Period 1	Day 22, Period 2
	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg + Carbamazepine 200 mg
N	12	12
C <sub>max</sub> (ng/mL)	152 ± 44.9	106 ± 39.5
T <sub>max</sub> (h)	5.2 ± 0.4	5.1 ± 0.5
t <sub>1/2</sub> <sup>a</sup> (h)	18.8 ± 3.3	16.4 ± 3.4
AUC <sub>t</sub> (ng•h/mL)	1821 ± 623	1281 ± 492
AUC <sub>∞</sub> (ng•h/mL)	1952 ± 717	1349 ± 540
CL/F <sup>b</sup> (L/h)	14.2 ± 4.2	20.8 ± 6.5
Vdb/F <sup>b</sup> (L)	384 ± 106	503 ± 185

a. Harmonic mean ± pseudo-standard deviation.

b. Parameter was not tested statistically.

## ABT-333 and M1 Metabolite

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-333 and M1 metabolite in Arm 1.

Parameter (Unit)	Day 1, Period 1	Day 22, Period 2
	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg	Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg + Carbamazepine 200 mg
ABT-333		
N	12	12
C <sub>max</sub> (ng/mL)	1474 ± 569	674 ± 283
T <sub>max</sub> (h)	4.1 ± 1.2	4.1 ± 1.0
t <sub>1/2</sub> <sup>a</sup> (h)	6.2 ± 1.1	4.2 ± 0.7
AUC <sub>t</sub> (ng•h/mL)	13217 ± 5292	3885 ± 1371
AUC <sub>∞</sub> (ng•h/mL)	13365 ± 5258	3974 ± 1375
CL/F <sup>b</sup> (L/h)	21.9 ± 9.3	70.2 ± 23.6
V <sub>db</sub> /F <sup>b</sup> (L)	196 ± 75	442 ± 174
ABT-333 M1		
N	12	12
C <sub>max</sub> (ng/mL)	780 ± 308	780 ± 473
T <sub>max</sub> (h)	4.7 ± 1.0	4.4 ± 0.9
t <sub>1/2</sub> <sup>a</sup> (h)	5.1 ± 0.8	3.5 ± 0.6
AUC <sub>t</sub> (ng•h/mL)	6201 ± 2826	4095 ± 2290
AUC <sub>∞</sub> (ng•h/mL)	6521 ± 2961	4160 ± 2305

a. Harmonic mean ± pseudo-standard deviation.

b. Parameter was not tested statistically.

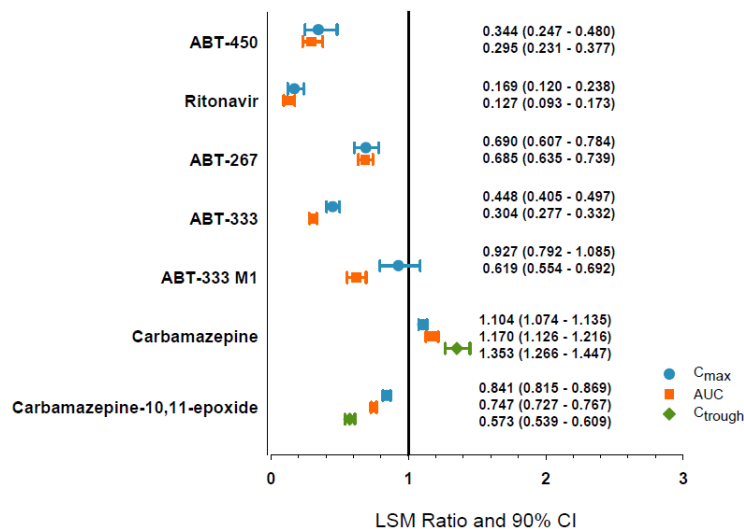
## Carbamazepine and Carbamazepine Metabolite (CBZE)

Table 9 shows the mean ± SD pharmacokinetic parameters of carbamazepine and CBZE in Arm 1.

Parameter (unit)	Day 21, Period 2	Day 22, Period 2
	Carbamazepine 200 mg BID	Carbamazepine 200 mg + Single Dose ABT-450/r/ABT-267 150/100/25 mg + ABT-333 250 mg
Carbamazepine		
N	12	12
C <sub>max</sub> (µg/mL)	6.18 ± 1.05	6.84 ± 1.34
T <sub>max</sub> (h)	3.8 ± 1.3	5.5 ± 2.7
AUC <sub>12</sub> (µg•h/mL)	61.9 ± 8.81	73.2 ± 15.5
C <sub>12</sub> (µg/mL)	4.42 ± 0.61	6.07 ± 1.45
CBZE		
N	12	12
C <sub>max</sub> (µg/mL)	0.91 ± 0.28	0.76 ± 0.22
T <sub>max</sub> (h)	4.6 ± 0.8	1.8 ± 0.8
AUC <sub>12</sub> (µg•h/mL)	9.70 ± 2.84	7.22 ± 2.06
C <sub>12</sub> (µg/mL)	0.72 ± 0.21	0.42 ± 0.14

## Statistical Evaluation of the Pharmacokinetic Parameters

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, carbamazepine, and CBZE.



AUC<sub>∞</sub>: DAAs; AUC<sub>12</sub> and C<sub>12</sub>: Carbamazepine and carbamazepine-10,11-epoxide.

#### Reviewer's Interpretation of Alteration in Exposures of the Various Medications Evaluated in Trial M14-027

- The systemic exposure of ABT-450, ritonavir, ABT-267, and ABT-333 significantly decreased when co-administered with carbamazepine. Although CYP enzymes have a different degree of involvement in the metabolism of the DAAs (major pathway for ABT-450 metabolism compared with minor contribution to the metabolism of ABT-333 and ABT-267), the DAAs are substrates of P-glycoprotein (P-gp). Since carbamazepine is an inducer of CYP3A and P-glycoprotein, the decrease in systemic exposures of DAAs may be due to the combined induction effect of carbamazepine on CYP3A and P-gp.
- The systemic exposures of M1, a metabolite of ABT-333, were decreased in the presence of carbamazepine, suggesting that CYP3A4 may not play a major role in the formation of M1 metabolite. This observation is further supported by the fact that in presence of gemfibrozil, a potent CYP2C8 inhibitor, the systemic exposure of ABT-333 (primarily metabolized by CYP2C8) was increased approximately 11-fold whereas the AUC of the M1 metabolite was decreased by approximately 78 %, thereby suggesting that CYP2C8 may play a role in the formation of the M1 metabolite (trial M12-196).
- The increase in the exposures of carbamazepine and decrease in the exposures of CBZE may be due to CYP3A inhibition by ritonavir. Of note, increase in the exposures of carbamazepine when combined with protease inhibitors has been previously observed when carbamazepine was co-administered with Prezista.

#### Safety

No deaths or other serious adverse events were reported in this study. Increases in ALT and AST were observed when DAAs were co-dosed with carbamazepine. After Day 22, when DAAs were co-dosed with carbamazepine, in all 12 subjects, an elevated ALT



and AST trend on Study Days 23 through 27 compared with baseline (Day –1) through Day 21 was noted. Per the sponsor, in 8 of these subjects the ALT and AST levels were higher than the ULN, but predominantly below  $3 \times$  ULN, and subsequently returned to baseline levels. In Subjects 105 and 112, ALT and AST levels exceeded the upper limit of the reference range. For subject 105, the ALT and AST levels returned to baseline in 1.5 months; for subject 112, the AST level returned to baseline in 10 days. It should be noted that similar increase in ALT and AST was also noted in another trial (Study M13-104) where the induction effect of efavirenz was evaluated using ATRIPLA (efavirenz, emtricitabine and tenofovir) administered with an ABT-450/r + ABT-333 regimen. Study M13-104 was discontinued for safety and tolerability reasons (nausea, vomiting, and liver function test elevations).

## Results

Co-administration of ABT-450/r/ABT-267 and ABT-333 with carbamazepine:

- Decreased the mean  $C_{\max}$  and AUC of ABT-450 by 66 % and 70 %, respectively.
- Decreased the mean  $C_{\max}$  and AUC of ritonavir by 83 % and 87 %, respectively.
- Decreased the mean  $C_{\max}$  and AUC of ABT-267 by 31 % and 31%, respectively.
- Decreased the mean  $C_{\max}$  and AUC of ABT-333 by 55 % and 70 %, respectively.
- Decreased the mean  $C_{\max}$  and AUC of ABT-333 M1 metabolite by 8 % and 32 %, respectively.
- Increased the mean  $C_{\max}$  and AUC of carbamazepine by 10 % and 17 %, respectively.
- Decreased the mean  $C_{\max}$  and AUC of CBZE by 16 % and 25 %, respectively.

## Conclusion

Based on decrease in exposures of all the DAAs when combined with carbamazepine (which may potentially decrease in the efficacy of the DAA regimen) and observations of increase in ALT and AST enzymes, co-administration of ABT-450/ritonavir/ABT-267 + ABT-33 with strong CYP3A inducers such as carbamazepine is not recommended.

**Drug-Drug Interaction Trial with Gemfibrozil**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M12-196**

**Title**

**Effect of CYP2C8 Inhibitor, Gemfibrozil, on the Pharmacokinetics of ABT-333 and ABT-450 with Ritonavir (ABT-450/r) when Coadministered in Healthy Adult Subjects.**

**Trial Period**

March 5, 2012 to May 21, 2012  
Final report date: December 3, 2012

**Trial Objectives**

The objective of the trial was to evaluate the effect of the CYP2C8 inhibitor, gemfibrozil, on the pharmacokinetics of the 2-DAA combination ABT-333 and ABT-450/ritonavir when co-administered in healthy subjects.

**Trial Design**

Phase 1, single-center, multiple-dose, open-label, two period study to evaluate the effect of gemfibrozil on two DAAs (ABT-333 and ABT-450/r) when dosed in combination.

ABT-333 (400 mg) and ABT-450/r (150/100 mg) were administered on Study Days 1 and 6, approximately 30 minutes after starting a standardized breakfast. On Study Days 4, 5, 7, and 8, gemfibrozil (600 mg) was administered approximately 30 minutes before the start of a standardized breakfast. Only on study day 6, the morning doses of gemfibrozil, ABT-333, and ABT-450/r were co-administered approximately 30 minutes after start of the breakfast. On study days 4 through 8, the evening dose of gemfibrozil were administered approximately 30 minutes before the start of an evening snack. All doses of study drug were taken orally with approximately 240 mL of water.

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), for all meals during confinement. The meal content was identical on the intensive pharmacokinetic sampling days (study day 1 and study day 6).

**Rationale for Conducting the Trial**

In vitro studies in human liver microsomes in the presence of known inhibitors of specific CYP P450 indicated that CYP2C8 had the most significant impact on the metabolism of

ABT-333 followed by CYP3A4 and cytochrome P450 2D6 (CYP2D6) (~60%, 30%, and 10% of the control activity was inhibited by quercetin, ketoconazole and quinidine, respectively). Gemfibrozil is known to inhibit CYP2C8 *in vitro* ( $K_i = 69\text{--}75\text{ }\mu\text{M}$ ) the *in vivo* inhibitory potency of gemfibrozil is mainly based on its glucuronide metabolite, which is a mechanism-based CYP2C8 inhibitor. To ensure CYP2C8 inhibition during assessment of the pharmacokinetics of ABT-450, ritonavir, and ABT-333 when gemfibrozil, ABT-450,ritonavir and ABT-3333 were co-administered, gemfibrozil was administered twice daily on days 7 and 8.

#### Reviewer's Note:

*According to the LOPID (gemfibrozil) prescribing information, the average gemfibrozil AUC is reduced by 14-44 %, when LOPID™ was administered with meals compared to 30 minutes before meals. Although the morning dose of gemfibrozil on day 6 (when gemfibrozil was co-administered with ABT-450,ritonavir, and ABT-333) was given under fed conditions (30 minutes after breakfast), the effect of gemfibrozil on ABT-333 is anticipated to be similar (or slightly lower) as compared with the effect of gemfibrozil (given under fasted conditions) on ABT-333.*

### Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), and ABT-333 (400 mg) were the doses under evaluation in the Phase2a studies at the time of conduct of this drug-drug interaction trial. The dose of gemfibrozil (600 mg twice daily) is the dose commonly used in the DDI trials (including some DDI trials described in the prescribing information of gemfibrozil).

### Identity of Investigational Products

Table 1 shows the identity of the investigational products used in the trial.

	ABT-333	ABT-450	Ritonavir	Lopid® (Gemfibrozil)
Dosage Form	Tablet	Tablet	Soft Gelatin Capsule	Tablet
Strength	400 mg	50 mg	100 mg	600 mg
Bulk Product Lot Number	11-002720	10-003507	11-005635	12-000485
Manufacturing Site	Abbott Abbott Park, IL	(b) (4)	Abbott Abbott Park, IL	Pfizer New York, NY
Finishing Lot Number	12-000754	12-000755	12-000756	12-000757
Retest Date	(b) (4)			

Lopid® (gemfibrozil) 600 mg tablets were manufactured by Pfizer, New York, NY, as Lot V111123, NDC #0071-0737-20.

### Sample Collection

Blood samples for assay of ABT-333, ABT-333 M1 metabolite, ABT-450 and ritonavir were collected by venipuncture on the following days:

Day 1: prior to dosing (0 hour) and up to 48 hours after dosing.

Day 6: prior to morning dosing (0 hour) and up to 72 hours after dosing

Blood samples for assay of gemfibrozil were collected at 2 and 4 hours after morning dosing on Study Day 6.

### **Pharmacokinetic Analysis**

The pharmacokinetic parameters were computed using non-compartmental methods.

## **Results**

### ***Bioanalytical methods***

Table 2 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	1.72, 28.7, 359	5.5 % to 7.9 %	-1.5 % to 6.2 %
Ritonavir	4.93-3540	4.93	14,233,2920	4.5 % to 4.8 %	-1.2 % to 2.1 %
ABT-267	0.424-305	0.424	1.25, 20.8, 259	5.3 % to 7.3 %	-1.3 % to 6.1 %
ABT-333	4.57-3290	4.57	13.5, 225, 2810	4.8 % to 6.4 %	0.9 % to 4.6 %
ABT-333 M1	4.72-3400	4.72	13.8, 230, 2880	5.7 % to 7.1 %	-0.7 % to 1.8 %
Gemfibrozil	50-50,000	50	150,2750, 25,000, 38,000	N/A	-2.9 % to 5 %

N/A: % CV not computed as there was only one run.

*Reviewer's Note: Although ABT-267 was not dosed in the study, all samples were assayed for ABT-267 because ABT-267 was one of the 5 analytes validated in the analytical method. No quantifiable concentrations were observed from any study sample.*

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

Adult male and female subjects (N = 12) were enrolled in the study, and 11 subjects (10 males and 1 female) completed the study. Subject 308, 53 year-old Black male, discontinued from the study due to pruritus after receiving ABT-333 400 mg and ABT-450/r 150/100 mg on Study Day 1 and therefore, did not undergo day 6 blood sample collection. This subject was not included in the repeated measure analysis to assess the effect of gemfibrozil on ABT-333, ABT-333 M1 metabolite, ABT-450, ritonavir, but was included in the calculation of the pharmacokinetic parameters on study day 1.

Table 3 below shows the demographic summary of all subjects enrolled in the trial.

	Mean ± SD (N = 12)	Min – Max
Age (years)	34.8 ± 10.5	22 – 53
Weight (kg)	81.8 ± 17.3	57 – 107
Height (cm)	178 ± 11.9	161 – 195
Sex	11 Males (92%), 1 Female (8%)	
Race	8 White (67%), 4 Black (33%)	

## Pharmacokinetics

### ABT-333

Table 4 below shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 metabolite on study day 1 and study day 6.

Pharmacokinetic Parameters	Units	Study Day 1 ABT-333 400 mg + ABT-450/r 150/100 mg (N = 12)	Study Day 6 ABT-333 400 mg QD + ABT-450/r 150/100 mg QD + Gemfibrozil 600 mg BID (N = 11)
		ABT-333	
C <sub>max</sub>	ng/mL	1120 ± 393	2140 ± 541
T <sub>max</sub>	h	3.3 ± 1.4	5.4 ± 1.9
t <sub>1/2</sub> <sup>a</sup>	h	--	90.1 ± 18.9
AUC <sub>t</sub>	ng•h/mL	10200 ± 5700	--
AUC <sub>0-72</sub>	ng•h/mL	10300 ± 5830	102000 ± 22000
Pharmacokinetic Parameters	Units	ABT-333 M1 Metabolite	
C <sub>max</sub>	ng/mL	587 ± 159	30.3 ± 18.0
T <sub>max</sub>	h	4.1 ± 1.1	16.1 ± 9.9
t <sub>1/2</sub> <sup>a</sup>	h	--	79.6 ± 58.3 <sup>b</sup>
AUC <sub>t</sub>	ng•h/mL	4730 ± 1730	--
AUC <sub>0-72</sub>	ng•h/mL	4800 ± 1730	1080 ± 566

a. Harmonic mean ± pseudo-standard deviation. Since blood samples were collected only up to 72 hours after dosing on Study Day 6, the half-lives of ABT-333 and ABT-333 M1 metabolite may be underestimated as the estimated t<sub>1/2</sub> is longer than the sample collection duration.

b. N = 8.

Note: AUC<sub>∞</sub> was not reported for Study Day 6 because the extrapolated area was greater than 50%.

Following coadministration of gemfibrozil 600 mg BID with ABT-333 400 mg on Study Day 6, ABT-333 exposure was approximately 10-fold higher and ABT-333 M1 metabolite exposure was approximately 4-fold lower compared to ABT-333 administered without gemfibrozil on Study Day 1. The mean terminal phase elimination half-lives of ABT-333 and ABT-333 M1 metabolite were prolonged from approximately 5 hours on Study Day 1 to 90 and 80 hours, respectively, on Study Day 6. As blood samples were collected only up to 72 hours after dosing on Study Day 6, the half-lives of ABT-333 and ABT-333 M1 metabolite may be underestimated as the estimated t<sub>1/2</sub> is longer than the

sample collection duration.  $AUC_{\infty}$  was not reported for Study Day 6 because the extrapolated area was greater than 50 %.

#### ABT-450

Table 5 below shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 on study day 1 and study day 6.

ABT-450 Pharmacokinetic Parameters	Units	Study Day 1 ABT-333 400 mg + ABT-450/r 150/100 mg (N = 12)	Study Day 6 ABT-333 400 mg QD + ABT-450/r 150/100 mg QD + Gemfibrozil 600 mg BID (N = 11)
$C_{max}$	ng/mL	618 $\pm$ 802	794 $\pm$ 814
$T_{max}$	h	5.7 $\pm$ 1.8	5.1 $\pm$ 0.8
$t_{1/2}$ <sup>a</sup>	h	--	5.05 $\pm$ 0.80
$AUC_t$	ng•h/mL	3810 $\pm$ 3650	5160 $\pm$ 4090
$AUC_{\infty}$	ng•h/mL	3830 $\pm$ 3650	5170 $\pm$ 4080

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

#### Ritonavir

Table 6 below shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir on study day 1 and study day 6.

Ritonavir Pharmacokinetic Parameters	Units	Study Day 1 ABT-333 400 mg + ABT-450/r 150/100 mg (N = 12)	Study Day 6 ABT-333 400 mg QD + ABT-450/r 150/100 mg QD + Gemfibrozil 600 mg BID (N = 11)
$C_{max}$	ng/mL	1080 $\pm$ 499	867 $\pm$ 408
$T_{max}$	h	4.6 $\pm$ 0.8	4.8 $\pm$ 0.9
$t_{1/2}$ <sup>a</sup>	h	--	3.99 $\pm$ 0.52
$AUC_t$	ng•h/mL	8410 $\pm$ 4850	6840 $\pm$ 3490
$AUC_{\infty}$	ng•h/mL	8490 $\pm$ 4830	6930 $\pm$ 3470

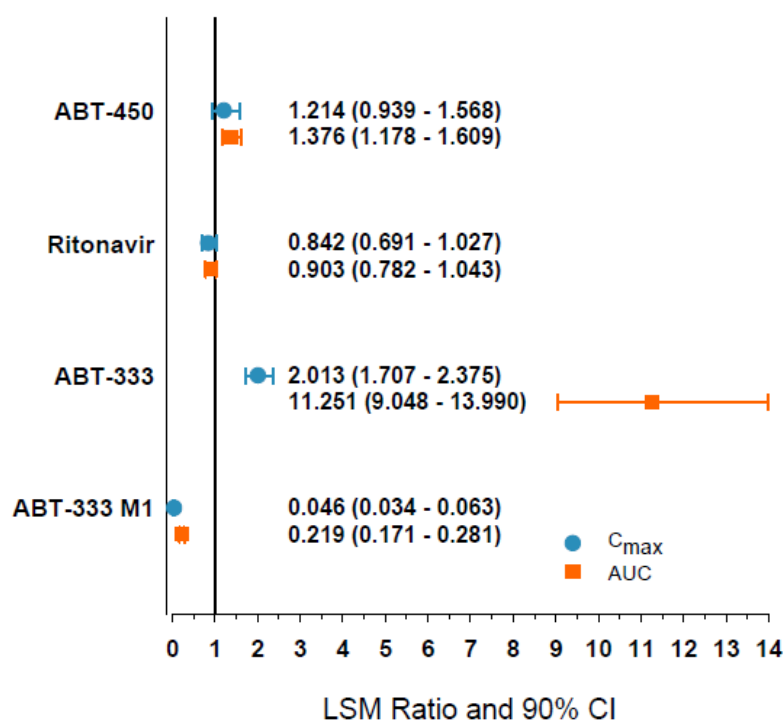
a. Harmonic mean  $\pm$  pseudo-standard deviation.

#### Gemfibrozil

The mean  $\pm$  gemfibrozil plasma concentration at 2 and 4 hours after the morning dose on day 6 was 22000  $\pm$  8660 ng/mL and 10000  $\pm$  3280 ng/mL, respectively.

#### Statistical Evaluation of the Pharmacokinetic Parameters

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 metabolite.



#### Reviewer's Interpretation of Alteration in Exposures of the Various Medications Evaluated in Trial M12-196

- The mean systemic exposures of ABT-333 (a CYP2C8 substrate) were increased by 11-fold when ABT-450/3 + ABT-333 was co-administered with gemfibrozil (a CYP2C8 inhibitor).
- The mean systemic exposures of the ABT-333 M1 metabolite were decreased by 78 %, suggesting that the conversion of ABT-333 to ABT-333 M1 metabolite may be mediated, in part, by CYP2C8.
- Gemfibrozil, in addition to being a CYP2C8 inhibitor, is also an inhibitor of OATP1B1 transporters. This may explain the mean increase in the systemic exposure of ABT-450 (a substrate of OATP1B1) by approximately 38 % when ABT-450/ritonavir +ABT-333 was co-administered with gemfibrozil.

#### Safety

No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study. One subject discontinued from the study due to pruritus after receiving ABT-333 400 mg and ABT-450/r 150/100 mg on Study Day 1. One subject had an adverse event of elevated triglyceride levels on Study Day 30, which occurred beginning 22 days after receiving the last dose of gemfibrozil 600 mg BID + ABT-333 400 mg + ABT-450/r 150/100 mg on Study Day 8.

## Results

Co-administration of ABT-450/r and ABT-333 with gemfibrozil:

- Increased the mean  $C_{\max}$  and AUC of ABT-450 by 21 % and 38 % , respectively.
- Decreased the mean  $C_{\max}$  and AUC of ritonavir by 16 % and 10 % , respectively.
- Increased the mean  $C_{\max}$  and AUC of ABT-333 by 101 % and 1025 % , respectively.
- Decreased the mean  $C_{\max}$  and AUC of ABT-333 M1 metabolite by 95 % and 78 % , respectively.

## Conclusion

Co-administration of the DAA regimen (ABT-450/r/267 +ABT-333) and gemfibrozil is contraindicated based on following:

- Significant increase in the exposures of ABT-333.
- Safety findings from the Phase 2 trials that suggest that ABT-333 doses greater than the exposures observed with ABT-333 400 mg (based on the Phase 2 formulation; equivalent in terms of systemic exposures to the 250 mg (b) (4) formulation used in this trial and the clinically recommended formulation) were associated with hemoglobin decrease and potential to prolong the QTc.



**Drug-Drug Interaction Trial with Atripla**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M13-104**

**Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-Administration of Atripla (efavirenz, emtricitabine, and tenofovir disoproxil fumarate) and ABT-333 plus ABT-450 with Ritonavir (ABT-450/r), with and without ABT-267 in Healthy Adult Subjects.**

**Trial Period**

January 17, 2012 to March 24, 2012

Final report date: October 9, 2012

**Trial Objectives**

The objectives were to evaluate the pharmacokinetics, safety and tolerability of the coadministration of ABT-333 plus ABT-450/r with and without ABT-267 on efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) at steady state in healthy subjects, and to evaluate the pharmacokinetics, safety and tolerability of Atripla on coadministration of ABT-333 plus ABT-450/r with and without ABT-267 at steady state in healthy subjects.

**Trial Design**

This was a Phase 1, single center, randomized, multiple-dose, non-fasting, open-label study to evaluate the coadministration of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) with 2 direct-acting antiviral agents (DAAs) (Arm 1: ABT-333 and ABT-450/r) or with 3 DAAs (Arm 2: ABT-333, ABT-450/r, and ABT-267).

**Table 1 shows the dosing sequences in the trial:**

Arm	Cohort	Subject Numbers	N	Regimens	
				Period 1	Period 2
1	1	502, 504, <sup>a</sup> 505, 507, <sup>a</sup> 511, 512, 513, 515, <sup>a</sup> 516	9	A	B
	2	501, 503, <sup>a</sup> 506, <sup>a</sup> 508, <sup>a</sup> 509, <sup>a</sup> 510, <sup>a</sup> 514 <sup>a</sup>	7	C	B

a. Subjects who discontinued from the study due to adverse events.

Regimen A = ABT-333 400 mg BID + ABT-450/r 150/100 mg QD administered under non-fasting conditions

Regimen B = ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) 600/200/300 mg QD administered under non-fasting conditions

Regimen C = efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) 600/200/300 mg QD administered under non-fasting conditions

In Arm 1 Cohort 1, ABT-333 400 mg BID and ABT-450/r 150/100 mg QD were to be administered for 28 days. Starting on study day 15, efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) was to be administered for 14 days (study day 15 through 28). In Arm 1 Cohort 2, efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) was to be administered for 28 days (study days 1 through 28). Starting on study day 15, ABT-333 400 mg BID and ABT-450/r 150/100 mg QD were to be administered for 14 days (study day 15 through 28).

**Arm 1 consisted of 16 subjects: Cohort 1 (N =9) and Cohort 2 (N = 7). This study was terminated during Arm 1 (Study Day 17 of Period 2) due to safety reasons. None of the subjects completed the study.**

Major Safety Findings from the Trial:

- **Subject 503**, a 30 year-old White/Hispanic male, discontinued from the study due to nausea and vomiting on Study Day 15; headache on Study Day 16; and ear pain and elevations of ALT and AST on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 15.
- **Subject 504**, a 25 year-old Black male, discontinued from the study due to dizziness, headache and vomiting on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 16.
- **Subject 506**, a 46 year-old Black male, discontinued from the study due to nausea on Study Day 15 and moderate elevations of ALT and AST on Study Day 17. The last dosing of study drugs occurred on the evening of Study Day 15.
- **Subject 507**, a 30 year-old White male, discontinued from the study due to presyncope on Study Day 15 and altered mood on Study Day 16. The last dosing of study drugs occurred on the evening of Study Day 15.
- **Subject 508**, a 34 year-old Black male, discontinued from the study due to feeling abnormal, vomiting, dizziness, hot flush, haemoptysis and nausea on Study Day 15 and elevations of ALT and AST on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 15.
- **Subject 509**, a 42 year-old Black-American Indian/Alaska Native male, discontinued from the study due to elevation of ALT on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 17.
- **Subject 510**, a 47 year-old White male, discontinued from the study due to dizziness and elevation of ALT on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 17.
- **Subject 514**, a 36 year-old White male, discontinued from the study due to hot flush, vomiting, presyncope and elevation of ALT on Study Day 17. The last dosing of study drugs occurred on the morning of Study Day 17.
- **Subject 515**, a 29 year-old White male, discontinued from the study due to feeling abnormal, dizziness, headache and nausea on Study Day 15; chills on Study Day 16; and tinnitus on Study Day 17. The last dosing of study drugs occurred on the evening of Study Day 15.

## Pharmacokinetic Assessments

Since the study was terminated during Arm 1 (study day 17 of period 2) due to safety reasons (tolerability and increased enzyme levels), no statistical analysis was performed on the pharmacokinetic data and no drug drug interaction between Atripla and DAAs (ABT-333 and ABT-450/r) was evaluated.

## Conclusion

Co-administration of the 3-DAA regimen (ABT-450/r/ABT-267 + ABT-333) with efavirenz based regimens is contraindicated.

*Reviewer's Note:*

*The applicant conducted trial M13-783 in which the potential for drug-drug interaction between the 3-DAA regimen and emtricitabine/tenofovir (Truvada) was evaluated. The results of the trial showed that the 3-DAA regimen can be co-administered with Truvada without any dose adjustments. Because Atripla contains efavirenz (in addition to emtricitabine and tenofovir), the results of trial M13-104 suggest that the adverse events observed in the trial may be attributed to efavirenz in the regimen. Hence, the clinical recommendation applies to all efavirenz containing regimens.*

**Drug-Drug Interaction Trial with Oral Contraceptives**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M12-205**

**Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-Administration of an Oral Contraceptive with Combination Therapy of ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) with or without ABT-333 in Healthy Premenopausal Female Subjects.**

**Trial Period**

June 6, 2013 through February 20, 2014

Final report date: March 19, 2014

**Trial Objectives**

- [Arm 1 and Arm 2] To evaluate the effect of combination therapy of ABT-450/r/ABT-267 with or without ABT-333 on the pharmacokinetics, safety, and tolerability of a COC containing Ethinyl Estradiol (EE) + Norgestimate (NGM) at steady-state in healthy premenopausal female subjects.
- [Arm 1 and Arm 2] To determine the effect of a COC containing EE + NGM on the pharmacokinetics, safety, and tolerability of combination therapy of ABT-450/r/ABT-267 with or without ABT-333 at steady-state in healthy premenopausal female subjects.
- [Arm 3] To evaluate the effect of combination therapy of ABT-450/r/ABT-267 with ABT-333 on the pharmacokinetics, safety and tolerability of a progestin only pill (POP) containing norethindrone (NET) at steady-state in healthy premenopausal female subjects.
- [Arm 3] To determine the effect of a POP containing NET on the pharmacokinetics, safety, and tolerability of combination therapy of ABT-450/r/ABT-267 with ABT-333 at steady-state in healthy premenopausal female subjects.
- [Arm 4] To evaluate the effect of combination therapy of ABT-450/r/ABT-267 with ABT-333 on the pharmacokinetics, safety and tolerability of a COC containing EE + NET oral contraceptive at steady-state in healthy premenopausal female subjects.
- [Arm 4] To determine the effect of a COC containing EE + NET on the pharmacokinetics, safety, and tolerability of combination therapy of ABT-450/r/ABT-267 with ABT-333 at steady-state in healthy premenopausal female subjects

## **Trial Design**

Phase 1, single-center, randomized, multiple-dose, non-fasting, open-label, four arm study to evaluate the effect of 2- and 3-DAA combinations (ABT-450/r/ABT-267 with or without ABT-333) on the pharmacokinetics, safety, and tolerability of an EE+NGM containing COC, and *vice versa*.

### **Arms 1 and 2**

After meeting the selection criteria, the subjects for Arm 1 and Arm 2 were enrolled in the following schedule:

- Subjects who were currently taking Ortho-Cyclen or equivalent for at least 3 months were enrolled on the first day of the next 28-day pack of Ortho-Cyclen therapy. An equivalent of Ortho-Cyclen was defined as one that contained EE and NGM with same doses as in Ortho-Cyclen.
- Subjects who were currently on EE and NGM based COC but with different doses compared to Ortho-Cyclen were enrolled if they were willing to switch to Ortho-Cyclen.
- Subjects who were currently receiving hormonal contraceptives other than the combination of EE and NGM were washed-out of current therapy for 14 days prior to confinement on Study Day –1.

### **Arms 3**

- Subjects who were currently taking Jolivette or equivalent for at least 3 months. An equivalent of Jolivette was defined as one that contained NET with same dose as in Jolivette.
- Subjects who were currently receiving hormonal contraceptives other than the POP containing NET were washed-out of current therapy for 14 days prior to confinement on Study Day –1.

### **Arms 4**

- Subjects who were currently taking Balziva or equivalent for at least 3 months were enrolled on the first day of the next 28-day pack of Balziva therapy. An equivalent of Balziva was defined as one that contained EE and NGM with same doses as in Balziva.
- Subjects who were currently on EE and NET based COC but with different doses compared to Balziva were enrolled if they were willing to switch to Balziva.
- Subjects who were currently receiving hormonal contraceptives other than the combination of EE and NET were washed-out of current therapy for 14 days

prior to confinement on Study Day –1.

**Equal number of subjects (planned: 12 subjects per arm) were to be randomly assigned to Arms 1 and 2, however enrollment was discontinued (N = 4 for Arm 1 and N = 6 for Arm 2) due to ALT elevations and a different progestin (NET) was evaluated in Arm 3.**

Equal number of subjects (12 subjects per arm) were sequentially (no randomization) assigned to Arms 3 and 4. Based on safety results from Arm 3, the effect of 3-DAA combination (ABT-450/r/ABT-267 + ABT-333) on the pharmacokinetics, safety, and tolerability of a COC containing EE + NET and vice versa was evaluated in Arm 4. Arm 4 would have been discontinued had the Arm 3 PK data demonstrated a > 2.5-fold increase in mean AUC values for NET. This proposal was based primarily on the magnitude of interaction observed when EE/NET was dosed with atazanavir; a 2.1-fold increase in NET AUC was observed. The interaction with atazanavir is mediated by UGT1A1 inhibition and possibly by CYP 3A4 inhibition, and a similar interaction can be expected with the 3-DAA regimen, which contains UGT 1A1 inhibitors (DAAs) and a strong CYP 3A4 inhibitor and UGT 1A1 inducer (ritonavir).

**Arm 4 was prematurely discontinued due to safety reasons and none of the subjects completed arm 4. The last dose of the study drug was administered on day 15.**

Table 1 shows the various sequence groups in the trial.

Arm	Subject Numbers	N	Regimens	
			Arms 1 and 2: Study Days 1 – 9 Arm 3: Study Days 1 – 3 Arm 4: Study Days 1 – 7	Arms 1 and 2: Study Days 10 – 28 Arm 3: Study Days 4 – 24 Arm 4: Study Days 8 – 28
1	101, <sup>a</sup> 102, 103, 110	4	A	B
2	104, <sup>b</sup> 105, 106, 107, <sup>b</sup> 108, 109	6	A	C
3	301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312	12	D	E
4	401, <sup>a</sup> 402, 403, 404, 405, 406, <sup>b</sup> 407, 408, 409, 410, 411, 412	12	F <sup>c</sup>	G <sup>c</sup>

a. Subject withdrew from the study.

b. Subject prematurely discontinued due to adverse event(s).

c. Arm 4 was initiated after completion of dosing and safety evaluation results confirmed a favorable profile in at least 6 subjects from Arm 3. Arm 4 was enrolled with the 3-DAA combination (ABT-450/r/ABT-267 and ABT-333) and COC containing EE + NET based on results from Arm 3. Arm 4 would have been discontinued, had the Arm 3 pharmacokinetic (PK) data demonstrated a > 2.5-fold increase in mean area under the plasma concentration-time curve (AUC) values for NET.

Note: Enrollment was discontinued for Arms 1 and 2 and Arm 4 was prematurely discontinued on Study Day 15 due to safety reasons.

Study drug was administered beginning on study day 1 as follows:

**Regimen A:** Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions for 9 days (Study Days 1 through 9).

**Regimen B:** Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions for 12 days (Study Days 10 through 21). ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions for 19 days (Study Days 10 through 28) with the QD doses being administered in the morning.

**Regimen C** Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions for 12 days (Study Days 10 through 21). ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions for 19 days (Study Days 10 through 28).

**Regimen D** Jolivette (NET 0.35 mg) QD administered under non-fasting conditions for 3 days (Study Days 1 through 3).

**Regimen E** Jolivette (NET 0.35 mg) QD administered under non-fasting conditions for 14 days (Study Days 4 through 17). ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions for 21 days (Study Days 4 through 24) with QD doses being administered in the morning.

**Regimen F:** Balziva (EE/NET 35 µg/0.4 mg) QD administered under non-fasting conditions for 7 days (Study Days 1 through 7).

**Regimen G:** Balziva (EE/NET 35 µg/0.4 mg) QD administered under non-fasting conditions for 14 days (Study Days 8 through 21). ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions for 21 days (Study Days 8 through 28) with the QD doses being administered in the morning.

In Arm 1, Arm 2 and Arm 4, subjects were to be confined to the study site and supervised for approximately 30 days. Confinement began on the day prior to dosing (Study Day – 1) and was to end after the collection of the 24-hour DAA blood sample and completion of all scheduled study procedures on Study Day 29. In Arms 1 and 2, intensive pharmacokinetic sampling for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 (ABT-333 and ABT-333 M1 for Arm 1) occurred on Study Days 10, 21 and 28 and for EE and NGM metabolites, norelgestromin (NGMN), and norgestrel (NG) occurred on Study Days 9, 10 and 21. In Arm 4, intensive pharmacokinetic sampling for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 was to occur on Study Days 8, 21 and 28 and for EE and NET on Study Days 7, 8 and 21. Arm 4 was prematurely discontinued due to safety reasons therefore intensive pharmacokinetic sampling actually occurred on Study Day 8 for DAAs and Study Days 7 and 8 for EE and NET.

In Arm 3, subjects were confined to the study site and supervised for approximately 26 days. The confinement began on the day prior to dosing (Study Day –1) and ended after the collection of the 24-hour DAA blood sample and completion of all scheduled study

procedures on Study Day 25 for Arm 3. Intensive pharmacokinetic sample for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 occurred on Study Days 4, 17, and 24 and for NET occurred on Study Days 3, 4, and 17.

Subjects received a standardized diet, providing approximately 40% of the daily calories from fat and up to 45% of the daily calories from carbohydrates (approximately 2,200 calories/day), for all meals during confinement.

In the morning of study day 1, each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast. Each evening dose of ABT-333 (for Arms 1, 3 and 4) was taken orally with approximately 240 mL of water approximately 30 minutes after the start of the evening snack.

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

Oral contraceptives containing a combination of an EE and a progestin are among the most frequently used methods of birth control. EE is metabolized by sulfotransferases, CYP3A4, and UGTs. The metabolism of most of the progestins is not well established; however, CYP3A4 and UGTs may play a role in their metabolism. Therefore, the metabolism of EE, NGM, and NET may be affected by drugs that alter activity of UGTs or sulfate conjugation, by drugs that are inhibitors or inducers of CYP3A4, or via other mechanisms. The DAA regimens contain ABT-450 and ritonavir, which are potent inhibitors of UGT 1A1 and CYP 3A, respectively. In addition, ritonavir induces UGT 1A1. Therefore, the sponsor evaluated the effect of DAAs on the metabolism of oral contraceptives.

### **Rationale for Dose Selection**

The dose of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), ABT-267 (25 mg once daily), and ABT-333 (250 mg twice daily) evaluated in the trial is identical to the dose of ABT-450, ritonavir, ABT-267, and ABT-333 doses used in Phase 3 trials. The doses of oral contraceptives used in the trial are the approved doses.

### **Identity of Investigational Products**

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



Investigational Products	ABT-450/r/ABT-267		ABT-333	
Dosage Form	Tablet		Tablet	
Strength (mg)	75/50/12.5 mg		250 mg	
Bulk Product Lot Number	12-008149		12-007842	
Potency (% of label claim)	(b) (4)			
Manufacturer	AbbVie		AbbVie	
Finishing Lot Number	13-002304	13-004395	13-002305	13-004396
Retest/Expiration Date	(b) (4)			
Investigational Products	Ortho-Cyclen <sup>®</sup> (EE/NGM)	Jolivet <sup>®</sup> (NET)	Balziva <sup>®</sup> (EE/NET)	
Dosage Form	Tablet	Tablet	Tablet	
Strength (mg)	35/250 µg <sup>a</sup>	0.35 mg	35 µg/0.4 mg <sup>b</sup>	
Bulk Product Lot Number	13-002272/ 2GM500	13-004391/ 13BM697	13-004467	
Potency (% of label claim)	NA	NA	NA	
Manufacturer	Janssen	Watson Pharmaceuticals	Barr Laboratories	
Finishing Lot Number	13-002306	13-004399	13-004492	
Retest/Expiration Date	(b) (4)			

NA = Not Available

a. Only active blue tablets were administered from Study Days 1 to 21. Green placebo tablets were not dosed.

b. Only active light peach tablets were administered from Study Days 1 to 15. White placebo tablets were not dosed.

## Key Inclusion and Exclusion Criteria

### Inclusion Criteria:

- Premenopausal female between 18 and 49 years of age, inclusive.
- Subjects had a history of regular menstrual cycles while not on hormonal contraception with a length of 24-32 days with at least 3 and no more than 7 days of bleeding per month for at least the past 3 months prior to study drug administration.
- Subject agreed to use an acceptable method of non hormonal contraception consistently during Screening phase of the study, while receiving study drug, and for 30 days after the last dose of study drug. Acceptable methods of birth control included the following:
  - total abstinence from sexual intercourse as the preferred lifestyle of the subject, periodic abstinence was not acceptable;
  - vasectomized partner(s);
  - non-hormonal intrauterine device (IUD); or
  - double-barrier method (condoms, contraceptive sponge, or diaphragm with spermicidal jellies or creams).

Hormonal contraceptives other than those administered during this study (including oral, topical, injectable or implantable varieties) were not used until 2 weeks after the end of study drug dosing unless approved by the AbbVie Study Designated Physician.

- Female had negative results for pregnancy test performed at screening on a urine specimen obtained within 28 days prior to initial study drug administration, and prior to dosing a serum sample obtained on study day -1.
- Body mass index (BMI) was  $\geq 18$  to  $< 30 \text{ Kg/m}^2$ .

#### Exclusion Criteria:

- Required any over-the-counter and/or prescription medication, vitamins, and herbal supplements on a regular basis.
- Used any medications (prescription and over-the-counter), vitamins, and/or herbal supplements within the 2-week period prior to the first dose of study drug administration or within 10 half-lives of the respective medication, whichever was longer.
- Used known inhibitors (e.g., ketoconazole) or inducers (e.g., carbamazepine) of cytochrome P450 3A (CYP3A) or cytochrome P450 2C8 (CYP2C8) (e.g., gemfibrozil, montelukast), or OATP1B1 (e.g. cyclosporine) within 1 month prior to study drug administration.
- Received any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks prior to study drug administration.
- Consumed grapefruit, star fruit, Seville oranges, or products containing any of these ingredients within the 72-hour period prior to study drug administration.

### Pharmacokinetic Analysis

The pharmacokinetic parameters were computed using non-compartmental methods.

### Protocol and Changes to Analysis

Subjects in arms 1 and 2 were enrolled under the original protocol. Per amendment # 1, the trial design was modified to include arm 3 and optional arm 4 and the entry criteria was modified for subjects enrolling into arm 3 and optional arm 4. Amendment # 2 provided details of the pharmacokinetic results from arm 3 which would result in arm 4 of the study not being initiated or being discontinued.

Since Arm 4 was prematurely discontinued on Study Day 15, statistical analysis could not be performed on study days as indicated in the protocol. Instead, statistical analysis for determination of effect of the 3-DAA combination on EE + NET combined oral contraceptives was performed for Study Days 7 and 8 and steady-state analysis was performed when EE+ NET was administered without DAAs (Study Days 5, 6, 7 and 8). No statistical analysis was performed for DAA pharmacokinetic data.

## Results

### *Bioanalytical methods*

Table 3 shows 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	1.38, 40, 344	5.6 % to 8.8 %	-3.5 % to -1.4 %
Ritonavir	4.71-3380	4.71	11, 320, 2760	3.2 % to 7 %	-1.1 % to 2.5 %
ABT-267	0.417-299	0.41	1.04, 30.2, 260	5.2 to 17.3 %	-2.6 % to 0 %
ABT-333	4.39-3150	4.39	11, 319, 2740	6.4 % to 10.9 %	-6.9 % to 2.5 %
ABT-333 M1	4.58-3290	4.58	10.7, 311, 2680	3.5 % to 10.2 %	-4.9 % to -2.6 %
Ethinyl Estradiol	0.002-2.05	0.002	0.004, 0.08, 1.62	4 %-9.1 %	-9.3 % to -2.5 %
Norelgestromin	0.02-10.4	0.02	0.05, 0.646, 8.08	1.9 %-4.3%	-12.7 % to -9.3 %
Norgestrel	0.02-10.3	0.02	0.05, 0.63, 7.89	10.7 % to 18.2 %	-6.3 % to -5.2 %
Norethindrone	0.1-60	0.1	0.3, 1.87, 46.9	6.8 %-8.5 %	-3.4 % to 3.7 %

### *Subject Disposition and Demographics*

Table 4 below shows the disposition of subjects enrolled in the trial:

Assessment	Arm 1	Arm 2	Arm 3	Arm 4
Number of Subjects Planned	12	12	12	12
Number of Subjects Enrolled	4	6	12	12
Completed Study	3	4	12	0
Withdrew Consent	1	0	0	1
Prematurely Discontinued due to Adverse Event(s)	0	2	0	1
Prematurely Discontinued – Other	0	0	0	10 <sup>a</sup>

a. Arm 4 was prematurely discontinued due to safety reasons.

The data of all subjects were included in the analysis with the following exceptions:

- Subject 101 (Arm 1), a 25 year old White female, withdrew consent due to a family emergency. The last dosing of study drug occurred in the morning on Study Day 6. No PK data was collected and the subject was excluded from all pharmacokinetic summaries and analysis.
- Subject 104 (Arm 2), a 26 year old Asian female, was prematurely discontinued on day study day 25 due to grade 3 ALT elevations. The last dose of study drug occurred in the morning on Study Day 25; pharmacokinetic samples collected on

- study days 27 and 28 were excluded and the subject was excluded from statistical analysis of the pharmacokinetic parameters of the DAAs.
- Subject 107 (Arm 2), a 27 year old Asian female, was prematurely discontinued on Study Day 21 due to due to grade 3 ALT elevations. The last dose of study drug occurred in the morning on Study Day 21, therefore, pharmacokinetic samples collected on days 26, 27, and 28 were excluded and the subject was excluded from statistical analysis of the pharmacokinetic parameters of the DAAs.
  - Subject 401 (Arm 4), a 31 year old White female, withdrew consent; subject experienced multiple adverse events and wanted to stop dosing. The last dose of study drug occurred in the morning on Study Day 14.
  - Subject 406 (Arm 4), a 37 year old Black female, was prematurely discontinued due to an adverse event of transaminases increased that began on Study Day 11. The last dose of study drug occurred in the morning on Study Day 13.

Table 5 below shows the demographic summary of all subjects.

	Arm 1		Arm 2	
	Mean ± SD (N = 4)	Min – Max	Mean ± SD (N = 6)	Min – Max
Age (years)	29.5 ± 9.33	22 – 43	31.8 ± 9.47	25 – 45
Weight (kg)	58.8 ± 4.72	52 – 62	70.8 ± 12.5	51 – 89
Height (cm)	157 ± 5.69	149 – 162	167 ± 9.64	158 – 181
Race	3 White (75%), 1 Asian (25%)		4 White (67%), 2 Asian (33%)	
	Arm 3		Arm 4	
	Mean ± SD (N = 12)	Min – Max	Mean ± SD (N = 12)	Min – Max
Age (years)	30.6 ± 8.41	22 – 46	31.8 ± 8.64	21 – 49
Weight (kg)	67.1 ± 11.3	51 – 91	66.1 ± 10.7	47 – 81
Height (cm)	163 ± 7.20	153 – 174	166 ± 6.09	156 – 174
Race	8 White (67%), 4 Black or African American (33%)		7 White (58%), 5 Black or African American (42%)	
Overall				
	Mean ± SD (N = 34)	Min – Max		
Age (years)	31.1 ± 8.41	21 – 49		
Weight (kg)	66.4 ± 10.8	47 – 91		
Height (cm)	164 ± 7.41	149 – 181		
Race	22 White (65%), 9 Black or African American (27%), 3 Asian (9%)			

### Pharmacokinetics

Arm 1 (ABT-450/r/ABT-267, ABT-333 and Ortho Cyclen) and Arm 2 (ABT-450/r/ABT-267 and Ortho Cyclen)

## ABT-450

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 (Arms 1 and 2)

		Arm 1		
Parameter (Unit)		Day 10	Day 21	Day 28
N		3	3	3
C <sub>max</sub>	ng/mL	1280 $\pm$ 478	6000 $\pm$ 6960	7310 $\pm$ 1860
T <sub>max</sub>	h	4.7 $\pm$ 1.2	5.3 $\pm$ 2.3	4.7 $\pm$ 1.2
AUC <sub>24</sub>	ng•h/mL	7550 $\pm$ 4130	72500 $\pm$ 109000	73700 $\pm$ 71900
C <sub>24</sub>	ng/mL	70.1 $\pm$ 83.9	1560 $\pm$ 2630	1150 $\pm$ 1920
		Arm 2		
Parameter (Unit)		Day 10	Day 21	Day 28
N		6	6	4
C <sub>max</sub>	ng/mL	1210 $\pm$ 1020	5530 $\pm$ 3750	6550 $\pm$ 3200
T <sub>max</sub>	h	4.7 $\pm$ 1.6	4.0 $\pm$ 0.0	3.0 $\pm$ 1.2
AUC <sub>24</sub>	ng•h/mL	7200 $\pm$ 7050	34300 $\pm$ 35400	48600 $\pm$ 46100
C <sub>24</sub>	ng/mL	30.8 $\pm$ 32.5	144 $\pm$ 229	360 $\pm$ 607
Arm 1: Ortho-Cyclen (EE/NGM 35/250 $\mu$ g) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 $\mu$ g) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				

## Ritonavir (Arm 1 and 2)

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir (Arms 1 and 2)

		Arm 1		
Parameter (Unit)		Day 10	Day 21	Day 28
N		3	3	3
C <sub>max</sub>	ng/mL	1260 $\pm$ 577	1940 $\pm$ 1160	2440 $\pm$ 540
T <sub>max</sub>	h	4.7 $\pm$ 1.2	5.3 $\pm$ 2.3	4.7 $\pm$ 1.2
AUC <sub>24</sub>	ng•h/mL	6710 $\pm$ 3190	13400 $\pm$ 8820	18700 $\pm$ 3960
C <sub>24</sub>	ng/mL	21.6 $\pm$ 17.2	75.6 $\pm$ 99.1	87.1 $\pm$ 109
		Arm 2		
Parameter (Unit)		Day 10	Day 21	Day 28
N		6	6	4
C <sub>max</sub>	ng/mL	1270 $\pm$ 400	2010 $\pm$ 650	1970 $\pm$ 501
T <sub>max</sub>	h	3.7 $\pm$ 0.8	4.0 $\pm$ 0.0	2.5 $\pm$ 1.0
AUC <sub>24</sub>	ng•h/mL	7220 $\pm$ 2790	11400 $\pm$ 5140	13900 $\pm$ 7760
C <sub>24</sub>	ng/mL	16.7 $\pm$ 9.20	36.5 $\pm$ 38.3	59.0 $\pm$ 72.3
Arm 1: Ortho-Cyclen (EE/NGM 35/250 $\mu$ g) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 $\mu$ g) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				

## ABT-267 (Arm 1 and 2)

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 (Arms 1 and 2)

Arm 1				
Parameter (Unit)		Day 10	Day 21	Day 28
N		3	3	3
C <sub>max</sub>	ng/mL	126 ± 57.8	113 ± 47.0	123 ± 60.0
T <sub>max</sub>	h	4.7 ± 1.2	5.3 ± 1.2	4.7 ± 1.2
AUC <sub>24</sub>	ng•h/mL	1060 ± 468	1540 ± 387	1580 ± 538
C <sub>24</sub>	ng/mL	18.0 ± 2.97	39.9 ± 7.49	37.5 ± 7.19
Arm 2				
		Day 10	Day 21	Day 28
N		6	6	4
C <sub>max</sub>	ng/mL	119 ± 30.9	122 ± 15.4	106 ± 16.3
T <sub>max</sub>	h	4.0 ± 0.0	4.0 ± 0.0	4.5 ± 1.0
AUC <sub>24</sub>	ng•h/mL	1060 ± 181	1460 ± 214	1450 ± 173
C <sub>24</sub>	ng/mL	15.8 ± 2.72	34.9 ± 8.60	35.7 ± 8.46
Arm 1: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				

## ABT-333 and ABT-333 M1 Metabolite (Arm 1)

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 (Arms 1)

ABT-333 Arm 1				
Parameter (Unit)		Day 10	Day 21	Day 28
N		3	3	3
C <sub>max</sub>	ng/mL	1060 ± 495	682 ± 406	1330 ± 661
T <sub>max</sub>	h	4.7 ± 1.2	5.3 ± 2.3	3.3 ± 2.3
AUC <sub>12</sub>	ng•h/mL	5540 ± 2400	4330 ± 1120	9510 ± 3960
C <sub>12</sub>	ng/mL	246 ± 132	215 ± 64.0	408 ± 129
ABT-333 M1 Arm 1				
		Day 10	Day 21	Day 28
N		3	3	3
C <sub>max</sub>	ng/mL	640 ± 114	593 ± 330	869 ± 239
T <sub>max</sub>	h	4.7 ± 1.2	6.0 ± 2.0	4.7 ± 1.2
AUC <sub>12</sub>	ng•h/mL	3550 ± 1170	3930 ± 2310	6450 ± 1490
C <sub>12</sub>	ng/mL	160 ± 44.9	209 ± 135	298 ± 65.6
Arm 1: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				

## Ethinyl Estradiol PK (Arms1 and 2)

Table 10 shows the mean  $\pm$  SD pharmacokinetic parameters of ethinyl estradiol (Arms 1 and 2)

Parameter (Unit)		Arm 1		
		Day 9	Day 10	Day 21
N		3	3	3
C <sub>max</sub>	ng/mL	0.11 $\pm$ 0.06	0.13 $\pm$ 0.06	0.12 $\pm$ 0.04
T <sub>max</sub>	h	2.3 $\pm$ 1.5	2.7 $\pm$ 1.2	1.7 $\pm$ 0.6
AUC <sub>24</sub>	ng•h/mL	1.27 $\pm$ 0.36	1.42 $\pm$ 0.36	1.39 $\pm$ 0.56
t <sub>1/2</sub> <sup>a</sup>	h	--	--	17.0 $\pm$ 4.50
C <sub>24</sub>	ng/mL	0.03 $\pm$ 0.00	0.03 $\pm$ 0.01	0.03 $\pm$ 0.02
		Arm 2		
		Day 9	Day 10	Day 21
N		5	5	6
C <sub>max</sub>	ng/mL	0.12 $\pm$ 0.06	0.12 $\pm$ 0.05	0.14 $\pm$ 0.04
T <sub>max</sub>	h	1.8 $\pm$ 0.4	2.4 $\pm$ 0.9	1.3 $\pm$ 0.5
AUC <sub>24</sub>	ng•h/mL	1.15 $\pm$ 0.51	1.34 $\pm$ 0.55	1.16 $\pm$ 0.43
t <sub>1/2</sub> <sup>a</sup>	h	--	--	15.4 $\pm$ 2.49
C <sub>24</sub>	ng/mL	0.02 $\pm$ 0.01	0.03 $\pm$ 0.01	0.02 $\pm$ 0.01
Arm 1: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				
a. Harmonic mean $\pm$ pseudo-standard deviation.				

## Norelgestromin PK (Arms1 and 2)

Table 11 shows the mean  $\pm$  SD pharmacokinetic parameters of norelgestromin (Arms 1 and 2)

Parameter (Unit)		Arm 1		
		Day 9	Day 10	Day 21
N		3	3	3
C <sub>max</sub>	ng/mL	1.66 $\pm$ 0.30	2.31 $\pm$ 0.76	3.82 $\pm$ 1.37
T <sub>max</sub>	h	2.3 $\pm$ 1.5	2.7 $\pm$ 1.2	2.0 $\pm$ 0.0
AUC <sub>24</sub>	ng•h/mL	17.5 $\pm$ 1.16	29.8 $\pm$ 2.28	48.1 $\pm$ 14.2
t <sub>1/2</sub> <sup>a</sup>	h	--	--	37.0 $\pm$ 2.54
C <sub>24</sub>	ng/mL	0.45 $\pm$ 0.09	0.89 $\pm$ 0.18	1.53 $\pm$ 0.60
		Arm 2		
		Day 9	Day 10	Day 21
N		6	6	6
C <sub>max</sub>	ng/mL	1.70 $\pm$ 0.43	2.43 $\pm$ 0.38	3.25 $\pm$ 0.68
T <sub>max</sub>	h	1.8 $\pm$ 0.4	3.3 $\pm$ 1.0	2.0 $\pm$ 1.1
AUC <sub>24</sub>	ng•h/mL	16.1 $\pm$ 4.31	28.8 $\pm$ 4.77	41.7 $\pm$ 13.3
t <sub>1/2</sub> <sup>a</sup>	h	--	--	34.0 $\pm$ 5.19
C <sub>24</sub>	ng/mL	0.42 $\pm$ 0.15	0.88 $\pm$ 0.17	1.26 $\pm$ 0.45
Arm 1: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				
a. Harmonic mean $\pm$ pseudo-standard deviation.				

## Norgestrel PK (Arms1 and 2)

Table 12 shows the mean  $\pm$  SD pharmacokinetic parameters of norgestrel (Arms 1 and 2)

		Arm 1		
Parameter (Unit)		Day 9	Day 10	Day 21
N		3	3	3
C <sub>max</sub>	ng/mL	3.53 ± 1.11	3.46 ± 0.95	8.67 ± 5.65
T <sub>max</sub>	h	2.3 ± 1.5	13.1 ± 9.8	2.7 ± 2.3
AUC <sub>24</sub>	ng•h/mL	67.8 ± 25.9	75.0 ± 24.5	179 ± 122
t <sub>1/2</sub> <sup>a</sup>	h	--	--	55.2 ± 9.06
C <sub>24</sub>	ng/mL	2.37 ± 0.86	3.21 ± 1.14	6.75 ± 3.81
		Arm 2		
Parameter (Unit)		Day 9	Day 10	Day 21
N		6	6	6
C <sub>max</sub>	ng/mL	2.49 ± 1.11	2.41 ± 1.06	5.77 ± 3.08
T <sub>max</sub>	h	4.3 ± 4.1	7.7 ± 3.7	7.0 ± 2.8
AUC <sub>24</sub>	ng•h/mL	45.1 ± 22.2	50.3 ± 22.8	120 ± 67.4
t <sub>1/2</sub> <sup>a</sup>	h	--	--	41.2 ± 8.77
C <sub>24</sub>	ng/mL	1.53 ± 0.77	2.16 ± 0.98	4.65 ± 2.51
Arm 1: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 10 through 28.				
Arm 2: Ortho-Cyclen (EE/NGM 35/250 µg) QD administered under non-fasting conditions on Study Days 1 through 21; ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions on Study Days 10 through 28.				
a. Harmonic mean ± pseudo-standard deviation.				

### Arm 3 (ABT-450/r/ABT-267, ABT-333 Jolivet)

Table 13 shows the mean ± SD pharmacokinetic parameters of ABT-450 (Arm 3)

		Arm 3		
Parameter (Unit)		Day 4	Day 17	Day 24
N		12	12	12
C <sub>max</sub>	ng/mL	2040 ± 2300	3830 ± 2960	3260 ± 2770
T <sub>max</sub>	h	3.7 ± 1.4	4.0 ± 0.0	4.0 ± 0.0
AUC <sub>24</sub>	ng•h/mL	10800 ± 12000	20200 ± 18100	16700 ± 14800
C <sub>24</sub>	ng/mL	30.6 ± 26.5	76.6 ± 102	44.4 ± 43.7
Arm 3: Jolivet (NET 0.35 mg) QD administered under non-fasting conditions on Study Days 1 through 17; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 4 through 24.				

Table 14 shows the mean ± SD pharmacokinetic parameters of Ritonavir (Arm 3)



		Arm 3		
Parameter (Unit)		Day 4	Day 17	Day 24
N		12	12	12
C <sub>max</sub>	ng/mL	1350 ± 597	1930 ± 493	1930 ± 537
T <sub>max</sub>	h	3.5 ± 1.2	3.8 ± 0.6	3.8 ± 0.6
AUC <sub>24</sub>	ng•h/mL	7580 ± 4150	11300 ± 3370	10600 ± 3310
C <sub>24</sub>	ng/mL	18.0 ± 16.3	35.5 ± 17.5	27.5 ± 12.7

Arm 3: Jolivette (NET 0.35 mg) QD administered under non-fasting conditions on Study Days 1 through 17; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 4 through 24.

Table 15 shows the mean ± SD pharmacokinetic parameters of ABT-267 (Arm 3)

		Arm 3		
Parameter (Unit)		Day 4	Day 17	Day 24
N		12	12	12
C <sub>max</sub>	ng/mL	99.9 ± 31.3	102 ± 22.7	103 ± 31.3
T <sub>max</sub>	h	4.7 ± 1.3	4.2 ± 0.6	4.0 ± 0.0
AUC <sub>24</sub>	ng•h/mL	963 ± 347	1290 ± 341	1300 ± 378
C <sub>24</sub>	ng/mL	15.5 ± 6.98	32.5 ± 11.3	33.4 ± 10.9

Arm 3: Jolivette (NET 0.35 mg) QD administered under non-fasting conditions on Study Days 1 through 17; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 4 through 24.

Table 16 shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 metabolite (Arm 3)

		ABT-333 Arm 3		
Parameter (Unit)		Day 4	Day 17	Day 24
N		12	12	12
C <sub>max</sub>	ng/mL	1480 ± 493	1200 ± 357	1210 ± 388
T <sub>max</sub>	h	2.8 ± 1.0	3.7 ± 0.8	3.8 ± 0.6
AUC <sub>12</sub>	ng•h/mL	9030 ± 3520	8090 ± 2620	8620 ± 3020
C <sub>12</sub>	ng/mL	365 ± 198	341 ± 168	357 ± 167
		ABT-333 M1 Arm 3		
		Day 4	Day 17	Day 24
N		12	12	12
C <sub>max</sub>	ng/mL	645 ± 263	655 ± 240	641 ± 231
T <sub>max</sub>	h	4.4 ± 0.8	4.0 ± 0.0	4.0 ± 0.0
AUC <sub>12</sub>	ng•h/mL	4090 ± 1770	4380 ± 2120	4090 ± 1630
C <sub>12</sub>	ng/mL	173 ± 105	193 ± 160	153 ± 80.2

Arm 3: Jolivette (NET 0.35 mg) QD administered under non-fasting conditions on Study Days 1 through 17; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 4 through 24.

Table 17 shows the mean ± SD pharmacokinetic parameters of Norethindrone (Arm 3)

		Arm 3		
Parameter (Unit)		Day 3	Day 4	Day 17
N		12	12	12
C <sub>max</sub>	ng/mL	4.49 ± 1.59	4.97 ± 1.98	3.70 ± 1.40
T <sub>max</sub>	h	2.2 ± 0.9	2.3 ± 0.8	2.1 ± 0.7
AUC <sub>24</sub>	ng•h/mL	31.4 ± 13.7	37.3 ± 16.5	27.1 ± 10.1
t <sub>1/2</sub> <sup>a</sup>	h	8.0 ± 1.5	8.1 ± 3.1	8.1 ± 1.6
C <sub>24</sub>	ng/mL	0.32 ± 0.20	0.50 ± 0.28	0.31 ± 0.14

Arm 3: Jolivet (NET 0.35 mg) QD administered under non-fasting conditions on Study Days 1 through 17; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 4 through 24.

a. Harmonic mean ± pseudo-standard deviation.

### Arm 4 (ABT-450/r/ABT-267, ABT-333 and Balziva)

Table 18 shows the mean ± SD pharmacokinetic parameters of ABT-450 (Arm 4)

		Arm 4	
Parameter (Unit)		Day 8	Day 15 <sup>a</sup>
N		12	11
C <sub>max</sub>	ng/mL	1750 ± 872	--
T <sub>max</sub>	h	4.3 ± 0.8	--
AUC <sub>24</sub>	ng•h/mL	9870 ± 5320	--
C <sub>24</sub> <sup>b</sup>	ng/mL	30.7 ± 26.2 (24.9)	83.3 ± 176 (35.7)

Arm 4: Balziva (EE/NET 35 µg/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 24 hour sample was collected for Subject 401 at discontinuation on Study Day 14.

b. Mean ± standard deviation (geometric mean).

Table 19 shows the mean ± SD pharmacokinetic parameters of ritonavir (Arm 4)

		Arm 4	
Parameter (Unit)		Day 8	Day 15 <sup>a</sup>
N		12	11
C <sub>max</sub>	ng/mL	1480 ± 424	--
T <sub>max</sub>	h	3.3 ± 1.0	--
AUC <sub>24</sub>	ng•h/mL	8310 ± 2890	--
C <sub>24</sub> <sup>b</sup>	ng/mL	14.9 ± 13.6 (12.8)	30.3 ± 41.5 (19.3)

Arm 4: Balziva (EE/NET 35 µg/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 24 hour sample was collected for Subject 401 at discontinuation on Study Day 14.

b. Mean ± standard deviation (geometric mean).

Table 20 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 (Arm 4)

Parameter (Unit)		Day 8	Day 15 <sup>a</sup>
N		12	11
C <sub>max</sub>	ng/mL	133 $\pm$ 33.3	--
T <sub>max</sub>	h	4.7 $\pm$ 1.0	--
AUC <sub>24</sub>	ng•h/mL	1250 $\pm$ 334	--
C <sub>24</sub> <sup>b</sup>	ng/mL	19.5 $\pm$ 5.84 (18.7)	36.6 $\pm$ 8.47 (35.7)

Arm 4: Balziva (EE/NET 35  $\mu$ g/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

- a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 24 hour sample was collected for Subject 401 at discontinuation on Study Day 14.  
b. Mean  $\pm$  standard deviation (geometric mean).

Table 21 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 metabolite 267 (Arm 4)

		ABT-333 Arm 4	
Parameter (Unit)		Day 8	Day 15 <sup>a</sup>
N		12	11
C <sub>max</sub>	ng/mL	1340 $\pm$ 297	--
T <sub>max</sub>	h	3.2 $\pm$ 1.3	--
AUC <sub>12</sub>	ng•h/mL	8310 $\pm$ 2310	--
C <sub>12</sub> <sup>b</sup>	ng/mL	292 $\pm$ 117 (270)	265 $\pm$ 139 (239)
		ABT-333 M1 Arm 4	
Parameter (Unit)		Day 8	Day 15 <sup>a</sup>
N		12	11
C <sub>max</sub>	ng/mL	764 $\pm$ 130	--
T <sub>max</sub>	h	4.0 $\pm$ 0.9	--
AUC <sub>12</sub>	ng•h/mL	4660 $\pm$ 1080	--
C <sub>12</sub> <sup>b</sup>	ng/mL	169 $\pm$ 79.2 (153)	172 $\pm$ 107 (148)

Arm 4: Balziva (EE/NET 35  $\mu$ g/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

- a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 12 hour sample was collected for Subject 401 at discontinuation on Study Day 14.  
b. Mean  $\pm$  standard deviation (geometric mean).

Table 22 shows the mean  $\pm$  SD pharmacokinetic parameters of ethinyl estradiol (Arm 4)

Parameter (Unit)		Day 7	Day 8	Day 15 <sup>a</sup>
N		12	12	11
C <sub>max</sub>	ng/mL	0.10 $\pm$ 0.03	0.11 $\pm$ 0.03	--
T <sub>max</sub>	h	2.8 $\pm$ 1.1	2.5 $\pm$ 0.9	--
AUC <sub>24</sub>	ng•h/mL	1.04 $\pm$ 0.22	1.27 $\pm$ 0.27	--
C <sub>24</sub> <sup>b</sup>	ng/mL	0.02 $\pm$ 0.01 (0.02)	0.03 $\pm$ 0.01 (0.03)	0.02 $\pm$ 0.01 (0.02)

Arm 4: Balziva (EE/NET 35  $\mu$ g/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

- a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 24 hour sample was collected for Subject 401 at discontinuation on Study Day 14.  
b. Mean  $\pm$  standard deviation (geometric mean)

Table 23 shows the mean  $\pm$  SD pharmacokinetic parameters of Norethindrone (Arm 4)

Parameter (Unit)	Arm 4		
	Day 7	Day 8	Day 15 <sup>a</sup>
N	12	12	11
C <sub>max</sub> ng/mL	7.70 $\pm$ 2.22	8.57 $\pm$ 2.06	--
T <sub>max</sub> h	1.8 $\pm$ 0.8	2.5 $\pm$ 0.9	--
AUC <sub>24</sub> ng•h/mL	62.7 $\pm$ 15.0	81.5 $\pm$ 20.8	--
t <sub>1/2</sub> <sup>b</sup> h	8.7 $\pm$ 2.6	9.5 $\pm$ 3.0	--
C <sub>24</sub> <sup>c</sup> ng/mL	0.87 $\pm$ 0.41 (0.77)	1.40 $\pm$ 0.70 (1.26)	1.71 $\pm$ 0.79 (1.55)

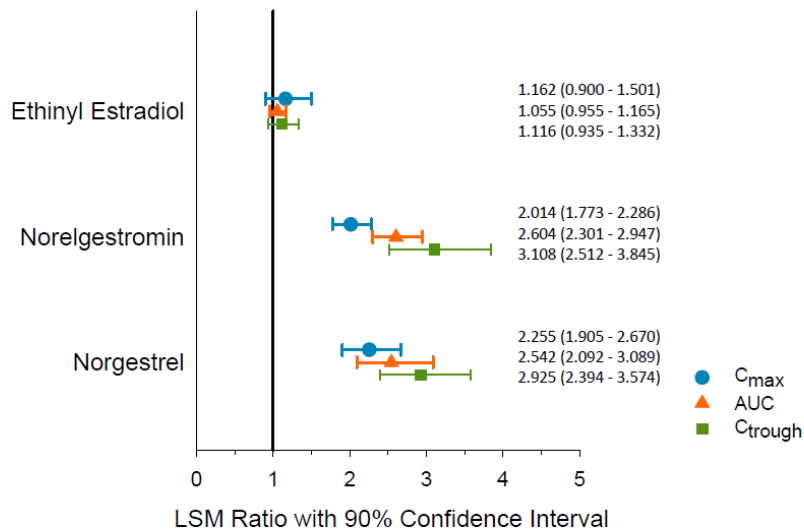
Arm 4: Balziva (EE/NET 35 µg/0.4 mg) QD administered under non-fasting conditions on Study Days 1 through 15; ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID administered under non-fasting conditions on Study Days 8 through 15. Arm 4 was prematurely discontinued; the last dose of study drug was administered in the morning on Study Day 15.

- a. Samples collected at discontinuation, which was Study Day 15 for all subjects with the exception of Subject 406 which was Study Day 13. No 24 hour sample was collected for Subject 401 at discontinuation on Study Day 14.
- b. Harmonic mean  $\pm$  pseudo-standard deviation.
- c. Mean  $\pm$  standard deviation (geometric mean).

## Statistical Comparison of the Pharmacokinetic Parameters

### Effect of DAAs on the COC Containing EE +NGM (Arms 1 and 2)

Fig 1 shows the least squares mean ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals for EE, NGMN, and NG (Study Day 21/Study Day 9), Arms 1 and 2.



AUC = AUC<sub>24</sub>

C<sub>trough</sub> = C<sub>24</sub>

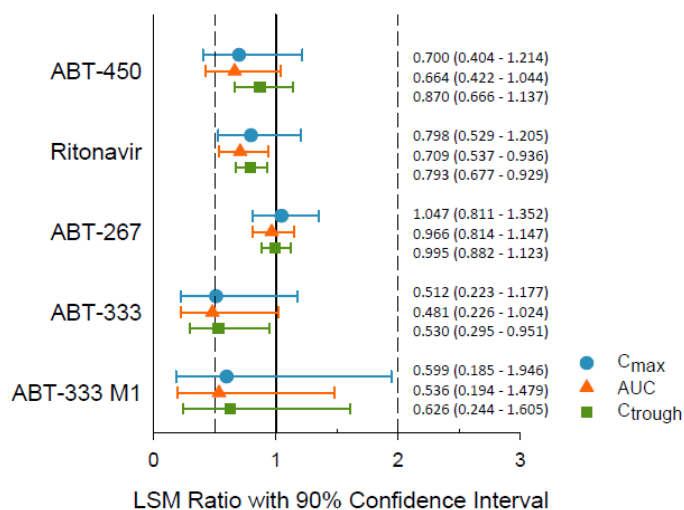
Study Day 9 = Ortho-Cyclen (EE/NGM 35/250 µg) QD

Study Day 21 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID (Arm 1) or

ABT-450/r/ABT-267 150/100/25 mg QD (Arm 2) + Ortho-Cyclen (EE/NGM 35/250 µg) QD

### Effect of COC Containing EE+NGM on DAAs (Arms 1 and 2)

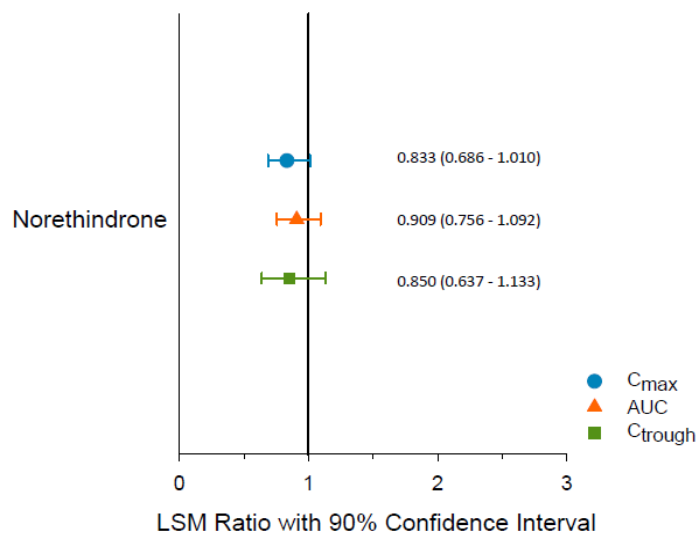
Fig 2 shows the least squares mean ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals for DAAs (Study Day 21/Study Day 28), Arms 1 and 2



AUC = AUC<sub>24</sub> for ABT-450, ritonavir and ABT-267; AUC<sub>12</sub> for ABT-333 and ABT-333 M1  
C<sub>trough</sub> = C<sub>24</sub> for ABT-450, ritonavir and ABT-267; C<sub>12</sub> for ABT-333 and ABT-333 M1  
Note: N = 7 for ABT-450, ritonavir and ABT-267; N = 3 for ABT-333 and ABT-333 M1.  
Study Day 21 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID (Arm 1) or  
ABT-450/r/ABT-267 150/100/25 mg QD (Arm 2) + Ortho-Cyclen (EE/NGM 35/250 µg) QD  
Study Day 28 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID (Arm 1) or  
ABT-450/r/ABT-267 150/100/25 mg QD (Arm 2) Alone

### Effect of DAAs on POP Containing NET (Arm 3)

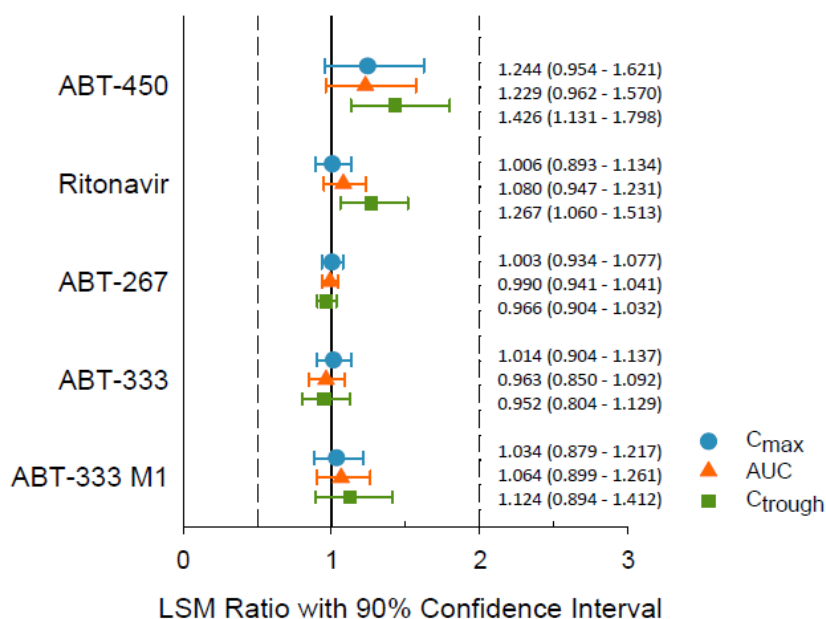
Fig 3 shows the least squares mean ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals for NET (Study Day 17/Study Day 3), Arm 3



AUC = AUC<sub>24</sub>  
C<sub>trough</sub> = C<sub>24</sub>  
Study Day 3 = Jolivet (NET 0.35 mg) QD  
Study Day 17 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID) + Jolivet (NET 0.35 mg) QD

### Effect of NET on DAAs (Arm 3)

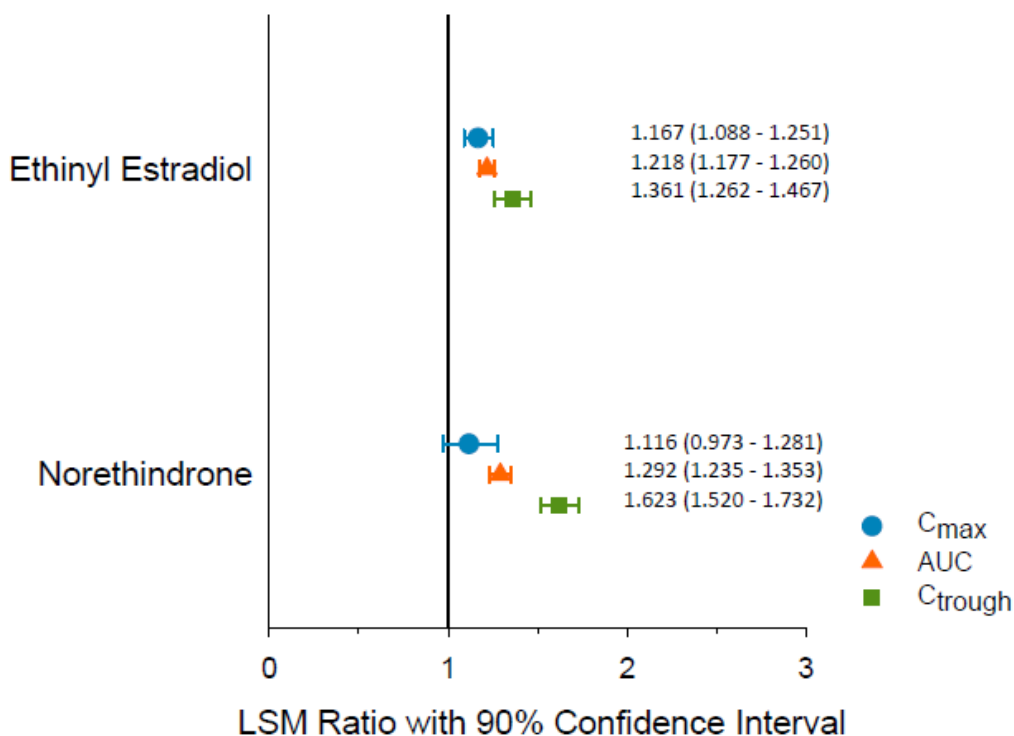
Fig 4 shows the least squares mean ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals for DAAs (Study Day 17/Study Day 24), Arm 3



AUC = AUC<sub>24</sub> for ABT-450, ritonavir and ABT-267; AUC<sub>12</sub> for ABT-333 and ABT-333 M1  
C<sub>trough</sub> = C<sub>24</sub> for ABT-450, ritonavir and ABT-267; C<sub>12</sub> for ABT-333 and ABT-333 M1  
Study Day 17 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID) + Jolivet (NET 0.35 mg) QD  
Study Day 24 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID) Alone

## Effect of COC Containing EE+NET on DAAs (Arms 4)

Fig 5 shows the least squares mean ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals for EE and NET (Study Day 8/Study Day 7), Arm 4.



AUC = AUC<sub>24</sub>

C<sub>trough</sub> = C<sub>24</sub>

Study Day 7 = Balziva (EE/NET 35 µg/0.4 mg) QD

Study Day 8 = DAAs (ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID) +  
Balziva (EE/NET 35 µg/0.4 mg) QD

## Conclusion

Due to the ALT elevations observed in Arms 1, 2 and 4, co-administration of the 3-DAA regimen with oral contraceptives containing ethinyl estradiol is contraindicated.

Progestin only contraceptives can be co-administered with the 3-DAA regimen without any dose adjustments.

**Drug-Drug Interaction Trial with Darunavir/ritonavir**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M12-202**

**Title**

**A Phase 1, Open Label Study to Assess the Pharmacokinetics, Safety, and Tolerability of the Co-administration of Darunavir Once Daily Administered in the Evening with ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) in the Morning With and Without Twice a Day ABT-333 in Healthy Adult Subjects**

**Trial Period**

May 13, 2013 to July 23, 2013

Final report date: March 14, 2014

***Reviewer's Note: As the proposed labeling recommendations in NDA 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**Trial Objectives**

The objectives of the trial were:

- to determine the pharmacokinetics, safety, and tolerability of the combination of ABT-450/ritonavir and ABT-267 with or without ABT-333 when dosed with darunavir once daily administered in the evening in healthy subjects.
- to determine the pharmacokinetics, safety, and tolerability of darunavir and ritonavir administered once daily in the evening when co-administered with a combination of ABT-450/ritonavir/ABT-267 with or without ABT-333 in healthy subjects.

**Trial Design**

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

Table 1 shows the dosing sequences



	Cohort	Subject Number	Regimens	
			Period 1	Period 2
Arm 1	1	101, 103, 106, 107, 108, 111, 113, 116, 117, 119, 122, 123	A	B
	2	102, 104, 105, 109, 110, 112, 114, <sup>b</sup> 115, 118, 120, 121, 124 <sup>c</sup>	C	B
Arm 2 <sup>a</sup>	1	--	D	E
	2	--	F	E

- a. Based on a review of the available pharmacokinetic, safety and tolerability results from Arm 1, a decision was made not to conduct Arm 2. Information regarding Arm 2 can be found in the protocol ([Appendix 16.1\\_\\_1](#)).
- b. Subject 114 was discontinued from the study due to atrioventricular block first degree (preferred term) on Study Day 15 while receiving Regimen B (ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + darunavir 800 mg QD + ritonavir 100 mg QD) in Period 2 of Arm 1/Cohort 2. The last dosing of study drugs occurred in the evening of Study Day 14.
- c. Subject 124 was discontinued from the study due to rash maculopapular (preferred term) on Study Day 11 while receiving Regimen C (darunavir 800 mg QD + ritonavir 100 mg QD) in Period 1 of Arm 1/Cohort 2. The last dosing of study drugs occurred in the evening of Study Day 10.

Table 2 shows the various treatments administered in the trial.

Regimen A	ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions (Study Days 1 through 14).
Regimen B	ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions (Study Days 15 through 28).
Regimen C	Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions (Study Days 1 through 14).
Regimen D <sup>a</sup>	ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions (Study Days 1 through 14).
Regimen E <sup>a</sup>	ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions (Study Days 15 through 28).
Regimen F <sup>a</sup>	Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions (Study Days 1 through 14).

- a. Based on a review of the available pharmacokinetic, safety and tolerability results from Arm 1, a decision was made not to conduct Arm 2 (Regimens D, E, and F). Information regarding Arm 2 can be found in the protocol

**Of note, based on the results of Arm1 from the trial, the applicant made a decision not to conduct Arm 2 of the trial.**

## Rationale for Conducting the Trial

The trial was conducted to collect quantitative drug-drug interaction information for the safe and effective use of darunavir/ritonavir once daily administered in the evening 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), ABT-267 (25 mg) and ABT-333 (400 mg) were the doses that were determined to be safe and efficacious in the Phase 2 trials. Further, these doses (or doses that provided comparable systemic exposures) were also 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/r/ABT-267	ABT-333
Dosage Form	Tablet	Tablet
Strength	75/50/12.5 mg	250 mg
Bulk Product Lot Number	12-008149	12-007842
Manufacturing Site	AbbVie, Lake County, IL	AbbVie, Ireland
Finishing Lot Number	13-002162	13-002164
Retest Date	(b) (4)	
	Norvir® (ritonavir)	Prezista® (darunavir)
Dosage Form	Soft Gelatin Capsule	Tablet
Strength (mg)	100 mg	800 mg
Bulk Product Lot Number	11-005635	13-002147
Manufacturing Site	AbbVie Lake County, IL	Janssen Ortho, LLC, Gurabo, Puerto Rico
Vendor Lot Number	110262E	13CG820
Finishing Lot Number	13-002165	13-002170
Expiration Date	(b) (4)	

## Sample Collection

PK samples for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and darunavir were collected on the following days:

Blood Samples for DAAs and Ritonavir:

### Cohort 1:

- Prior to morning dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 16 and 24 (Study Day 15) hours after morning dosing on Study Day 14.

### Cohorts 1 and 2:

- Prior to morning dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 16, 24 (Study Day 29), 36 (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.

### Cohort 2

- Prior to evening dosing of darunavir and ritonavir (0 hour) and at 1, 2, 3, 4 (Study Day 14), 6 (Study Day 14), 9 (Study Day 14), 12 (Study Day 14), 16 (Study Day 14) and 24 hours (Study Day 14) after evening dosing on Study Day 13 (for measurement of ritonavir only).

### **Trough Concentrations**

- Cohort 1: Blood samples for measurement of DAA and ritonavir trough concentrations were collected immediately prior to the morning dose on Study Days 8, 11, 13, 23, 25, and 27.
- Cohort 2: Blood samples for measurement of ritonavir were collected immediately prior to the evening dose on Study Days 8, 10 and 12, and for measurement of DAA and ritonavir immediately prior to the morning dose on Study Days 23, 25, and 27.

Blood Samples for Darunavir:

### **Cohort 2**

- Prior to evening dose of darunavir (0 hour) and at 1, 2, 3, 4 (Study Day 14), 6 (Study Day 14), 9 (Study Day 14), 12 (Study Day 14), 16 (Study Day 14) and 24 (Study Day 14) hours after evening dosing on Study Day 13.

### **Cohorts 1 and 2**

- Prior to evening dose of darunavir (0 hour) and at 1, 2, 3, 4 (Study Day 28), 6 (Study Day 28), 9 (Study Day 28), 12 (Study Day 28), 16 (Study Day 28), 24 (Study Day 28), 36 (Study Day 29), 48 (Study Day 29) and 72 (Study Day 30) hours after evening dosing on Study Day 27 or upon subject discontinuation due to an adverse event.

### **Trough Concentrations**

- Cohort 2: Blood samples for measurement of darunavir trough concentrations were collected immediately prior to the evening dose on Study Days 8, 10, and 12.
- Cohorts 1 and 2: Blood samples for measurement of darunavir trough concentrations were drawn immediately prior to the evening dose on Study Days 22, 24 and 26.

### **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	0.6-431	0.6	1.58, 26.4, 330	2.2 % to 5.4 %	3.4 % to 8.9 %
Ritonavir	4.71-3380	4.71	12.7, 211, 2640	3.5 % to 5.6 %	3.8 % to 6.3 %
ABT-267	0.417-299	0.41	1.09, 18.1, 227	3.3 % to 4.4 %	3.1 % to 4.4 %
ABT-333	4.39-3150	4.39	11.7, 195, 2430	3 % to 5.3 %	3.6 % to 5.3 %
ABT-333 M1	4.58-3290	4.58	12, 199, 2490	2.5 % to 3.5 %	2 % to 3.3 %
Darunavir	25-12500	25	75, 6250, 9750	4.9 % to 6.2 %	-4.1 % to -3.5 %

### *Subject Disposition and Demographics*

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

	Mean ± SD (N = 24)	Min – Max
Age (years)	33.1 ± 8.0	18 – 51
Weight (kg)	76.0 ± 11.6	56 – 105
Height (cm)	169 ± 9.1	156 – 186
Sex	17 Male (71%), 7 Female (29%)	
Race	10 White (42%), 11 Black (46%), 2 Asian (8%), 1 Multi Race (4%)	

SD = Standard deviation

### *Pharmacokinetics*

#### Arm 1

#### ABT-450

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm1.

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 1/Cohort 1	
		Regimen A: Day 14	Regimen B: Day 28
N		12	12
C <sub>max</sub>	(ng/mL)	2380 ± 1130	2010 ± 1460
T <sub>max</sub>	(h)	4.1 ± 1.1	4.4 ± 1.0
AUC <sub>0-24</sub>	(ng·h/mL)	11100 ± 5170	10300 ± 7620
t <sub>1/2</sub> <sup>a</sup>	(h)	--	6.3 ± 2.0
C <sub>24</sub>	(ng/mL)	32.6 ± 17.7	62.5 ± 57.1

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 1/Cohort 2	
		Regimen C: Day 14	Regimen B: Day 28
N		--	10
C <sub>max</sub>	(ng/mL)	--	2850 ± 2990
T <sub>max</sub>	(h)	--	4.2 ± 1.0
AUC <sub>0-24</sub>	(ng·h/mL)	--	19000 ± 32200
t <sub>1/2</sub> <sup>a</sup>	(h)	--	4.9 ± 1.5
C <sub>24</sub>	(ng/mL)	--	169 ± 405

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).  
 Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).  
 Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).  
 a. Harmonic mean ± pseudo-standard deviation.

## Ritonavir

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 1.

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 1/Cohort 1	
		Regimen A: Day 14	Regimen B: Day 28
N		12	12
C <sub>max</sub>	(ng/mL)	2160 $\pm$ 480	2590 $\pm$ 682
T <sub>max</sub>	(h)	4.0 $\pm$ 0.7	4.2 $\pm$ 0.6
AUC <sub>24</sub>	(ng•h/mL)	12300 $\pm$ 3200	21000 $\pm$ 5590
t <sub>1/2</sub> <sup>a</sup>	(h)	--	6.3 $\pm$ 1.9
C <sub>24</sub>	(ng/mL)	37.0 $\pm$ 19.7	498 $\pm$ 201
Arm 1/Cohort 2			
Pharmacokinetic Parameters	(Units)	Regimen C: Day 13	Regimen B: Day 28
		11	10
C <sub>max</sub>	(ng/mL)	1080 $\pm$ 350	2740 $\pm$ 979
T <sub>max</sub>	(h)	5.6 $\pm$ 0.8	4.4 $\pm$ 0.8
AUC <sub>24</sub>	(ng•h/mL)	8520 $\pm$ 2500	23700 $\pm$ 8440
t <sub>1/2</sub> <sup>a</sup>	(h)	--	6.2 $\pm$ 1.7
C <sub>24</sub>	(ng/mL)	55.7 $\pm$ 28.0	485 $\pm$ 226

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).  
 Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).  
 Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).  
 a. Harmonic mean  $\pm$  pseudo-standard deviation.

## ABT-267

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 1/Cohort 1	
		Regimen A: Day 14	Regimen B: Day 28
N		12	12
C <sub>max</sub>	(ng/mL)	86.1 $\pm$ 21.6	75.0 $\pm$ 18.2
T <sub>max</sub>	(h)	4.9 $\pm$ 1.2	5.2 $\pm$ 1.0
AUC <sub>24</sub>	(ng•h/mL)	1080 $\pm$ 294	946 $\pm$ 293
t <sub>1/2</sub> <sup>a</sup>	(h)	--	31.2 $\pm$ 12.9
C <sub>24</sub>	(ng/mL)	23.3 $\pm$ 7.78	20.6 $\pm$ 8.04
Arm 1/Cohort 2			
Pharmacokinetic Parameters	(Units)	Regimen C: Day 14	Regimen B: Day 28
		--	10
C <sub>max</sub>	(ng/mL)	--	91.9 $\pm$ 31.8
T <sub>max</sub>	(h)	--	5.2 $\pm$ 1.0
AUC <sub>24</sub>	(ng•h/mL)	--	1150 $\pm$ 465
t <sub>1/2</sub> <sup>a</sup>	(h)	--	34.1 $\pm$ 8.60
C <sub>24</sub>	(ng/mL)	--	26.1 $\pm$ 13.8

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).  
 Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).  
 Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).  
 a. Harmonic mean  $\pm$  pseudo-standard deviation.

## ABT-333

Table 9 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 1/Cohort 1	
		Regimen A: Day 14	Regimen B: Day 28
N		12	12
C <sub>max</sub>	(ng/mL)	1140 $\pm$ 312	871 $\pm$ 285
T <sub>max</sub>	(h)	3.9 $\pm$ 0.8	4.1 $\pm$ 0.7
AUC <sub>12</sub>	(ng•h/mL)	7270 $\pm$ 2400	5230 $\pm$ 1650
t <sub>1/2</sub> <sup>a,b</sup>	(h)	--	5.8 $\pm$ 1.8 <sup>c</sup>
C <sub>12</sub>	(ng/mL)	287 $\pm$ 130	179 $\pm$ 55.3
Arm 1/Cohort 2			
		Regimen C: Day 14	Regimen B: Day 28
N		--	10
C <sub>max</sub>	(ng/mL)	--	923 $\pm$ 406
T <sub>max</sub>	(h)	--	4.1 $\pm$ 1.1
AUC <sub>12</sub>	(ng•h/mL)	--	5360 $\pm$ 2290
t <sub>1/2</sub> <sup>a,b</sup>	(h)	--	6.3 $\pm$ 2.1 <sup>d</sup>
C <sub>12</sub>	(ng/mL)	--	183 $\pm$ 103

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).

Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).

Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. Harmonic mean could only be estimated in 10 subjects in Cohort 1 and in 6 subjects in Cohort 2.

c. N = 10.

d. N = 6.

## ABT-333 M1

Table 10 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 1/Cohort 1	
		Regimen A: Day 14	Regimen B: Day 28
N		12	12
C <sub>max</sub>	(ng/mL)	747 $\pm$ 218	539 $\pm$ 202
T <sub>max</sub>	(h)	4.7 $\pm$ 1.0	4.5 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	4310 $\pm$ 1170	3060 $\pm$ 1080
t <sub>1/2</sub> <sup>a,b</sup>	(h)	--	5.7 $\pm$ 1.1 <sup>c</sup>
C <sub>12</sub>	(ng/mL)	150 $\pm$ 47.6	95.4 $\pm$ 38.6
Arm 1/Cohort 2			
		Regimen C: Day 14	Regimen B: Day 28
N		--	10
C <sub>max</sub>	(ng/mL)	--	498 $\pm$ 179
T <sub>max</sub>	(h)	--	4.6 $\pm$ 1.0
AUC <sub>12</sub>	(ng•h/mL)	--	2880 $\pm$ 1380
t <sub>1/2</sub> <sup>a,b</sup>	(h)	--	6.5 $\pm$ 2.4 <sup>d</sup>
C <sub>12</sub>	(ng/mL)	--	94.9 $\pm$ 87.4

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).

Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).

Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. Harmonic mean could only be estimated in 4 subjects in Cohort 1 and in 3 subjects in Cohort 2.

c. N = 4.

d. N = 3.



## Darunavir

Table 11 shows the mean  $\pm$  SD pharmacokinetic parameters of darunavir in Arm 1.

Pharmacokinetic Parameters	(Units)	Darunavir Arm 1/Cohort 1	
		Regimen A: Day 13	Regimen B: Day 27
N		--	12
C <sub>max</sub>	(ng/mL)	--	6110 $\pm$ 1800
T <sub>max</sub>	(h)	--	3.8 $\pm$ 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	66700 $\pm$ 21700
t <sub>1/2</sub> <sup>a</sup>	(h)	--	11.0 $\pm$ 4.6
C <sub>24</sub>	(ng/mL)	--	1190 $\pm$ 670

Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2	
		Regimen C: Day 13	Regimen B: Day 27
N		11	10
C <sub>max</sub>	(ng/mL)	7980 $\pm$ 2260	6240 $\pm$ 834
T <sub>max</sub>	(h)	3.7 $\pm$ 2.0	3.8 $\pm$ 1.3
AUC <sub>24</sub>	(ng•h/mL)	95400 $\pm$ 27500	70900 $\pm$ 18400
t <sub>1/2</sub> <sup>a</sup>	(h)	--	9.4 $\pm$ 3.5
C <sub>24</sub>	(ng/mL)	1980 $\pm$ 558	1090 $\pm$ 309

Regimen A: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions on Study Days 1 through 14 (Cohort 1).

Regimen B: ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered in the morning under non-fasting conditions + darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 15 through 28 (Cohorts 1 and 2).

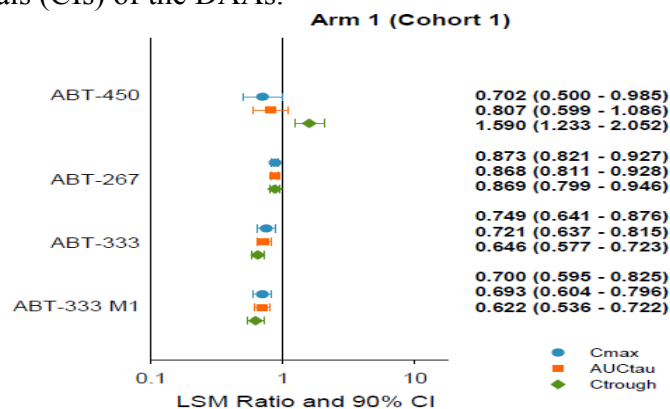
Regimen C: Darunavir 800 mg QD + ritonavir 100 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

## Statistical Comparison of the Pharmacokinetic Parameters:

### Effect of Darunavir on DAAs

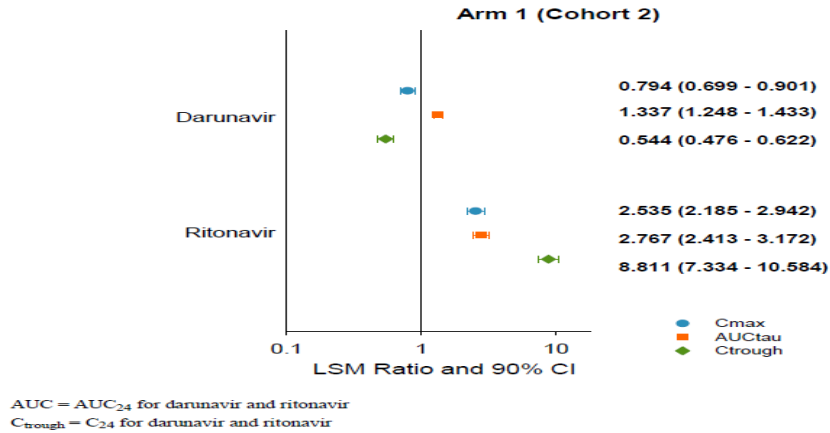
Fig 2 shows the least squares mean (LSM) ratios of C<sub>max</sub>, AUC, and C<sub>trough</sub> and 90 % Confidence Intervals (CIs) of the DAAs.



AUC = AUC<sub>24</sub> for ABT-450 and ABT-267; AUC<sub>12</sub> for ABT-333 and ABT-333 M1 metabolite  
C<sub>trough</sub> = C<sub>24</sub> for ABT-450 and ABT-267; C<sub>12</sub> for ABT-333 and ABT-333 M1 metabolite

## Effect of DAAs on Darunavir

Fig 3 shows the least squares mean (LSM) ratios of  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  and 90 % Confidence Intervals (CIs) of darunavir and ritonavir (co-administered with darunavir in the evening)



## Results

- Co-administration of ABT-450/r, ABT-267 and ABT-333 with darunavir once daily (administered in the evening with ritonavir 100 mg )
  - Decreased the mean  $C_{\max}$  and AUC of ABT-450 by 30 % and 19 %, respectively, and increase the mean  $C_{\text{trough}}$  of ABT-450 by 59 % respectively.
  - Increased the  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ritonavir (comparison based on day 28 vs day 14 of Arm 1, Cohort 1) by 18 %, 70 %, and 1315 % (data not shown in figure 2).
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ABT-267 by 13 %, 13 %, and 13 %, respectively.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ABT-333 by 25 %, 28 %, and 35 %, respectively.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ABT-333 M1 by 30 %, 31 %, and 38 %, respectively.
  - Decreased the mean  $C_{\max}$  and  $C_{\text{trough}}$  of darunavir by 20 % and 45 %, respectively, and increased the mean AUC of darunavir by 34 %.
  - Increased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ritonavir (comparison based on day 28 vs day 14 of Arm 1, Cohort 2) by 153 %, 176 %, and 781 %, respectively.

## Conclusion

- Co-administration of the 3-DAA regimen with Darunavir/ritonavir (800 mg/100 mg once daily administered in the evening) is not recommended is due to decrease in the mean  $C_{\text{trough}}$  of darunavir.



**Drug-Drug Interaction Trial with Darunavir/ritonavir**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**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), ABT-267 (25 mg) and ABT-333 (400 mg) were the doses that were determined to be safe and efficacious in the Phase 2 trials. Further, these doses (or doses that provided comparable systemic exposures) were also 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 (b) (4)
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	Janssen Ortho, LLC, Gurabo, Puerto Rico	Janssen Ortho, LLC, Gurabo, Puerto Rico
Finishing Lot Number	12-000255, 12-003950, 12-006198	12-000404	12-000690
Expiration Date	(b) (4)		

## Sample Collection

PK samples for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, 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 %
ABT-333	4.57-3290	4.57	12.3, 209, 2610	4.2 % to 5.4 %	-4.2 % to 1.6 %
ABT-333 M1	4.72-3400	4.72	12.2, 208, 2590	2.5 % to 4.3 %	-1.4 % to 1.6 %
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 3 (Regimens G, H, and I) and Arm 4 (Regimens J, K, and L) are presented in this review.*

#### **Arm 3**

##### **ABT-450**

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 3

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 3/Cohort 1		
		Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
		9	9	9
N				
C <sub>max</sub>	(ng/mL)	1470 ± 1960	1710 ± 2000	2110 ± 2120
T <sub>max</sub>	(h)	4.6 ± 1.1	4.4 ± 0.9	4.4 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	8200 ± 10100	8570 ± 10200	10300 ± 11400
t <sub>1/2</sub> <sup>a</sup>	(h)	—	—	6.0 ± 1.0
C <sub>24</sub>	(ng/mL)	36.4 ± 41.8	38.8 ± 43.5	52.7 ± 68.4
		Arm 3/Cohort 2		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
		—	8	8
N				
C <sub>max</sub>	(ng/mL)	—	563 ± 570	1700 ± 2490
T <sub>max</sub>	(h)	—	4.0 ± 0.9	3.8 ± 1.0
AUC <sub>24</sub>	(ng•h/mL)	—	2500 ± 2010	8940 ± 14200
t <sub>1/2</sub> <sup>a</sup>	(h)	—	—	4.9 ± 1.5
C <sub>24</sub>	(ng/mL)	—	13.7 ± 14.8	33.7 ± 56.0

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: 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 3

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 3/Cohort 1		
		Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
		9	9	9
N				
C <sub>max</sub>	(ng/mL)	1640 ± 431	1640 ± 403	1400 ± 412
T <sub>max</sub>	(h)	4.9 ± 1.8	4.8 ± 1.7	4.1 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	10800 ± 3690	10600 ± 3760	9210 ± 3170
t <sub>1/2</sub> <sup>a</sup>	(h)	—	—	5.1 ± 1.2
C <sub>24</sub>	(ng/mL)	50.3 ± 33.5	58.1 ± 36.3	53.5 ± 38.8
		Arm 3/Cohort 2		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
		8	8	8
N				
C <sub>max</sub>	(ng/mL)	922 ± 444	1770 ± 571	1460 ± 425
T <sub>max</sub>	(h)	4.3 ± 0.7	3.8 ± 0.5	3.8 ± 0.5
AUC <sub>24</sub>	(ng•h/mL)	6330 ± 2440	9390 ± 2850	8480 ± 2560
t <sub>1/2</sub> <sup>a</sup>	(h)	—	—	4.9 ± 0.5
C <sub>24</sub>	(ng/mL)	54.2 ± 21.6	52.5 ± 24.5	37.4 ± 15.4

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: 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 3

Pharmacokinetic Parameters		ABT-267 Arm 3/Cohort 1		
	(Units)	Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
N		9	9	9
C <sub>max</sub>	(ng/mL)	105 ± 34.2	91.2 ± 31.1	89.6 ± 26.6
T <sub>max</sub>	(h)	5.3 ± 1.0	5.3 ± 1.0	4.7 ± 1.0
AUC <sub>24</sub>	(ng•h/mL)	1260 ± 486	1130 ± 430	1080 ± 340
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	25.7 ± 9.6
C <sub>24</sub>	(ng/mL)	27.9 ± 14.8	26.7 ± 13.0	23.5 ± 9.6
Arm 3/Cohort 2				
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
N		--	8	8
C <sub>max</sub>	(ng/mL)	--	69.5 ± 14.2	78.1 ± 18.9
T <sub>max</sub>	(h)	--	4.8 ± 1.4	4.6 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	688 ± 188	954 ± 229
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	23.3 ± 5.8
C <sub>24</sub>	(ng/mL)	--	10.6 ± 3.9	19.7 ± 4.9

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: 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-333

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 in Arm 3

Pharmacokinetic Parameters		ABT-333 Arm 3/Cohort 1		
	(Units)	Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
N		9	9	9
C <sub>max</sub>	(ng/mL)	1020 ± 511	1210 ± 685	1100 ± 553
T <sub>max</sub>	(h)	3.6 ± 1.1	3.8 ± 1.0	3.7 ± 1.0
AUC <sub>12</sub>	(ng•h/mL)	7180 ± 4070	8140 ± 5250	6590 ± 3700
t <sub>1/2</sub>	(h)	--	--	8.1 <sup>a</sup>
C <sub>12</sub>	(ng/mL)	302 ± 229	361 ± 312	270 ± 214
C <sub>24</sub>	(ng/mL)	286 ± 261	281 ± 223	194 ± 148
Arm 3/Cohort 2				
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
N		--	8	8
C <sub>max</sub>	(ng/mL)	--	845 ± 335	1050 ± 597
T <sub>max</sub>	(h)	--	3.4 ± 0.5	3.4 ± 0.7
AUC <sub>12</sub>	(ng•h/mL)	--	4610 ± 2250	6500 ± 3980
t <sub>1/2</sub>	(h)	--	--	ND
C <sub>12</sub>	(ng/mL)	--	143 ± 83.6	212 ± 151
C <sub>24</sub>	(ng/mL)	--	144 ± 124	177 ± 132

ND = Not determined

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

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

a. N = 1.

## ABT-333 M1

Table 10 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 3

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 3/Cohort 1		
		Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
		N	N	N
$C_{max}$	(ng/mL)	616 $\pm$ 329	560 $\pm$ 288	488 $\pm$ 192
$T_{max}$	(h)	4.1 $\pm$ 1.2	4.3 $\pm$ 1.0	4.0 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	3830 $\pm$ 2340	3460 $\pm$ 2040	2900 $\pm$ 1060
$t_{1/2}$	(h)	--	--	ND
$C_{12}$	(ng/mL)	137 $\pm$ 114	135 $\pm$ 105	108 $\pm$ 55.7
$C_{24}$	(ng/mL)	115 $\pm$ 106	107 $\pm$ 73.5	77.1 $\pm$ 33.5

Pharmacokinetic Parameters	(Units)	Arm 3/Cohort 2		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
		N	N	N
$C_{max}$	(ng/mL)	--	517 $\pm$ 156	583 $\pm$ 241
$T_{max}$	(h)	--	3.6 $\pm$ 0.5	3.6 $\pm$ 0.5
AUC <sub>12</sub>	(ng•h/mL)	--	2630 $\pm$ 948	3710 $\pm$ 2290
$t_{1/2}$	(h)	--	--	ND
$C_{12}$	(ng/mL)	--	79.4 $\pm$ 49.1	118 $\pm$ 106
$C_{24}$	(ng/mL)	--	87.7 $\pm$ 69.0	98.7 $\pm$ 80.0

ND = Not determined

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

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

## Darunavir

Table 11 shows the mean  $\pm$  SD pharmacokinetic parameters of darunavir in Arm 3

Pharmacokinetic Parameters	(Units)	Darunavir Arm 3/Cohort 1		
		Regimen G: Day 14	Regimen H: Day 15	Regimen H: Day 28
		N	N	N
$C_{max}$	(ng/mL)	--	6020 $\pm$ 1120	6330 $\pm$ 1330
$T_{max}$	(h)	--	3.7 $\pm$ 1.0	3.4 $\pm$ 1.1
AUC <sub>24</sub>	(ng•h/mL)	--	50600 $\pm$ 13600	55100 $\pm$ 17300
$t_{1/2}$ <sup>a</sup>	(h)	--	--	8.7 $\pm$ 1.9
$C_{24}$	(ng/mL)	--	968 $\pm$ 409	940 $\pm$ 485

Pharmacokinetic Parameters	(Units)	Arm 3/Cohort 2		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
		N	N	N
$C_{max}$	(ng/mL)	7710 $\pm$ 950	8590 $\pm$ 1460	7100 $\pm$ 737
$T_{max}$	(h)	3.0 $\pm$ 0.9	3.5 $\pm$ 0.5	3.0 $\pm$ 0.9
AUC <sub>24</sub>	(ng•h/mL)	90500 $\pm$ 22300	94100 $\pm$ 23100	68200 $\pm$ 10800
$t_{1/2}$ <sup>a</sup>	(h)	--	--	10.3 $\pm$ 2.9
$C_{24}$	(ng/mL)	2450 $\pm$ 855	2150 $\pm$ 887	1300 $\pm$ 512

Regimen G: ABT-333 400 mg BID + 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 H: 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 on Study Days 15 to 28 (Cohorts 1 and 2).

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

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



## Arm 4

### ABT-450

Table 12 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 4

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
N		8	8	7
C <sub>max</sub>	(ng/mL)	464 $\pm$ 257	587 $\pm$ 402	300 $\pm$ 266
T <sub>max</sub>	(h)	5.4 $\pm$ 1.8	4.8 $\pm$ 1.0	4.1 $\pm$ 0.9
AUC <sub>24</sub>	(ng•h/mL)	2710 $\pm$ 1290	4020 $\pm$ 2340	1540 $\pm$ 896
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.7 $\pm$ 1.7
C <sub>24</sub>	(ng/mL)	12.8 $\pm$ 6.1	42.9 $\pm$ 30.2	10.1 $\pm$ 5.0

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
N		--	7	7
C <sub>max</sub>	(ng/mL)	--	352 $\pm$ 383	407 $\pm$ 492
T <sub>max</sub>	(h)	--	4.1 $\pm$ 0.9	4.1 $\pm$ 0.9
AUC <sub>24</sub>	(ng•h/mL)	--	1540 $\pm$ 1060	1680 $\pm$ 1250
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.1 $\pm$ 1.2
C <sub>24</sub>	(ng/mL)	--	9.2 $\pm$ 4.9	8.9 $\pm$ 4.2

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

### Ritonavir

Table 13 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 4

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
N		8	8	7
C <sub>max</sub>	(ng/mL)	1800 $\pm$ 743	1550 $\pm$ 696	1620 $\pm$ 526
T <sub>max</sub>	(h)	4.5 $\pm$ 0.9	4.5 $\pm$ 0.9	4.1 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	10100 $\pm$ 3140 <sup>a</sup>	8030 $\pm$ 3120	8840 $\pm$ 2620
t <sub>1/2</sub>	(h)	--	--	8.6 <sup>c</sup>
C <sub>12</sub>	(ng/mL)	37.4 $\pm$ 14.6 <sup>b</sup>	262 $\pm$ 103	195 $\pm$ 32.5

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
N		7	7	7
C <sub>max</sub>	(ng/mL)	1130 $\pm$ 475	1650 $\pm$ 624	1890 $\pm$ 1070
T <sub>max</sub>	(h)	3.9 $\pm$ 0.4	4.3 $\pm$ 0.8	4.0 $\pm$ 0.0
AUC <sub>12</sub>	(ng•h/mL)	6830 $\pm$ 2740	8810 $\pm$ 2960	8750 $\pm$ 3940
t <sub>1/2</sub>	(h)	--	--	7.6 <sup>c</sup>
C <sub>12</sub>	(ng/mL)	225 $\pm$ 109	244 $\pm$ 104	197 $\pm$ 91.9

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. AUC<sub>24</sub> (ritonavir 100 mg QD was administered on Study Days 1 to 14).

b. C<sub>24</sub> (ritonavir 100 mg QD was administered on Study Days 1 to 14).

c. N = 1.

## ABT-267

Table 14 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 4

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
$C_{max}$	(ng/mL)	88.5 $\pm$ 36.5	86.5 $\pm$ 31.0	61.6 $\pm$ 18.7
$T_{max}$	(h)	5.3 $\pm$ 1.0	4.8 $\pm$ 1.0	4.9 $\pm$ 1.1
$AUC_{24}$	(ng•h/mL)	1080 $\pm$ 378	1040 $\pm$ 366	751 $\pm$ 274
$t_{1/2}$ <sup>a</sup>	(h)	--	--	20.3 $\pm$ 8.5
$C_{24}$	(ng/mL)	22.5 $\pm$ 11.2	22.6 $\pm$ 10.8	15.9 $\pm$ 7.4
Pharmacokinetic Parameters	(Units)	ABT-267 Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
$C_{max}$	(ng/mL)	--	60.4 $\pm$ 10.7	80.0 $\pm$ 10.8
$T_{max}$	(h)	--	5.0 $\pm$ 1.3	4.6 $\pm$ 1.0
$AUC_{24}$	(ng•h/mL)	--	594 $\pm$ 125	926 $\pm$ 146
$t_{1/2}$ <sup>a</sup>	(h)	--	--	21.6 $\pm$ 3.4
$C_{24}$	(ng/mL)	--	9.5 $\pm$ 1.7	19.6 $\pm$ 3.2

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

## ABT-333

Table 15 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 in Arm 4

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
$C_{max}$	(ng/mL)	907 $\pm$ 427	1090 $\pm$ 474	735 $\pm$ 294
$T_{max}$	(h)	3.5 $\pm$ 0.5	3.5 $\pm$ 0.5	3.5 $\pm$ 0.5
$AUC_{12}$	(ng•h/mL)	6250 $\pm$ 3270	7350 $\pm$ 3570	4400 $\pm$ 1860
$t_{1/2}$	(h)	--	--	9.9 <sup>a</sup>
$C_{12}$	(ng/mL)	228 $\pm$ 115	287 $\pm$ 145	125 $\pm$ 59.0
$C_{24}$	(ng/mL)	256 $\pm$ 170	373 $\pm$ 176	182 $\pm$ 118
Pharmacokinetic Parameters	(Units)	ABT-333 Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
		N	N	N
$C_{max}$	(ng/mL)	--	562 $\pm$ 228	610 $\pm$ 209
$T_{max}$	(h)	--	3.6 $\pm$ 1.1	3.4 $\pm$ 0.5
$AUC_{12}$	(ng•h/mL)	--	2980 $\pm$ 1100	3540 $\pm$ 1230
$t_{1/2}$	(h)	--	--	ND
$C_{12}$	(ng/mL)	--	78.5 $\pm$ 27.6	90.1 $\pm$ 29.1
$C_{24}$	(ng/mL)	--	108 $\pm$ 33.6	120 $\pm$ 34.4

ND = Not determined

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. N = 1.

## ABT-333 M1

Table 16 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 4

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
N		8	8	7
C <sub>max</sub>	(ng/mL)	493 $\pm$ 204	478 $\pm$ 162	338 $\pm$ 129
T <sub>max</sub>	(h)	4.4 $\pm$ 1.1	4.1 $\pm$ 0.8	4.1 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	3040 $\pm$ 1340	3090 $\pm$ 1120	1890 $\pm$ 670
t <sub>1/2</sub>	(h)	--	--	ND
C <sub>12</sub>	(ng/mL)	99.6 $\pm$ 48.3	114 $\pm$ 49.0	51.3 $\pm$ 19.8
C <sub>24</sub>	(ng/mL)	99.6 $\pm$ 49.0	130 $\pm$ 41.6	70.0 $\pm$ 26.8

Pharmacokinetic Parameters	(Units)	Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
N		--	7	7
C <sub>max</sub>	(ng/mL)	--	366 $\pm$ 150	351 $\pm$ 178
T <sub>max</sub>	(h)	--	3.9 $\pm$ 1.1	3.9 $\pm$ 1.1
AUC <sub>12</sub>	(ng•h/mL)	--	1800 $\pm$ 725	1890 $\pm$ 792
t <sub>1/2</sub>	(h)	--	--	ND
C <sub>12</sub>	(ng/mL)	--	42.6 $\pm$ 14.9	44.7 $\pm$ 5.5
C <sub>24</sub>	(ng/mL)	--	67.0 $\pm$ 27.5	62.7 $\pm$ 20.5

ND = Not determined

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

## Darunavir

Table 17 shows the mean  $\pm$  SD pharmacokinetic parameters of darunavir in Arm 4

Pharmacokinetic Parameters	(Units)	Darunavir Arm 4/Cohort 1		
		Regimen J: Day 14	Regimen K: Day 15	Regimen K: Day 28
N		--	8	7
C <sub>max</sub>	(ng/mL)	--	5270 $\pm$ 1140	5430 $\pm$ 1120
T <sub>max</sub>	(h)	--	3.1 $\pm$ 0.6	3.0 $\pm$ 0.6
AUC <sub>12</sub>	(ng•h/mL)	--	32500 $\pm$ 8540	36400 $\pm$ 7440
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	10.3 $\pm$ 4.3 <sup>b</sup>
C <sub>12</sub>	(ng/mL)	--	1120 $\pm$ 481	1130 $\pm$ 284
C <sub>24</sub>	(ng/mL)	--	2930 $\pm$ 1200	2640 $\pm$ 930

Pharmacokinetic Parameters	(Units)	Arm 4/Cohort 2		
		Regimen L: Day 14	Regimen K: Day 15	Regimen K: Day 28
N		7	7	7
C <sub>max</sub>	(ng/mL)	7110 $\pm$ 1880	7540 $\pm$ 1230	6080 $\pm$ 1030
T <sub>max</sub>	(h)	2.7 $\pm$ 1.1	3.1 $\pm$ 0.7	2.9 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	55500 $\pm$ 16400	62100 $\pm$ 13400	43600 $\pm$ 9940
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	10.1 $\pm$ 1.4
C <sub>12</sub>	(ng/mL)	3110 $\pm$ 1110	3020 $\pm$ 881	1790 $\pm$ 687
C <sub>24</sub>	(ng/mL)	4030 $\pm$ 975	3420 $\pm$ 953	2860 $\pm$ 844

Regimen J: ABT-333 400 mg BID + 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 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 administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

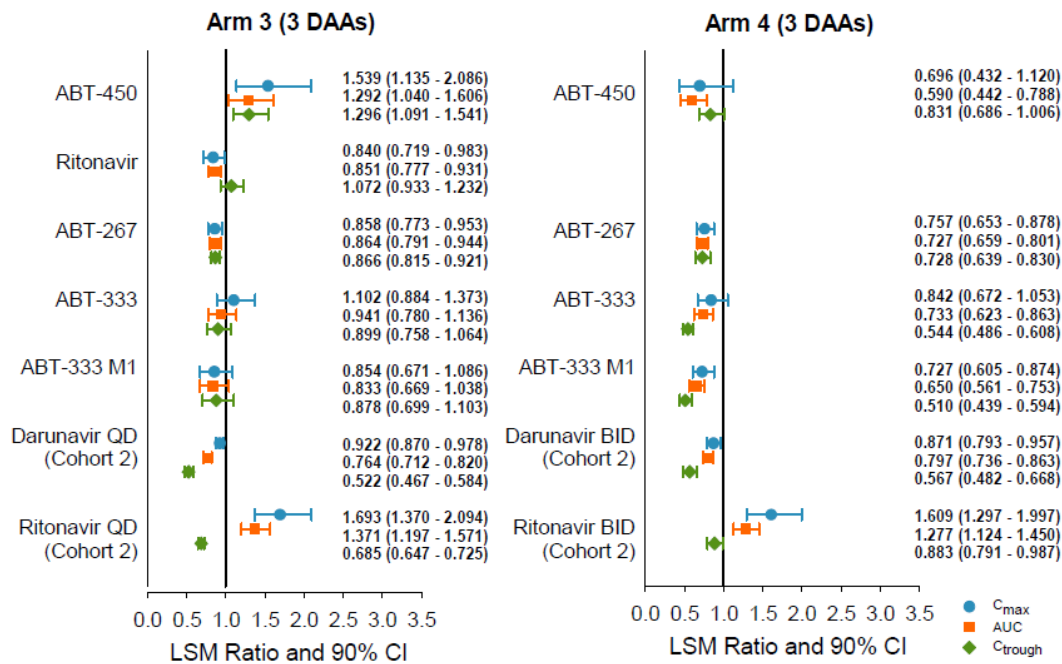
Regimen L: Darunavir 600 mg BID + RTV 100 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. N = 6.

## Statistical Comparison of the Pharmacokinetic Parameters:

Fig 1 shows the least squares mean (LSM) ratios of  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  and 90 % Confidence Intervals (CIs) for the DAAs (Arm 3 and 4), ritonavir (Arm 3) and darunavir (Arm 3 and Arm 4)



Arms 3 and 4 (3 DAAs): ABT-450/r + ABT-267 + ABT-333

AUC<sub>24</sub> and C<sub>24</sub>: ABT-450 and ABT-267 (Arms 1 to 4), and darunavir and ritonavir (Arms 1 to 3).

AUC<sub>12</sub> and C<sub>12</sub>: ABT-333 and ABT-333 M1 metabolite (Arms 1, 3 and 4), and darunavir and ritonavir (Arm 4).

## Results

- Co-administration of ABT-450/r, ABT-267 and ABT-333 with darunavir once daily (administered in the morning with the 3-DAA regimen) [Arm 3]
  - Increased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of ABT-450 by 54 %, 30 %, and 30 %, respectively.
  - There were no significant changes in the mean pharmacokinetic parameters of ritonavir (using ritonavir given as part of the 3-DAA regimen as reference), ABT-267, ABT-333, and ABT-333 M1.
  - Decreased the mean  $C_{\max}$ , AUC, and  $C_{\text{trough}}$  of darunavir by 7 %, 23 %, and 48 %, respectively.
    - Increased ritonavir (using ritonavir given as part of DRV/rtv 800/100 mg as reference) mean  $C_{\max}$  and AUC by 70 % and 37 %, respectively and decreased mean  $C_{\text{trough}}$  by 31 %.
- Administration of ABT-450/r, ABT-267 and ABT-333 with darunavir twice daily (evening dose of darunavir administered with ritonavir)[Arm 4]

- Decreased the mean  $C_{max}$ , AUC, and  $C_{trough}$  of ABT-450 by 30 %, 40 %, and 17 %, respectively.
- Increased the mean  $C_{max}$  and AUC of ritonavir by 60 % and 28 % and decreased the mean  $C_{trough}$  by 12 % (comparison based on day 28 vs day 14 in Arm 4, Cohort 2; data not shown in figure 1).
- Decreased the mean  $C_{max}$ , AUC, and  $C_{trough}$  of ABT-267 by 24 %, 27 %, and 27 %, respectively.
- Decreased the mean  $C_{max}$ , AUC, and  $C_{trough}$  of ABT-333 by 16 %, 27 %, and 45 %, respectively.
- Decreased the mean  $C_{max}$ , AUC, and  $C_{trough}$  of ABT-333 M1 by 27 %, 35 %, and 49 %, respectively.
- Decreased the mean  $C_{max}$ , AUC, and  $C_{trough}$  of darunavir by 13 %, 20 %, and 43 %, respectively.
- Increased the mean  $C_{max}$  and AUC of ritonavir (using ritonavir given twice daily in regimen L as reference) by 61 % and 28 %, respectively, and decreased the decreased mean  $C_{trough}$  by 12 %.

### ***Reviewer's Interpretation of Results of Trial M12-202 and M13-506***

*The table below summarizes the morning and evening administration of the various components of the 3-DAA regimen and Devan the observed % decrease in DRV  $C_{trough}$  in trials M13-506 and M12-202. Of note, in trial M13-506, the applicant evaluated the drug-drug interaction between the 3-DAA regimen and DRV 800 mg once daily given in the morning and DRV/rtv 600/100 mg twice daily (morning dose of darunavir was administered with the 3-DAA regimen; no additional ritonavir administered).*

<b>Trial # (Arm and Cohort)</b>	<b>Morning Dose</b>	<b>Evening Dose</b>	<b>Mean Decrease in DRV <math>C_{trough}</math> (%)</b>
M13-506 Arm 3, Cohort 2, Regimen H <sup>1</sup>	ABT-450/r +ABT-267 +ABT-333 +DRV 800 mg	ABT-333	48
M13-506 (Arm 4, Cohort 2), Regimen K <sup>2</sup>	ABT-450/r +ABT-267 + ABT-333 +DRV 600 mg	DRV 600 mg /RTV 100 mg +ABT-333	43
M12-202 (Arm 1, Cohort 2), Regimen B <sup>3</sup>	ABT-450/r +ABT-267+ABT-333	DRV 800 mg/RTV 100 mg +ABT-333	45

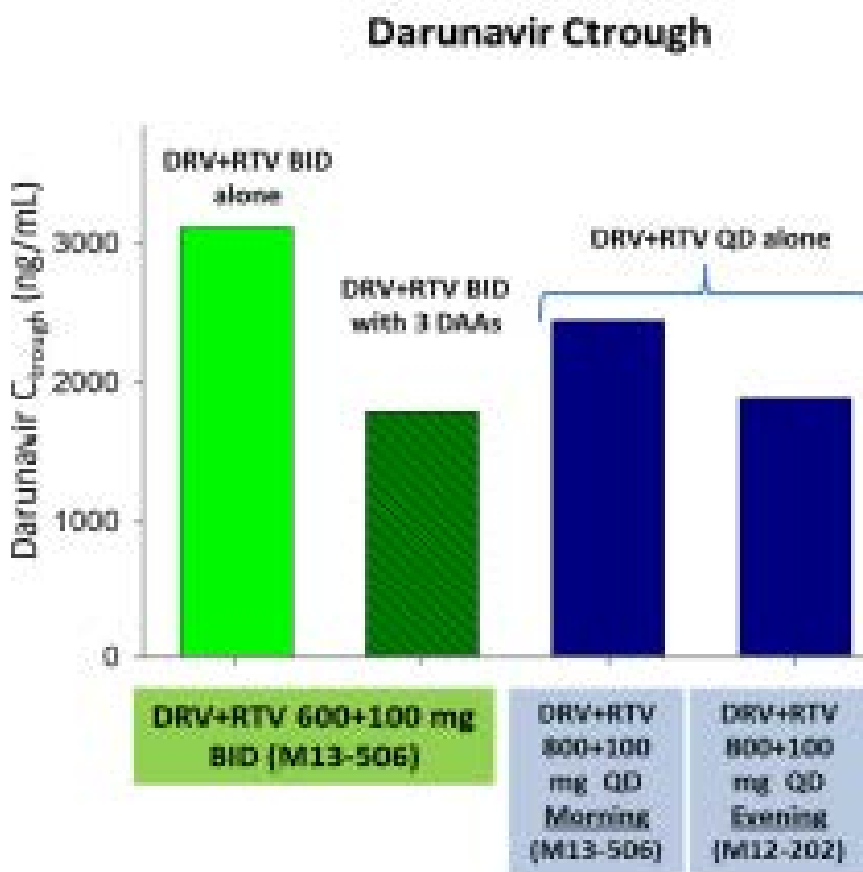
1: Regimen I (DRV/rtv 800/100 mg once daily was the reference regimen; morning dose of DRV administered with the DAA regimen; no additional dose of ritonavir administered)

2: Regimen L (DRV/rtv 600/100 mg twice daily was the reference regimen; morning dose of DRV administered with the DAA regimen; no additional dose of ritonavir administered)

3: Regimen C (DRV/rtv 800/100 mg once daily administered in the evening was the reference regimen)

The decrease in the  $C_{trough}$  of DRV observed in trials M13-506 and M12-202 was similar to the decrease in DRV  $C_{trough}$  when darunavir (600/100 mg twice daily) was co-administered with telaprevir (42 % decrease [with telaprevir 750 mg every 8 hours] and 58 % decrease [with telaprevir 1125 mg every 12 hours] and boceprevir (59 % decrease). Of note, the approved prescribing information of telaprevir and boceprevir recommends against co-administration of darunavir/ritonavir with telaprevir darunavir/ritonavir with boceprevir, respectively.

The figure below compares the darunavir  $C_{trough}$  when administered alone (twice daily and once daily in the morning in trial M13-506 and once daily in the evening in trial M12-202) or with the 3-DAA regimen in trial M13-506



Source: Summary of Darunavir Drug-Drug Interaction Trials submitted by the applicant on November 27, 2013.

Comparison of the mean  $C_{trough}$  of darunavir across the trials the various regimens suggest that the mean  $C_{trough}$  of DRV twice daily when co-administered with the 3-DAA regimen is lower than the mean  $C_{trough}$  of darunavir after the once daily regimens. Hence, based on the available information, co-administration of the 3-DAA regimen with

*DRV/rtv once daily (morning administration and evening administration) and DRV/rtv twice daily is not recommended.*

*Considering the importance of providing multiple treatment options for HIV/HCV coinfecting population and to further assess the clinical relevance of the decrease in darunavir  $C_{trough}$ , the applicant is currently evaluating the co-administration of DRV/rtv and the 3-DAA regimen as part of trial M14-004.*

*At least 20 HIV patients who are currently on DRV/r (800/100 mg) once daily will be randomized (1:1) into:*

- Group 1 (n=10): Patients will continue on the DRV/r (800/100 mg) once daily regimen.*
- Group 2 (n=10): Patients will be switched to DRV/r (600/100 mg) twice daily regimen.*

*DRV exposure should be evaluated in all patients (n=20) using a mixture of intensive pharmacokinetic sampling and sparse sampling. The results from the assessments described above are expected to provide additional information regarding the safe and effective use of the 3-DAA regimen with darunavir.*

## **Conclusion**

- Co-administration of the 3-DAA regimen with Darunavir/ritonavir (800 mg/100 mg once daily; darunavir given in the morning with the DAA regimen) is not recommended due to the decrease in the mean  $C_{trough}$  of darunavir.
- Co-administration of the 3-DAA regimen with Darunavir/ritonavir (600 mg/100 mg twice daily; darunavir given in the morning with the DAA regimen and in the evening with ritonavir) is not recommended due to the decrease in the  $C_{trough}$  of darunavir.



**Drug-Drug Interaction Trial with Rilpivirine**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**M13-782**

**Title**

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

**Trial Period**

November 12, 2012 to June 21, 2013

Final report date: November 7, 2013

**Trial Objectives**

The objectives of the trial were:

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

**Trial Design**

Phase 1, single-center, randomized, multiple dose, non-fasting, open-label study. After meeting the selection criteria, 20 subjects per arm were assigned randomly in equal numbers (10 subjects per cohort) to one of the two treatment sequences (cohorts) as shown in table 1 below.

Arms 1 to 3	Cohort 1	Study Days 1 to 14	Study Days 15 to 28
		DAA's	DAA's + Rilpivirine 25 mg
	Cohort 2	Study Days 1 to 14	Study Days 15 to 28
		Rilpivirine 25 mg	DAA's + Rilpivirine 25 mg

Arm 1: All study drugs were administered under non-fasting conditions for both Cohorts 1 and 2. Rilpivirine was administered in the morning.

Arm 2: DAAs were administered under non-fasting conditions for both Cohorts 1 and 2. Rilpivirine was administered at night under non-fasting conditions on Study Days 1 to 14 in Cohort 2, and at 4 hours after dinner during Study Days 15 to 28 in Cohorts 1 and 2.

Arm 3: All study drugs were administered under non-fasting conditions for both Cohorts 1 and 2. Rilpivirine was administered in the evening with dinner.

Arms 1 through 3: (3 DAAs): ABT-450/r + ABT-267 + ABT-333

Regimens: ABT-450/r 150/100 mg QD, ABT-267 25 mg QD, ABT-333 400 mg BID, rilpivirine 25 mg QD

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



### Reviewer's Note:

*Rilpivirine was co-dosed with the DAAs or dosing was separated by ~12 hours to determine the drug-drug interaction of rilpivirine with the 3-DAA combination. Rilpivirine is approved for administration with food (rilpivirine exposures are approximately 40 % lower in the fasting state compared to fed conditions), hence rilpivirine was administered with food in this study. Rilpivirine exposures were significantly higher during co-administration with DAAs, therefore, administration of rilpivirine at night without the evening snack was explored to allow greater separation between food intake (dinner) and rilpivirine administration.*

### Rationale for Conducting the Trial

The trial was conducted to collect quantitative drug-drug interaction information for the safe and effective use of rilpivirine 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), ABT-267 (25 mg) and ABT-333 (400 mg) were the doses that were determined to be safe and efficacious in the Phase 2 trials. Further, these doses (or doses that provided comparable systemic exposures) were also evaluated in the Phase 3 trials. The dose of rilpivirine (25 mg once daily) is the approved dose.

### Identity of Investigational Products

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

	ABT-450/Ritonavir	ABT-267
Dosage Form	Tablet	Tablet
Strength (mg)	75/50 mg	25 mg
Bulk Product Lot Number	12-002722	11-002033
Manufacturing Site	AbbVie Waukegan, IL	AbbVie Waukegan, IL
Finishing Lot Number	12-007826	12-007817
Potency	(b) (4)	
Expiration Date		
	ABT-333	Rilpivirine
Dosage Form	Tablet	Tablet
Strength (mg)	400 mg	25 mg
Bulk Product Lot Number	12-001228	12-007242
Manufacturing Site	AbbVie Waukegan, IL	Janssen Therapeutics Raritan, NJ
Finishing Lot Number	12-007823	12-007825/BLLOE00
Potency	(b) (4)	
Expiration Date		

### Sample Collection

PK samples for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and rilpivirine were collected at steady state in the three arms.

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and rilpivirine 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	0.6-412	0.6	1.57, 26.2, 328	3.8 % to 9.6 %	-10.7 % to -9.1 %
Ritonavir	4.71-3240	4.71	12.4, 207, 2580	4.9 % to 5.6 %	-5.8 % to -3.2 %
ABT-267	0.463-318	0.463	1.22, 20.3, 253	2.7 % to 6.1 %	-8.4 % to -6.6 %
ABT-333	4.57-3140	4.57	12, 200, 2500	5.7 % to 6.2 %	-2.5 % to 0 %
ABT-333 M1	4.5-3090	4.5	11.6, 193, 2420	3.8 % to 6 %	-6.2 % to -5.2 %
Rilpivirine	0.5-250	0.5	1.2, 3, 12, 40, 200 and 500	3.37 % to 10.1 %	1.01 % to 3.8 %

### Subject Disposition and Demographics

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

	Mean ± SD (N = 60)	Min – Max
Age (years)	33.1 ± 8.27	20 – 55
Weight (kg)	75.7 ± 11.4	57.7 – 109
Height (cm)	173 ± 9.41	149 – 193
Sex	43 Males (71.7%), 17 Females (28.3%)	
Race	30 White (50%), 29 Black (48.3%), 1 Asian (1.7%)	

Three subjects (subject 113, Arm 1, Cohort 2; subject 120, Arm 1, Cohort 2, and subject 307 (Arm 3, Cohort 2) were prematurely discontinued from the trial either due to adverse

events (subjects 113 and 307) or due to investigator discretion (subject 120). The pharmacokinetic data from these 3 subjects was excluded from all statistical analysis of the pharmacokinetic parameters.

## Pharmacokinetics

### Arm 1

#### ABT-450

Table 5 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
$C_{max}$	(ng/mL)	2450 $\pm$ 1970	2430 $\pm$ 1990	2800 $\pm$ 2140
$T_{max}$	(h)	4.3 $\pm$ 0.5	4.4 $\pm$ 0.5	4.2 $\pm$ 0.6
$AUC_{24}$	(ng•h/mL)	12600 $\pm$ 11700	11700 $\pm$ 10400	13900 $\pm$ 11900
$t_{1/2}$ <sup>a</sup>	(h)	--	--	4.24 $\pm$ 0.63
$C_{24}$	(ng/mL)	34.4 $\pm$ 25.1	32.4 $\pm$ 25.3	33.7 $\pm$ 28.8
		Arm 1/Cohort 2 (N = 10)		
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>b</sup>
$C_{max}$	(ng/mL)	--	1450 $\pm$ 1000	4160 $\pm$ 3180
$T_{max}$	(h)	--	5.3 $\pm$ 1.5	3.8 $\pm$ 0.5
$AUC_{24}$	(ng•h/mL)	--	8340 $\pm$ 5970	22200 $\pm$ 18800
$t_{1/2}$ <sup>a</sup>	(h)	--	--	4.78 $\pm$ 0.75
$C_{24}$	(ng/mL)	--	55.0 $\pm$ 57.1	54.0 $\pm$ 44.6

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

### Ritonavir

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 1.

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
C <sub>max</sub>	(ng/mL)	2080 ± 700	2150 ± 667	2300 ± 824
T <sub>max</sub>	(h)	4.3 ± 0.5	4.4 ± 0.5	4.1 ± 0.7
AUC <sub>24</sub>	(ng•h/mL)	11600 ± 4530	11900 ± 4170	12300 ± 4340
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.09 ± 0.65
C <sub>24</sub>	(ng/mL)	32.6 ± 17.9	33.1 ± 17.4	31.8 ± 17.9
		Arm 1/Cohort 2 (N = 10)		
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>b</sup>
C <sub>max</sub>	(ng/mL)	--	1570 ± 835	2440 ± 778
T <sub>max</sub>	(h)	--	4.5 ± 0.5	3.9 ± 0.4
AUC <sub>24</sub>	(ng•h/mL)	--	9980 ± 5550	14600 ± 6140
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.00 ± 0.76
C <sub>24</sub>	(ng/mL)	--	41.0 ± 36.1	49.7 ± 44.0

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

b. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

## ABT-267

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

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
C <sub>max</sub>	(ng/mL)	127 ± 29.8	135 ± 25.9	141 ± 31.0
T <sub>max</sub>	(h)	5.0 ± 0.0	4.9 ± 0.3	4.9 ± 0.3
AUC <sub>24</sub>	(ng•h/mL)	1430 ± 381	1430 ± 320	1550 ± 350
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	29.2 ± 7.58
C <sub>24</sub>	(ng/mL)	30.6 ± 10.3	29.5 ± 9.64	31.8 ± 9.86
		Arm 1/Cohort 2 (N = 10)		
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>b</sup>
C <sub>max</sub>	(ng/mL)	--	121 ± 44.8	151 ± 63.5
T <sub>max</sub>	(h)	--	4.9 ± 0.3	4.9 ± 0.4
AUC <sub>24</sub>	(ng•h/mL)	--	1050 ± 375	1780 ± 829
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	30.1 ± 11.4
C <sub>24</sub>	(ng/mL)	--	15.5 ± 5.11	38.3 ± 19.7

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

b. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

## ABT-333

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-333 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
C <sub>max</sub>	(ng/mL)	1420 ± 510	1450 ± 530	1690 ± 630
T <sub>max</sub>	(h)	3.8 ± 0.8	4.0 ± 0.7	4.1 ± 0.6
AUC <sub>12</sub>	(ng•h/mL)	8990 ± 3450	9320 ± 3710	10500 ± 3900
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.76 ± 0.39
C <sub>12</sub>	(ng/mL)	368 ± 167	351 ± 153	400 ± 150
Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2 (N = 10)		
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>b</sup>
C <sub>max</sub>	(ng/mL)	--	1780 ± 658	1800 ± 530
T <sub>max</sub>	(h)	--	3.7 ± 0.7	3.5 ± 0.5
AUC <sub>12</sub>	(ng•h/mL)	--	11200 ± 4000	11200 ± 3960
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.72 ± 2.32
C <sub>12</sub>	(ng/mL)	--	429 ± 173	407 ± 174

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

b. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

## ABT-333 M1

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 M1 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
C <sub>max</sub>	(ng/mL)	854 ± 282	877 ± 211	937 ± 258
T <sub>max</sub>	(h)	4.4 ± 0.7	4.5 ± 0.5	4.5 ± 0.5
AUC <sub>12</sub>	(ng•h/mL)	5260 ± 2150	5380 ± 2010	5820 ± 1920
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.50 ± 0.20 <sup>b,c</sup>
C <sub>12</sub>	(ng/mL)	211 ± 113	226 ± 141	222 ± 98.7
Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2 (N = 10)		
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>d</sup>
C <sub>max</sub>	(ng/mL)	--	1090 ± 422	961 ± 278
T <sub>max</sub>	(h)	--	4.5 ± 0.5	4.0 ± 0.5
AUC <sub>12</sub>	(ng•h/mL)	--	6710 ± 2880	5880 ± 2190
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.63 ± 1.05 <sup>b,e</sup>
C <sub>12</sub>	(ng/mL)	--	301 ± 196	214 ± 137

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

b. For some Subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 6.

d. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

e. N = 4.

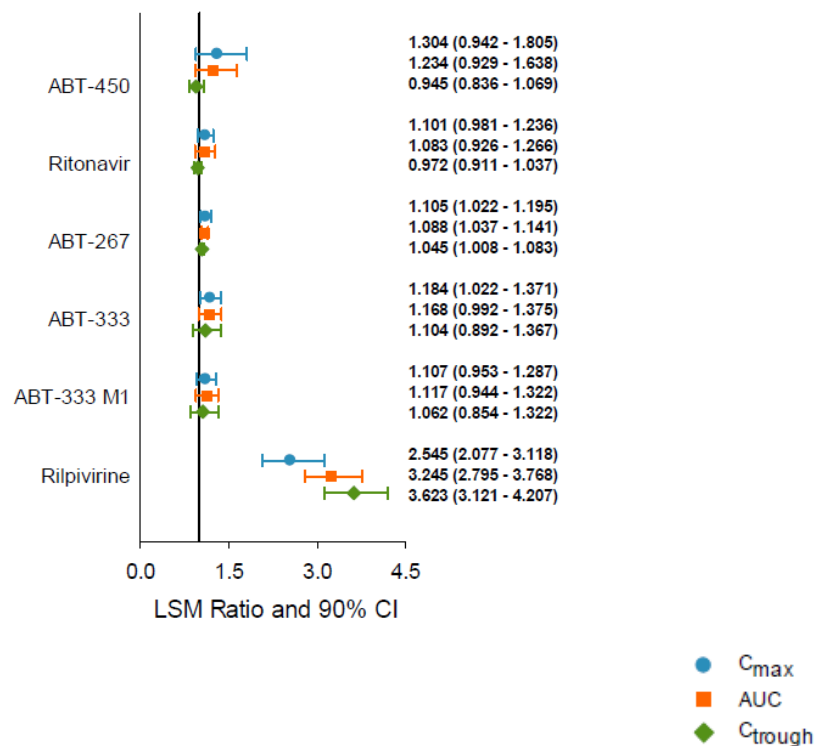
## Rilpivirine

Table 10 shows the mean ± SD pharmacokinetic parameters of rilpivirine in Arm 1.

Pharmacokinetic Parameters	(Units)	Rilpivirine Arm 1/Cohort 1 (N = 10)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 28
C <sub>max</sub>	(ng/mL)	--	156 ± 34	575 ± 219
T <sub>max</sub>	(h)	--	4.2 ± 0.4	4.8 ± 2.3
AUC <sub>24</sub>	(ng•h/mL)	--	1700 ± 308	9060 ± 3100
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	53.5 ± 17.6
C <sub>24</sub>	(ng/mL)	--	54.3 ± 9.12	316 ± 109
Arm 1/Cohort 2 (N = 10)				
		Regimen C: Day 14	Regimen B: Day 15	Regimen B: Day 28 <sup>b</sup>
C <sub>max</sub>	(ng/mL)	241 ± 68.9	277 ± 83.7	615 ± 236
T <sub>max</sub>	(h)	3.6 ± 0.5	4.3 ± 1.7	5.3 ± 4.4
AUC <sub>24</sub>	(ng•h/mL)	3150 ± 1030	4290 ± 1200	10300 ± 4330
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	63.1 ± 21.1
C <sub>24</sub>	(ng/mL)	101 ± 36.2	163 ± 48.0	362 ± 142

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).  
Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + rilpivirine 25 mg QD in the morning + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).  
Regimen C: Rilpivirine 25 mg QD in the morning administered under non-fasting conditions on Study Days 1 to 14 (Cohort 2).  
a. Harmonic mean ± pseudo-standard deviation.  
b. N = 8 (Subjects 113 and 120 prematurely discontinued from the study and were not included in Study Day 28 analyses.)

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and rilpivirine in Arm 1.



## Arm 2

Table 11 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 16	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	2510 ± 2730	1980 ± 1980	2980 ± 3930
T <sub>max</sub>	(h)	4.6 ± 1.0	4.8 ± 1.0	4.6 ± 1.0
AUC <sub>24</sub>	(ng•h/mL)	12500 ± 12300	10600 ± 10000	15200 ± 19300
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.07 ± 0.94
C <sub>24</sub>	(ng/mL)	45.3 ± 48.3	42.8 ± 45.2	61.8 ± 85.0
		Arm 2/Cohort 2 (N = 10)		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	--	1620 ± 1710	3400 ± 3450
T <sub>max</sub>	(h)	--	4.7 ± 1.2	4.0 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	--	9130 ± 9470	25100 ± 34600
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.92 ± 0.56
C <sub>24</sub>	(ng/mL)	--	48.9 ± 58.4	142 ± 246

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).  
Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).  
Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

Table 12 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 2.

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 16	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	1960 ± 840	1840 ± 848	1870 ± 1110
T <sub>max</sub>	(h)	4.6 ± 1.0	4.4 ± 0.8	4.4 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	12000 ± 5920	11700 ± 6060	11500 ± 6920
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.58 ± 0.93
C <sub>24</sub>	(ng/mL)	50.4 ± 41.3	52.1 ± 45.9	49.5 ± 41.5
		Arm 2/Cohort 2 (N = 10)		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	--	1530 ± 681	2040 ± 624
T <sub>max</sub>	(h)	--	4.3 ± 0.9	4.7 ± 1.6
AUC <sub>24</sub>	(ng•h/mL)	--	9000 ± 4450	12700 ± 4950
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.14 ± 0.67
C <sub>24</sub>	(ng/mL)	--	31.6 ± 26.1	52.0 ± 41.9

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).  
Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).  
Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

Table 13 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 2.



Pharmacokinetic Parameters	(Units)	ABT-267 Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 16	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	122 ± 37.7	107 ± 31.4	119 ± 40.0
T <sub>max</sub>	(h)	4.9 ± 1.2	5.0 ± 1.1	5.4 ± 1.0
AUC <sub>24</sub>	(ng•h/mL)	1480 ± 497	1310 ± 430	1410 ± 534
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	28.5 ± 7.01
C <sub>24</sub>	(ng/mL)	31.9 ± 13.0	28.4 ± 10.8	30.7 ± 14.4
		Arm 2/Cohort 2 (N = 10)		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	--	95.1 ± 33.8	105 ± 37.4
T <sub>max</sub>	(h)	--	5.1 ± 1.2	4.7 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	931 ± 324	1320 ± 587
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	29.2 ± 9.45
C <sub>24</sub>	(ng/mL)	--	15.0 ± 6.51	30.9 ± 17.8

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## ABT-333

Table 14 shows the mean ± SD pharmacokinetic parameters of ABT-333 in Arm 2.

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 16	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	1380 ± 665	1310 ± 657	1270 ± 601
T <sub>max</sub>	(h)	4.2 ± 1.0	4.0 ± 0.8	4.4 ± 0.8
AUC <sub>11</sub>	(ng•h/mL)	8280 ± 4030	8020 ± 3680	7690 ± 3230
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.13 ± 1.79
C <sub>11</sub>	(ng/mL)	433 ± 213	413 ± 179	400 ± 176
		Arm 2/Cohort 2 (N = 10)		
		Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	--	1540 ± 551	1180 ± 299
T <sub>max</sub>	(h)	--	3.8 ± 0.9	4.3 ± 1.7
AUC <sub>11</sub>	(ng•h/mL)	--	8340 ± 2900	6890 ± 1490
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.99 ± 1.48 <sup>b,c</sup>
C <sub>11</sub>	(ng/mL)	--	426 ± 152	359 ± 108

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

b. For some Subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 9



Table 15 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 2.

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 16	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	838 $\pm$ 463	839 $\pm$ 501	790 $\pm$ 449
T <sub>max</sub>	(h)	4.6 $\pm$ 1.0	4.8 $\pm$ 1.0	4.8 $\pm$ 1.0
AUC <sub>11</sub>	(ng•h/mL)	5120 $\pm$ 3050	4930 $\pm$ 2950	4610 $\pm$ 2790
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.45 $\pm$ 0.36 <sup>b,c</sup>
C <sub>11</sub>	(ng/mL)	268 $\pm$ 167	242 $\pm$ 148	252 $\pm$ 189
Arm 2/Cohort 2 (N = 10)				
Pharmacokinetic Parameters	(Units)	Regimen F: Day 14	Regimen E: Day 15	Regimen E: Day 28
C <sub>max</sub>	(ng/mL)	--	973 $\pm$ 429	854 $\pm$ 254
T <sub>max</sub>	(h)	--	4.4 $\pm$ 0.8	4.4 $\pm$ 1.6
AUC <sub>11</sub>	(ng•h/mL)	--	5550 $\pm$ 2930	4980 $\pm$ 1910
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	7.36 $\pm$ 2.55 <sup>b,d</sup>
C <sub>11</sub>	(ng/mL)	--	324 $\pm$ 202	291 $\pm$ 197

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

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

b. For some Subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 4.

d. N = 3.

## Rilpivirine

Table 16 shows the mean  $\pm$  SD pharmacokinetic parameters of rilpivirine in Arm 2.

Pharmacokinetic Parameters	(Units)	Rilpivirine Arm 2/Cohort 1 (N = 10)		
		Regimen D: Day 14	Regimen E: Day 15	Regimen E: Day 27
C <sub>max</sub>	(ng/mL)	--	134 $\pm$ 33.8	562 $\pm$ 144
T <sub>max</sub>	(h)	--	4.0 $\pm$ 1.2	4.4 $\pm$ 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	1800 $\pm$ 445	9380 $\pm$ 2380
t <sub>1/2</sub>	(h)	--	--	41.8 $\pm$ 17.8
C <sub>24</sub>	(ng/mL)	--	57.0 $\pm$ 16.6	309 $\pm$ 75.0
Arm 2/Cohort 2 (N = 10)				
Pharmacokinetic Parameters	(Units)	Regimen F: Day 13	Regimen E: Day 15	Regimen E: Day 27
C <sub>max</sub>	(ng/mL)	217 $\pm$ 81.2	294 $\pm$ 114	636 $\pm$ 199
T <sub>max</sub>	(h)	4.9 $\pm$ 1.2	4.1 $\pm$ 1.2	5.3 $\pm$ 4.6
AUC <sub>24</sub>	(ng•h/mL)	3090 $\pm$ 913	4770 $\pm$ 1330	10500 $\pm$ 2770
t <sub>1/2</sub>	(h)	--	--	38.8 $\pm$ 10.2 <sup>b,c</sup>
C <sub>24</sub>	(ng/mL)	88.5 $\pm$ 27.5	169 $\pm$ 55.4	324 $\pm$ 86.1

Regimen D: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning administered under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) on Study Days 1 to 14 (Cohort 1).

Regimen E: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning under non-fasting conditions + ABT-333 400 mg BID (evening dose 1 hour after dinner) and rilpivirine 25 mg QD administered at night, approximately 4 hours after dinner (semi-fasting conditions), on Study Days 15 to 28 (Cohorts 1 and 2).

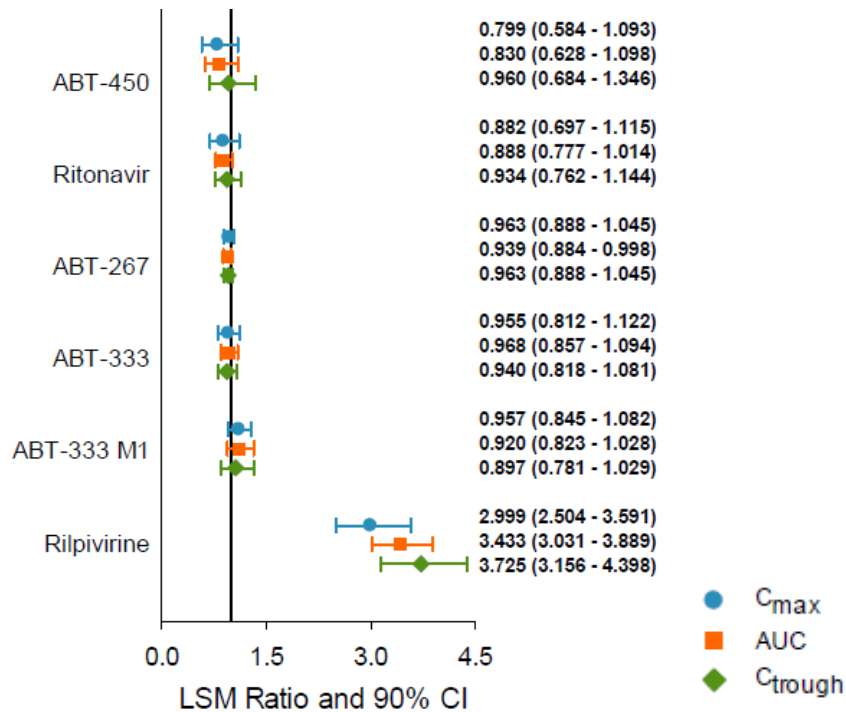
Regimen F: Rilpivirine 25 mg QD administered at night following a snack (non-fasting conditions) on Study Days 1 to 14 (Cohort 2).

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

b. For some subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 8.

Fig 2 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and rilpivirine in Arm 2.



Arm 3

Table 17 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 3.

Pharmacokinetic Parameters	(Units)	ABT-450 Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 14	Regimen H: Day 16	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	1890 $\pm$ 2620	1680 $\pm$ 2130	3000 $\pm$ 5350
T <sub>max</sub>	(h)	4.2 $\pm$ 1.0	4.9 $\pm$ 1.4	4.8 $\pm$ 1.8
AUC <sub>24</sub>	(ng•h/mL)	11400 $\pm$ 17200	12000 $\pm$ 18500	19700 $\pm$ 38600
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.59 $\pm$ 0.93
C <sub>24</sub>	(ng/mL)	41.6 $\pm$ 58.7	48.8 $\pm$ 69.9	83.1 $\pm$ 168
Pharmacokinetic Parameters	(Units)	ABT-450 Arm 3/Cohort 2 (N = 9)		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	--	1510 $\pm$ 1130	2540 $\pm$ 2110
T <sub>max</sub>	(h)	--	5.0 $\pm$ 1.7	4.0 $\pm$ 0.9
AUC <sub>24</sub>	(ng•h/mL)	--	7040 $\pm$ 3500	12700 $\pm$ 10600
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.67 $\pm$ 0.88 <sup>b,c</sup>
C <sub>24</sub>	(ng/mL)	--	35.6 $\pm$ 19.2	52.2 $\pm$ 66.5

Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b For some Subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c N = 8

Table 18 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 3.

Pharmacokinetic Parameters	(Units)	Ritonavir Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 14	Regimen H: Day 16	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	2000 ± 825	1810 ± 812	1920 ± 888
T <sub>max</sub>	(h)	4.1 ± 0.7	4.5 ± 1.4	4.3 ± 0.9
AUC <sub>24</sub>	(ng•h/mL)	12200 ± 5160	12200 ± 6000	12500 ± 8130
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.72 ± 1.11
C <sub>24</sub>	(ng/mL)	55.9 ± 35.9	56.1 ± 31.7	65.7 ± 75.7
		Arm 3/Cohort 2 (N = 9)		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	--	1830 ± 633	2250 ± 777
T <sub>max</sub>	(h)	--	4.0 ± 0.9	3.9 ± 0.3
AUC <sub>24</sub>	(ng•h/mL)	--	10700 ± 3710	14000 ± 6480
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.74 ± 0.99
C <sub>24</sub>	(ng/mL)	--	38.0 ± 23.1	49.4 ± 28.0

Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## ABT-267

Table 19 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 3.

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 14	Regimen H: Day 16	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	103 ± 48.0	101 ± 45.7	110 ± 50.7
T <sub>max</sub>	(h)	4.4 ± 0.8	5.4 ± 1.0	4.9 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	1300 ± 631	1260 ± 643	1400 ± 737
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	32.6 ± 7.43
C <sub>24</sub>	(ng/mL)	28.2 ± 15.8	27.5 ± 15.5	30.5 ± 17.5
		Arm 3/Cohort 2 (N = 9)		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	--	122 ± 35.2	126 ± 41.3
T <sub>max</sub>	(h)	--	4.6 ± 1.1	4.8 ± 1.2
AUC <sub>24</sub>	(ng•h/mL)	--	1070 ± 257	1510 ± 539
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	28.9 ± 11.9
C <sub>24</sub>	(ng/mL)	--	16.7 ± 3.72	32.0 ± 14.3

Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

a. Harmonic mean ± pseudo-standard deviation.

## ABT-333

Table 20 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 in Arm 3.

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 14	Regimen H: Day 16	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	1440 $\pm$ 992	1450 $\pm$ 1030	1430 $\pm$ 772
T <sub>max</sub>	(h)	4.1 $\pm$ 0.7	4.1 $\pm$ 1.1	4.2 $\pm$ 1.0
AUC <sub>12</sub>	(ng•h/mL)	8920 $\pm$ 6360	9020 $\pm$ 6140	9140 $\pm$ 5600
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.01 $\pm$ 0.96 <sup>b,c</sup>
C <sub>12</sub>	(ng/mL)	366 $\pm$ 288	375 $\pm$ 256	374 $\pm$ 281
		Arm 3/Cohort 2 (N = 9)		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	--	1800 $\pm$ 604	1720 $\pm$ 523
T <sub>max</sub>	(h)	--	4.0 $\pm$ 1.3	3.8 $\pm$ 0.4
AUC <sub>12</sub>	(ng•h/mL)	--	11200 $\pm$ 3300	11200 $\pm$ 4280
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.80 $\pm$ 2.53
C <sub>12</sub>	(ng/mL)	--	471 $\pm$ 146	475 $\pm$ 254

Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. For some subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 9.

Table 21 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 3.

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 14	Regimen H: Day 16	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	857 $\pm$ 469	845 $\pm$ 457	887 $\pm$ 457
T <sub>max</sub>	(h)	4.4 $\pm$ 0.8	4.7 $\pm$ 1.2	4.3 $\pm$ 0.9
AUC <sub>12</sub>	(ng•h/mL)	5050 $\pm$ 3470	5290 $\pm$ 3610	5360 $\pm$ 3610
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.58 $\pm$ 0.74 <sup>b,c</sup>
C <sub>12</sub>	(ng/mL)	200 $\pm$ 193	218 $\pm$ 181	215 $\pm$ 208
		Arm 3/Cohort 2 (N = 9)		
		Regimen I: Day 14	Regimen H: Day 15	Regimen H: Day 28
C <sub>max</sub>	(ng/mL)	--	1020 $\pm$ 355	892 $\pm$ 264
T <sub>max</sub>	(h)	--	4.4 $\pm$ 1.2	4.1 $\pm$ 0.8
AUC <sub>12</sub>	(ng•h/mL)	--	5910 $\pm$ 1860	5420 $\pm$ 1530
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.21 $\pm$ 0.69 <sup>b,d</sup>
C <sub>12</sub>	(ng/mL)	--	255 $\pm$ 83.7	204 $\pm$ 83.4

Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

b. For some subjects, a sufficient number of time points was not available to characterize the terminal elimination phase.

c. N = 5.

d. N = 4.

## Rilpivirine

Table 22 shows the mean  $\pm$  SD pharmacokinetic parameters of rilpivirine in Arm 3.

Pharmacokinetic Parameters	(Units)	Rilpivirine Arm 3/Cohort 1 (N = 10)		
		Regimen G: Day 13	Regimen H: Day 15	Regimen H: Day 27
C <sub>max</sub>	(ng/mL)	--	107 $\pm$ 37.0	387 $\pm$ 137
T <sub>max</sub>	(h)	--	5.6 $\pm$ 3.5	6.7 $\pm$ 4.7
AUC <sub>24</sub>	(ng•h/mL)	--	1300 $\pm$ 339	7100 $\pm$ 2380
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	39.7 $\pm$ 11.0
C <sub>24</sub>	(ng/mL)	--	41.2 $\pm$ 11.5	252 $\pm$ 99.8
Arm 3/Cohort 2 (N = 9)				
		Regimen I: Day 13	Regimen H: Day 15	Regimen H: Day 27
C <sub>max</sub>	(ng/mL)	245 $\pm$ 51.2	304 $\pm$ 67.5	540 $\pm$ 170
T <sub>max</sub>	(h)	5.3 $\pm$ 2.6	4.3 $\pm$ 1.3	6.1 $\pm$ 4.6
AUC <sub>24</sub>	(ng•h/mL)	3680 $\pm$ 757	5240 $\pm$ 1360	9540 $\pm$ 3610
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	36.4 $\pm$ 9.32
C <sub>24</sub>	(ng/mL)	106 $\pm$ 27.3	166 $\pm$ 58.4	324 $\pm$ 173

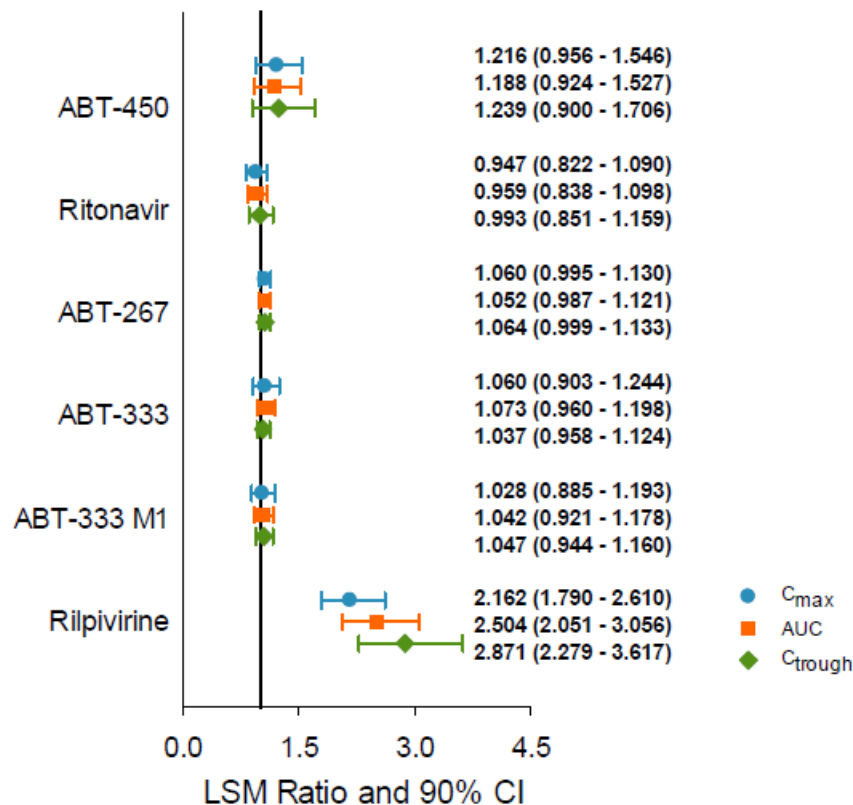
Regimen G: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning and ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen H: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD in the morning + ABT-333 400 mg BID and rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 15 to 28 (Cohorts 1 and 2).

Regimen I: Rilpivirine 25 mg QD administered in the evening under non-fasting conditions on Study Days 1 to 14 (Cohort 2).

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

Fig 3 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and rilpivirine in Arm 3.



### *Reviewer's Assessment of the Clinical Relevance of the Increase in Rilpivirine Exposures Observed in the Various Arms of Trial M13-782*

The mean systemic exposure (AUC) of rilpivirine increased by 224 %, 243 %, and 150 % in Arms 1, 2 and 3, respectively. The increase in rilpivirine exposures was expected as rilpivirine is a substrate of CYP3A4 and ritonavir is a potent inhibitor of CYP3A4. In fact, the magnitude of increase in rilpivirine exposure observed in this (M13-782) trial was greater than the magnitude of increase in rilpivirine exposure when rilpivirine is co-administered with boosted protease inhibitors, thereby suggesting that additional enzymes and transporters may be involved in rilpivirine disposition when rilpivirine was co-administered with the 3-DAAs.

Arm 3 was conducted following Arm 1 and before Arm 2. In Arm 3, rilpivirine was administered with an evening snack, coinciding with the evening dose of ABT-333 starting on Study Day 15 but separated from administration of ABT-450/r + ABT-267 by ~12 hours, with the hypothesis that separation of rilpivirine dosing from ABT-450/r + ABT-267 may decrease the magnitude of the interaction. Rilpivirine C<sub>max</sub>, AUC<sub>24</sub>, and C<sub>24</sub> values during coadministration with the 3-DAA combination at steady state (Study Day 27) in Arm 3 were increased by 116%, 150%, and 187%, respectively, suggesting a 15% to 25% lower extent of interaction compared with Arm 1.

In Arm 2, rilpivirine was administered with an evening snack during Period 1 of Cohort 2 (Study Days 1 to 14), and subsequently administered at night during Period 2 (Cohorts 1 and 2), approximately 4 hours after dinner and without an evening snack. In this way, rilpivirine was administered under semi-fasting conditions, separated from ABT-450/r + ABT-267 administration by ~16 hours and the evening dose of ABT-333 by ~3 hours. Rilpivirine  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  values during coadministration with the 3-DAA combination at steady state (Study Day 27) in Arm 2 were increased by 200 %, 243 %, and 273%, respectively, compared with rilpivirine administered alone at steady-state (Study Day 13). Administration of rilpivirine alone with food during Period 1 (Study Days 1 to 14), followed by administration under semi-fasting conditions when coadministered with DAAs during Period 2 (Study Days 15 to 28) was expected to reduce the extent of the drug-drug interaction. However, the magnitude of the interaction in Arm 2 was similar to when all of the agents were coadministered simultaneously in Arm 1.

In all the rilpivirine dosing strategies investigated in the trial (rilpivirine given in the morning under fed conditions, rilpivirine given in the evening (under fed conditions) and rilpivirine given under “semi fasting” conditions (3 hours after evening snack), the increases in rilpivirine exposures is of clinical concern. The approved prescribing information of rilpivirine (EDURANT) provides the following information:

*When supratherapeutic doses of 75 mg once daily and 300 mg once daily of EDURANT were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline-correction were 10.7 (15.3) and 23.3 (28.4) milliseconds, respectively. Steady-state administration of EDURANT 75 mg once daily and 300 mg once daily resulted in a mean steady-state  $C_{max}$  approximately 2.6-fold and 6.7-fold, respectively, higher than the mean  $C_{max}$  observed with the recommended 25 mg once daily dose of EDURANT*

The  $C_{max}$  of rilpivirine at the 25 mg once daily, 75 mg once daily, and 300 mg once daily doses were 220 ng/mL, 605 ng/mL, and 1620 ng/mL, respectively (Information taken from the Clinical Pharmacology Review of NDA 202022 available at Drugs@FDA). Of note, the increased steady-state rilpivirine  $C_{max}$  values during co-administration with the DAAs across Arms 1-3 were in the same range (100 % to 200 %, ratio: 2 to 3-fold) as those observed following administration of the supratherapeutic 75 mg QD rilpivirine dose relative to the therapeutic dose of 25 mg QD.

## **Safety**

No deaths occurred during the study. One subject experienced a serious adverse event of abortion spontaneous after the completion of the study (25 days following the last dose of study drug). Two subjects discontinued from the study due to non-serious adverse events; one of these subjects discontinued for maculopapular rash that occurred while the subject was receiving rilpivirine alone in Cohort 2 of Arm 3. One subject discontinued for blood creatine phosphokinase increase while receiving DAAs + rilpivirine in Cohort 2 of Arm 1.

## Results

- Co-administration of ABT-450/r, ABT-267 and ABT-333 with rilpivirine (Arm 1) increased the mean  $C_{\max}$ , AUC, and  $C_{24}$  of rilpivirine by 154 %, 224 %, and 162 %, respectively, as compared to administration of rilpivirine alone (day 14). There were no significant changes in the mean pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1.
- Administration of rilpivirine under “semi fasting” conditions (Arm 2) increased the mean  $C_{\max}$ , AUC, and  $C_{24}$  of rilpivirine by 200 %, 243 %, and 272 %, respectively, as compared to administration of rilpivirine alone (day 13). There were no significant changes in the mean pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1.
- Administration of rilpivirine with an evening snack (Arm 3; evening administration) increased the mean  $C_{\max}$ , AUC, and  $C_{24}$  of rilpivirine by 116 %, 150 %, and 187 %, respectively, as compared to administration of rilpivirine alone (day 13). There were no significant changes in the mean pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1.

## Conclusion

Co-administration of the 3-DAA regimen (ABT-450/r/ABT-267 with ABT-333) with rilpivirine is not recommended based on concerns of QT prolongation which can be associated with increase in rilpivirine exposures observed in this trial (M13-782).



**Drug-Drug Interaction Trial with Atazanavir**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**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

Of note, in Arm 1, atazanavir was administered in the morning and in Arm 3, atazanavir was administered in the evening. Ritonavir (100 mg) was 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.

## 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 3-DAA regimen) 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), ABT-267 (25 mg) and ABT-333 (400 mg) were the doses that were determined to be safe and efficacious in the Phase 2 trials. Further, these doses (or doses that provided comparable systemic exposures) were also 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. (b) (4)	AbbVie Inc. Lake County, IL	AbbVie Inc. Lake County, IL	AbbVie Inc. Lake County, IL	Bristol Myers Squibb
Finishing Lot Numbers <sup>a</sup>	12-007095, 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, ABT-333, ABT-333 M1, and atazanavir were collected at steady state in the three arms. In Arms 1 and 2, intensive PK sampling occurred on study days 14, 15, and 28; in Cohort 1 of Arm 3, intensive PK sampling occurred on days 14, 15, 16, 27, and 28 and for subjects in cohort 2 of Arm 3 (when atazanavir was dosed once daily in the evening of Arm 3).

## Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and atazanavir 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 %
ABT-333	4.53-3090	4.53	12, 200, 2500	5.7 % to 6.2 %	-2.5 % to 0 %
ABT-333 M1	4.73-3220	4.73	11.6, 193, 2420	3.8 % to 6 %	-6.2 % to -5.2 %
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						Overall/Total
	Arm 1/Cohort 1	Arm 1/Cohort 2	Arm 2/Cohort 1	Arm 2/Cohort 2	Arm 3/Cohort 1	Arm 3/Cohort 2	
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 $\pm$ SD	37.2 $\pm$ 9.69	33.6 $\pm$ 6.80	33.2 $\pm$ 8.30	35.4 $\pm$ 6.89	33.9 $\pm$ 8.06	33.8 $\pm$ 8.53	34.5 $\pm$ 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 $\pm$ SD	77.2 $\pm$ 6.99	76.1 $\pm$ 13.85	76.1 $\pm$ 7.60	78.3 $\pm$ 12.55	79.0 $\pm$ 12.56	75.6 $\pm$ 13.65	77.0 $\pm$ 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 $\pm$ SD	167.3 $\pm$ 3.84	173.3 $\pm$ 11.50	171.7 $\pm$ 5.72	175.7 $\pm$ 9.73	171.0 $\pm$ 10.80	171.3 $\pm$ 9.13	171.7 $\pm$ 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

Out of the 72 subjects enrolled in the trial, the data from 71 subjects was included in the pharmacokinetic analysis and 66 subjects who completed dosing were included in the statistical analysis of the pharmacokinetic parameters. Six subjects discontinued from the study during the dosing periods and 1 subject was lost to follow up after completing dosing.

- Subject 107 (30-year-old White male) was discontinued from the study in Period 2 of Arm 1, Cohort 1 after Study Day 20 dosing due to a family emergency.
- Subject 110 (24-year-old Black female) was discontinued from the study in

- Period 2 of Arm1, Cohort 1 after Study Day 15 dosing due to an adverse event.
- Subject 202 (25-year-old White female) was discontinued from the study in Period 2 of Arm 2, Cohort 1 after Study Day 24 dosing due to an adverse event.
  - Subject 210 (23-year-old White male) was discontinued from the study in Period 2 of Arm 2, Cohort 1 after Study Day 21 dosing due to an adverse event.
  - Subject 214 (33-year-old White male) completed the dosing in Arm 2, Cohort 2 but was lost to follow up.
  - Subject 223 (38-year-old White male) was discontinued from the study in Period 1 of Arm 2, Cohort 2 after Study Day 10 dosing due to an adverse event. This subject was not included for pharmacokinetic parameters determination or in the statistical analyses of pharmacokinetic parameters.
  - Subject 305 (27-year-old White female) was discontinued from the study after completing dosing in Period 2 of Arm 3, Cohort 1 after Study Day 24 dosing due to an adverse event.

## Pharmacokinetics

*Note: Only the results from Arm 1 and Arm 3 are presented in this review.*

### Arm 1

#### ABT-450

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 1.

ABT-450 Pharmacokinetic Parameters (Unit)	Cohort 1		
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	4360 $\pm$ 2980	6610 $\pm$ 3060	5590 $\pm$ 2950
$T_{max}$ (h)	4.3 $\pm$ 1.2	3.9 $\pm$ 0.9	4.2 $\pm$ 1.3
$C_{24}$ (ng/mL)	93.3 $\pm$ 104	191 $\pm$ 159	378 $\pm$ 518
$t_{1/2}^a$ (h)	--	--	5.2 $\pm$ 1.4
$AUC_{24}$ (ng•h/mL)	26300 $\pm$ 21700	40700 $\pm$ 21700	47700 $\pm$ 36600
ABT-450 Pharmacokinetic Parameters (Unit)	Cohort 2		
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
	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 + ABT-333 400 mg BID + Atazanavir 300 mg QD	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QD
$C_{max}$ (ng/mL)	--	1660 $\pm$ 790	4210 $\pm$ 2750
$T_{max}$ (h)	--	4.3 $\pm$ 0.9	4.4 $\pm$ 1.0
$C_{24}$ (ng/mL)	--	57.9 $\pm$ 38.8	211 $\pm$ 330
$t_{1/2}^a$ (h)	--	--	4.9 $\pm$ 1.4
$AUC_{24}$ (ng•h/mL)	--	8900 $\pm$ 4190	31100 $\pm$ 27400

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

#### Ritonavir

Table 7 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 1.

Cohort 1			
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
Ritonavir Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
C <sub>max</sub> (ng/mL)	2400 ± 906	2800 ± 757	1920 ± 625
T <sub>max</sub> (h)	4.3 ± 1.1	4.0 ± 0.9	4.4 ± 1.2
C <sub>24</sub> (ng/mL)	53.6 ± 28.9	79.2 ± 38.8	76.1 ± 40.2
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	4.9 ± 0.7
AUC <sub>24</sub> (ng•h/mL)	15000 ± 4440	17600 ± 4290	13400 ± 3670
Cohort 2			
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
Ritonavir Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	Atazanavir 300 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ Ritonavir 100 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ Atazanavir 300 mg QD	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
C <sub>max</sub> (ng/mL)	2160 ± 530	2150 ± 719	1830 ± 683
T <sub>max</sub> (h)	3.8 ± 0.6	4.3 ± 0.9	4.5 ± 0.9
C <sub>24</sub> (ng/mL)	67.0 ± 46.1	69.2 ± 49.8	62.8 ± 41.6
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	4.7 ± 0.9
AUC <sub>24</sub> (ng•h/mL)	12900 ± 4350	13200 ± 4960	11800 ± 4060

a. Harmonic mean ± pseudo-standard deviation.

## ABT-267

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 1.

Cohort 1			
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
ABT-267 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
C <sub>max</sub> (ng/mL)	121 ± 26.3	99.4 ± 22.7	93.3 ± 26.8
T <sub>max</sub> (h)	4.5 ± 1.2	4.8 ± 1.0	5.4 ± 1.0
C <sub>24</sub> (ng/mL)	36.5 ± 12.6	33.0 ± 11.2	31.9 ± 9.74
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	35.7 ± 18.0
AUC <sub>24</sub> (ng•h/mL)	1610 ± 408	1380 ± 374	1330 ± 356
Cohort 2			
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
ABT-267 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	Atazanavir 300 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ Ritonavir 100 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ Atazanavir 300 mg QD	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
C <sub>max</sub> (ng/mL)	--	61.1 ± 22.9	75.7 ± 25.0
T <sub>max</sub> (h)	--	5.0 ± 1.0	5.3 ± 1.5
C <sub>24</sub> (ng/mL)	--	10.0 ± 4.18	25.8 ± 13.4
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	29.4 ± 12.6
AUC <sub>24</sub> (ng•h/mL)	--	610 ± 221	1070 ± 429

a. Harmonic mean ± pseudo-standard deviation.

## ABT-333

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 in Arm 1.



Cohort 1			
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
ABT-333 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	1560 ± 609	1560 ± 597	1320 ± 725
T <sub>max</sub> (h)	3.8 ± 1.1	3.7 ± 0.8	3.6 ± 0.7
C <sub>12</sub> (ng/mL)	437 ± 240	435 ± 228	379 ± 242
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	6.9 ± 2.5
AUC <sub>12</sub> (ng•h/mL)	10600 ± 4440	10500 ± 4180	8870 ± 4720

Cohort 2			
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
ABT-333 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	Atazanavir 300 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ Ritonavir 100 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
		+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
		+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	--	1050 ± 448	1100 ± 511
T <sub>max</sub> (h)	--	4.2 ± 0.9	4.3 ± 0.9
C <sub>12</sub> (ng/mL)	--	190 ± 49.0	298 ± 133
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	6.4 ± 1.9 <sup>b</sup>
AUC <sub>12</sub> (ng•h/mL)	--	5920 ± 2270	7270 ± 2880

a. Harmonic mean ± pseudo-standard deviation.

b. N = 10, two subjects could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

## ABT-333 M1

Table 10 shows the mean ± SD pharmacokinetic parameters of ABT-333 M1 in Arm 1.

Cohort 1			
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
ABT-333 M1 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	981 ± 253	1100 ± 319	805 ± 320
T <sub>max</sub> (h)	4.3 ± 0.9	4.1 ± 0.7	4.3 ± 0.9
C <sub>12</sub> (ng/mL)	274 ± 149	332 ± 124	274 ± 134
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	5.6 ± 0.7 <sup>b</sup>
AUC <sub>12</sub> (ng•h/mL)	6490 ± 2040	7370 ± 2130	5750 ± 2230

Cohort 2			
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
ABT-333 M1 Pharmacokinetic Parameters (Unit)	Study Day 14	Study Day 15	Study Day 28
	Atazanavir 300 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
	+ Ritonavir 100 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
		+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
		+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	--	702 ± 270	703 ± 269
T <sub>max</sub> (h)	--	4.7 ± 1.0	4.7 ± 1.0
C <sub>12</sub> (ng/mL)	--	144 ± 34.7	214 ± 98.3
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	5.8 ± 2.2 <sup>c</sup>
AUC <sub>12</sub> (ng•h/mL)	--	3900 ± 1320	4710 ± 1810

a. Harmonic mean ± pseudo-standard deviation.

b. N = 6, four subjects could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

c. N = 5, seven subjects could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

## Atazanavir

Table 11 shows the mean ± SD pharmacokinetic parameters of atazanavir in Arm 1.

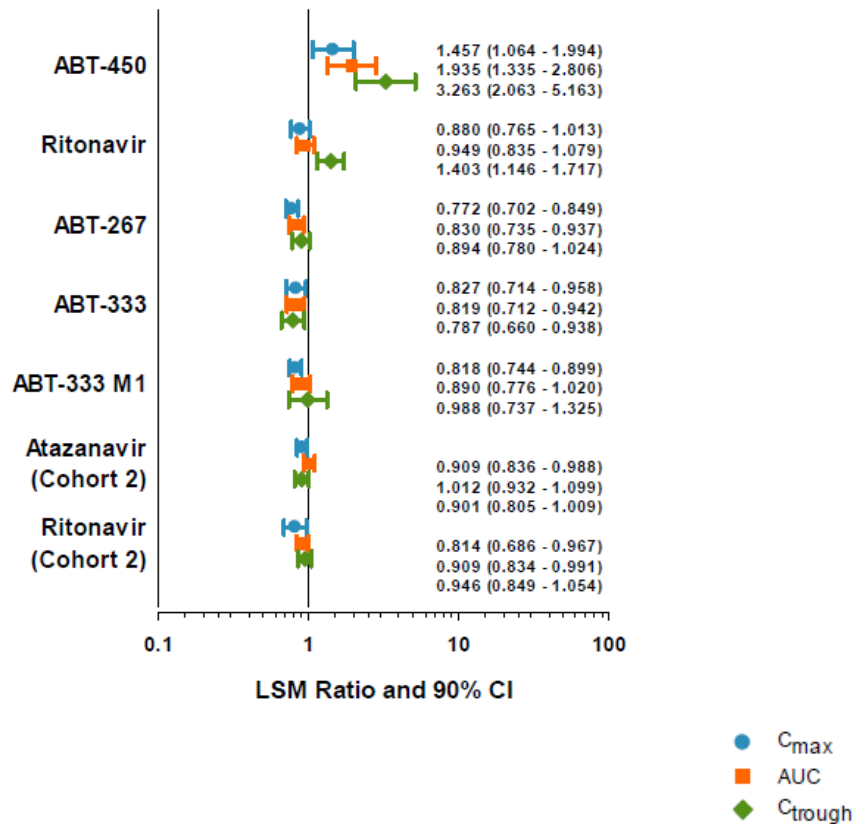
Cohort 1			
	Regimen A (N = 12)	Regimen B (N = 12)	Regimen B (N = 10)
	Study Day 14	Study Day 15	Study Day 28
Atazanavir	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
Pharmacokinetic	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
Parameters (Unit)	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	--	5280 ± 1470	6170 ± 2350
T <sub>max</sub> (h)	--	3.0 ± 0.9	2.8 ± 0.8
C <sub>24</sub> (ng/mL)	--	723 ± 287	1530 ± 1140
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	8.6 ± 2.6
AUC <sub>24</sub> (ng•h/mL)	--	42700 ± 11500	67800 ± 31400

Cohort 2			
	Regimen C (N = 12)	Regimen B (N = 12)	Regimen B (N = 12)
	Study Day 14	Study Day 15	Study Day 28
Atazanavir	Atazanavir 300 mg QD	ABT-450/r 150/100 mg QD	ABT-450/r 150/100 mg QD
Pharmacokinetic	+ Ritonavir 100 mg QD	+ ABT-267 25 mg QD	+ ABT-267 25 mg QD
Parameters (Unit)		+ ABT-333 400 mg BID	+ ABT-333 400 mg BID
		+ Atazanavir 300 mg QD	+ Atazanavir 300 mg QD
C <sub>max</sub> (ng/mL)	6580 ± 2300	6530 ± 2820	5960 ± 2020
T <sub>max</sub> (h)	3.0 ± 1.0	2.9 ± 0.8	3.3 ± 0.8
C <sub>24</sub> (ng/mL)	1550 ± 1050	1600 ± 1190	1440 ± 1170
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	6.7 ± 2.3
AUC <sub>24</sub> (ng•h/mL)	67900 ± 30000	70200 ± 33700	67900 ± 30200

a. Harmonic mean ± pseudo-standard deviation.

Fig 1 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and atazanavir in Arm 1.



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

AUC<sub>12</sub> and C<sub>12</sub>: ABT-333 and ABT-333 M1 metabolite.



### Arm 3

Table 12 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 3.

	Cohort 1		
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 16 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
ABT-450 Pharmacokinetic Parameters (Unit)			
$C_{max}$ (ng/mL)	2010 $\pm$ 2180	4500 $\pm$ 3750	3590 $\pm$ 2960
$T_{max}$ (h)	4.3 $\pm$ 0.8	5.1 $\pm$ 3.6	5.0 $\pm$ 3.7
$C_{24}$ (ng/mL)	52.1 $\pm$ 100	794 $\pm$ 1030	552 $\pm$ 734
$t_{1/2}$ <sup>a</sup> (h)	--	--	4.8 $\pm$ 1.3
$AUC_{24}$ (ng $\cdot$ h/mL)	11800 $\pm$ 15800	44600 $\pm$ 40100	33200 $\pm$ 32800
	Cohort 2		
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
	Study Day 13 ABT-450/r 150/100 mg QD + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
ABT-450 Pharmacokinetic Parameters (Unit)			
$C_{max}$ (ng/mL)	--	1180 $\pm$ 685	3280 $\pm$ 1980
$T_{max}$ (h)	--	5.9 $\pm$ 4.7	4.0 $\pm$ 0.7
$C_{24}$ (ng/mL)	--	154 $\pm$ 83.0	317 $\pm$ 220
$t_{1/2}$ <sup>a</sup> (h)	--	--	4.9 $\pm$ 1.5
$AUC_{24}$ (ng $\cdot$ h/mL)	--	9420 $\pm$ 4330	27200 $\pm$ 18600

QPM = Once daily dose in the evening.

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

Table 13 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 3.

	Cohort 1		
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 16 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
Ritonavir Pharmacokinetic Parameters (Unit)			
$C_{max}$ (ng/mL)	1950 $\pm$ 751	3320 $\pm$ 1070	2880 $\pm$ 795
$T_{max}$ (h)	4.3 $\pm$ 0.8	3.8 $\pm$ 0.4 <sup>b</sup>	4.0 $\pm$ 0.0 <sup>b</sup>
$C_{24}$ (ng/mL)	34.7 $\pm$ 18.8	1010 $\pm$ 424	792 $\pm$ 255
$t_{1/2}$ <sup>a</sup> (h)	--	--	4.9 $\pm$ 1.0
$AUC_{24}$ (ng $\cdot$ h/mL)	11000 $\pm$ 4500	40300 $\pm$ 13800	33100 $\pm$ 9490
	Cohort 2		
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
	Study Day 13 ABT-450/r 150/100 mg QD + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
Ritonavir Pharmacokinetic Parameters (Unit)			
$C_{max}$ (ng/mL)	2120 $\pm$ 623	3190 $\pm$ 920	2890 $\pm$ 987
$T_{max}$ (h)	4.5 $\pm$ 1.2	4.0 $\pm$ 0.0 <sup>b</sup>	3.8 $\pm$ 0.6 <sup>b</sup>
$C_{24}$ (ng/mL)	66.4 $\pm$ 48.2	988 $\pm$ 480	879 $\pm$ 481
$t_{1/2}$ <sup>a</sup> (h)	--	--	4.7 $\pm$ 0.8
$AUC_{24}$ (ng $\cdot$ h/mL)	15700 $\pm$ 5700	34900 $\pm$ 12200	35600 $\pm$ 13900

QPM = Once daily dose in the evening

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

b. For subjects with  $T_{max}$  > 12 hours, the evening dose time was used as reference.

Table 14 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-267 in Arm 3.

Cohort 1			
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
		Study Day 16 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID
ABT-267 Pharmacokinetic Parameters (Unit)	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
C <sub>max</sub> (ng/mL)	115 $\pm$ 19.0	110 $\pm$ 21.9	95.1 $\pm$ 25.3
T <sub>max</sub> (h)	4.7 $\pm$ 1.0	4.7 $\pm$ 1.0	5.3 $\pm$ 1.0
C <sub>24</sub> (ng/mL)	33.2 $\pm$ 12.2	34.2 $\pm$ 11.2	31.4 $\pm$ 9.61
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	35.3 $\pm$ 13.4
AUC <sub>24</sub> (ng•h/mL)	1440 $\pm$ 346	1400 $\pm$ 306	1260 $\pm$ 307
Cohort 2			
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
		Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID
ABT-267 Pharmacokinetic Parameters (Unit)	Study Day 13 Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
C <sub>max</sub> (ng/mL)	--	79.0 $\pm$ 23.0	87.4 $\pm$ 21.1
T <sub>max</sub> (h)	--	4.4 $\pm$ 1.2	5.1 $\pm$ 1.2
C <sub>24</sub> (ng/mL)	--	12.8 $\pm$ 4.93	28.6 $\pm$ 10.2
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	30.9 $\pm$ 10.3
AUC <sub>24</sub> (ng•h/mL)	--	782 $\pm$ 250	1190 $\pm$ 366

QPM = Once daily dose in the evening.

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

## ABT-333

Table 15 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 in Arm 3.

Cohort 1			
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
		Study Day 16 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID
ABT-333 Pharmacokinetic Parameters (Unit)	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
C <sub>max</sub> (ng/mL)	1480 $\pm$ 395	1550 $\pm$ 541	1160 $\pm$ 212
T <sub>max</sub> (h)	3.8 $\pm$ 1.0	3.8 $\pm$ 0.5	3.7 $\pm$ 0.5
C <sub>12</sub> (ng/mL)	325 $\pm$ 152	386 $\pm$ 161	240 $\pm$ 86.9
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	6.5 $\pm$ 2.4 <sup>b</sup>
AUC <sub>12</sub> (ng•h/mL)	8750 $\pm$ 2760	9620 $\pm$ 3210	6790 $\pm$ 1360
Cohort 2			
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
		Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID
ABT-333 Pharmacokinetic Parameters (Unit)	Study Day 13 Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	+ Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
C <sub>max</sub> (ng/mL)	--	1290 $\pm$ 345	1310 $\pm$ 261
T <sub>max</sub> (h)	--	3.6 $\pm$ 0.7	3.7 $\pm$ 0.7
C <sub>12</sub> (ng/mL)	--	232 $\pm$ 64.1	276 $\pm$ 89.0
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	5.7 $\pm$ 1.3
AUC <sub>12</sub> (ng•h/mL)	--	6990 $\pm$ 1780	7720 $\pm$ 1740

QPM = Once daily dose in the evening

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

b. N = 10, one subject could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

Table 16 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 in Arm 3.

	Cohort 1		
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 16 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
ABT-333 M1 Pharmacokinetic Parameters (Unit)			
C <sub>max</sub> (ng/mL)	858 $\pm$ 255	856 $\pm$ 261	694 $\pm$ 178
T <sub>max</sub> (h)	4.3 $\pm$ 0.8	4.7 $\pm$ 1.0	4.2 $\pm$ 0.6
C <sub>12</sub> (ng/mL)	168 $\pm$ 119	247 $\pm$ 116	158 $\pm$ 85.6
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	5.5 $\pm$ 0.7 <sup>b</sup>
AUC <sub>12</sub> (ng•h/mL)	4910 $\pm$ 1970	5840 $\pm$ 1860	4140 $\pm$ 1320
	Cohort 2		
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
	Study Day 13 Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 28 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
ABT-333 M1 Pharmacokinetic Parameters (Unit)			
C <sub>max</sub> (ng/mL)	--	718 $\pm$ 228	748 $\pm$ 227
T <sub>max</sub> (h)	--	4.1 $\pm$ 1.1	4.0 $\pm$ 0.9
C <sub>12</sub> (ng/mL)	--	147 $\pm$ 57.9	175 $\pm$ 71.2
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	4.8 $\pm$ 0.4 <sup>c</sup>
AUC <sub>12</sub> (ng•h/mL)	--	4080 $\pm$ 1340	4780 $\pm$ 1520

QPM = Once daily dose in the evening

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

b. N = 3, eight subjects could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

c. N = 7, five subjects could not be determined due to the lack of at least three concentration data points after T<sub>max</sub>.

## Atazanavir

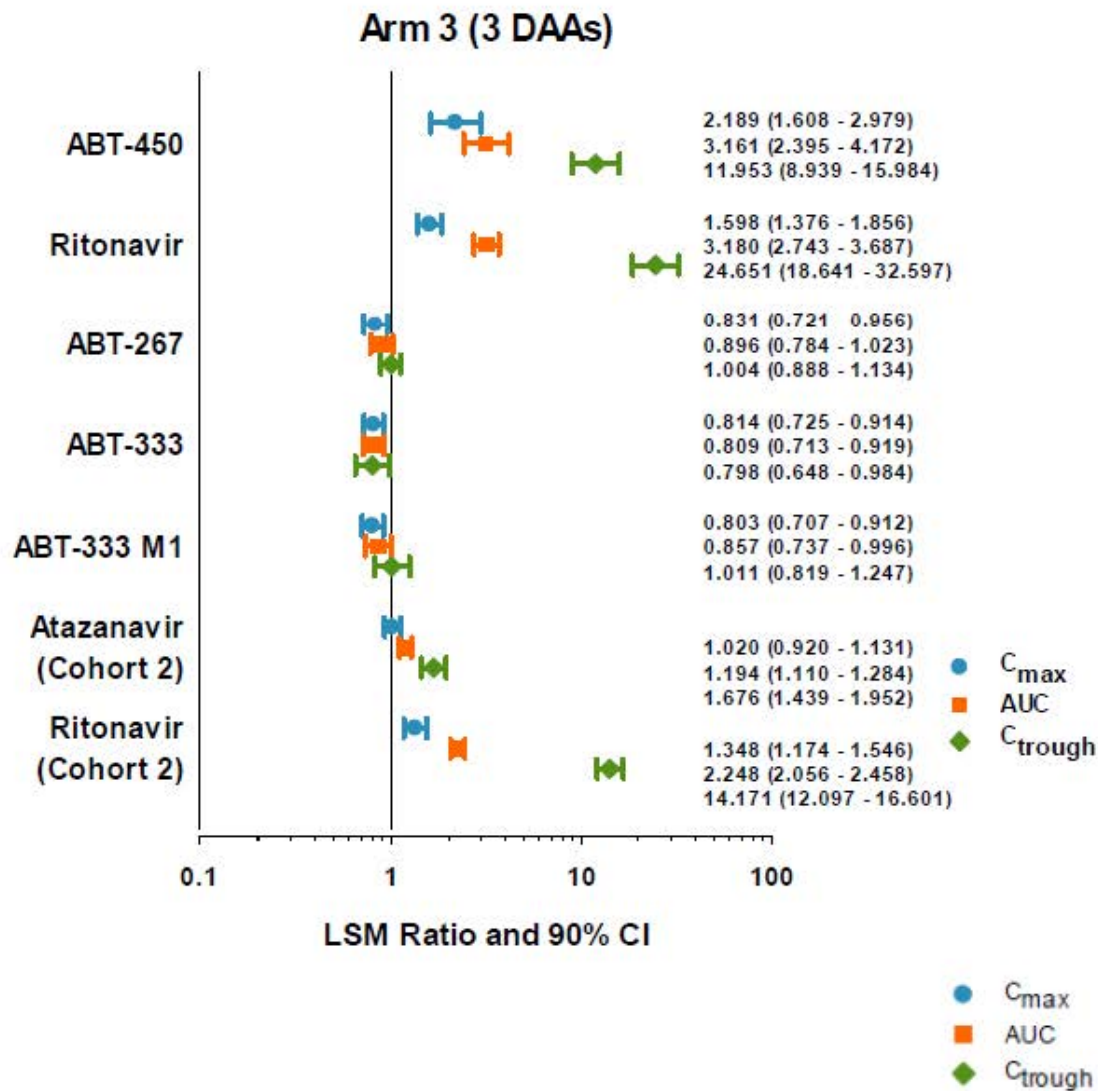
Table 17 shows the mean  $\pm$  SD pharmacokinetic parameters of atazanavir in Arm 3.

	Cohort 1		
	Regimen G (N = 12)	Regimen H (N = 12)	Regimen H (N = 11)
	Study Day 14 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 27 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
Atazanavir Pharmacokinetic Parameters (Unit)			
C <sub>max</sub> (ng/mL)	--	4080 $\pm$ 794	5250 $\pm$ 801
T <sub>max</sub> (h)	--	3.8 $\pm$ 1.2	3.5 $\pm$ 1.7
C <sub>24</sub> (ng/mL)	--	869 $\pm$ 183	1720 $\pm$ 537
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	8.6 $\pm$ 1.8
AUC <sub>24</sub> (ng•h/mL)	--	41900 $\pm$ 6270	71900 $\pm$ 12900
	Cohort 2		
	Regimen I (N = 12)	Regimen H (N = 12)	Regimen H (N = 12)
	Study Day 13 Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 15 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM	Study Day 27 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + Atazanavir 300 mg QPM + Ritonavir 100 mg QPM
Atazanavir Pharmacokinetic Parameters (Unit)			
C <sub>max</sub> (ng/mL)	5560 $\pm$ 1690	5490 $\pm$ 1930	5810 $\pm$ 2210
T <sub>max</sub> (h)	3.3 $\pm$ 0.8	4.4 $\pm$ 2.0	3.8 $\pm$ 1.3
C <sub>24</sub> (ng/mL)	1120 $\pm$ 634	1870 $\pm$ 677	1770 $\pm$ 689
t <sub>1/2</sub> <sup>a</sup> (h)	--	--	8.4 $\pm$ 2.7
AUC <sub>24</sub> (ng•h/mL)	64700 $\pm$ 23500	75600 $\pm$ 24100	76300 $\pm$ 24400

QPM = Once daily dose in the evening

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

Fig 2 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and atazanavir in Arm 3.



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

AUC<sub>12</sub> and C<sub>12</sub>: ABT-333 and ABT-333 M1 metabolite.

Arm 3: Atazanavir was administered in the evening. Study Days 27 versus 13 was compared for atazanavir, while Study Days 28 versus 13 was compared for ritonavir. The ritonavir regimens were 100 mg QD on Days 1 to 14 and 100 mg BID on Days 15 to 28.

### Reviewer’s Assessment of the Results from Trial M13-394

Co-administration of atazanavir with the 3 DAAs in the morning (Arm 1) increased ABT-450 C<sub>max</sub> AUC<sub>24</sub> and C<sub>24</sub> by 45%, 93%, and 226 %, respectively. Atazanavir is a known inhibitor of CYP3A and OATP transporters and ABT-450 has been shown to be a

substrate of CYP3A and OAT; therefore, the increase in the exposure of ABT-450 may be due to the inhibition of CYP3A and OATP by atazanavir. When evening doses of atazanavir and ritonavir were co-administered with the 3-DAA regimen (Arm 3), ABT-450  $C_{max}$  and AUC were 2.2- and 3.2-fold, respectively, of those observed when the 3-DAA regimen was administered without atazanavir and ritonavir. The higher extent of drug-drug interaction observed in Arm 3 compared to Arm 1 may be due to the increased daily dose of ritonavir (200 mg in Arm 3 compared to 100 mg in Arm 1).

## 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 and ABT-333 with atazanavir (Arm 1)
  - Increased the mean  $C_{max}$ , AUC, and  $C_{24}$  of ABT-450 by 45 %, 93 %, and 226 %, respectively.
  - There were no significant changes in the mean pharmacokinetic parameters of atazanavir, ritonavir, ABT-267, ABT-333, and ABT-333 M1.
- Administration of ABT-450/r, ABT-267 and ABT-333 with atazanavir (Arm 3)
  - Increased the mean  $C_{max}$ , AUC, and  $C_{24}$  of ABT-450 by 118 %, 216 %, and 1095 %, respectively.
  - Increased the mean  $C_{max}$ , AUC, and  $C_{24}$  of ritonavir by 59 %, 218 %, and 2365 %, respectively in Cohort 1 and 34 %, 124 %, and 1317 %, respectively, in Cohort 2.
  - Increased the mean  $C_{max}$ , AUC, and  $C_{24}$  of atazanavir by 2 %, 20 %, and 67 %, respectively.
  - There were no significant changes in the mean pharmacokinetic parameters of ABT-267, ABT-333, and ABT-333 M1.

## Conclusion

**Morning Administration:** ABT-450/r/ABT-267 once daily with ABT-333 twice daily can be administered with atazanavir in the morning without any dose adjustments. As ritonavir is part of the ABT-450/ritonavir/ABT-267 coformulated tablet, an additional dose of ritonavir with atazanavir is not needed.

**Evening Administration:** Administration of ABT-450/r/ABT-267 once daily with ABT-333 twice daily and atazanavir (administered in the evening) is not recommended.

**Drug-Drug Interaction Trial with Lopinavir/Ritonavir**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Coadministration of Lopinavir/ritonavir (LPV/r) Once Daily with ABT-450 Plus Ritonavir (ABT-450/r) and ABT-267 With or Without ABT-333 in Healthy Adult Subjects (M13-013)**

**Study period:** 29 December 2012 to 02 May 2013

**Objectives:** The objectives of this study were:

- To determine the pharmacokinetics, safety and tolerability of the combination of ABT-450/r and ABT-267 with or without ABT-333 when dosed with LPV/ritonavir (LPV/r) once daily in healthy subjects.
- To determine the pharmacokinetics, safety and tolerability of LPV/r once daily when coadministered with a combination of ABT-450/r and ABT-267 with or without ABT-333 in healthy subjects

**Methodology:**

This Phase 1, single center, randomized, multiple-dose, non-fasting, open-label study was designed to evaluate the combination of LPV/r and 2 or 3 Direct Acting Antivirals (DAAs) (ABT-450/r, ABT-333 and ABT-267, or ABT-450/r and ABT-267, depending on the arm of the study). Arm 1 evaluated the combination of LPV/r and 3 DAA combination (ABT-450/r, ABT-267 and ABT-333). Arm 2 evaluated the combination of LPV/r and 2 DAA combination (ABT-450/r and ABT-267).

Adult male and female subjects (N = 48) in general good health were selected to participate in the study according to the selection criteria.

Arm	Cohort	N	Regimens	
			Period 1	Period 2
Arm 1	1	12	A	B
	2	12	C	B
Arm 2 <sup>a</sup>	1	12	D	E
	2	12	F	E

- a. In Arm 2/Cohort 1, Subject 202 prematurely discontinued study drug due to an adverse event after receiving ABT-450/r + ABT-267 + LPV/r on Study Day 23.

Study drug was administered starting on Study Day 1 as follows:

**Regimen A** ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) + ABT-267 25 mg QD administered under non-fasting conditions with QD doses being administered in the morning

**Regimen B** ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions with QD doses being administered in the

morning + LPV/r 800/200 mg QD administered in the evening under non-fasting conditions

**Regimen C** LPV/r 800/200 mg QD administered in the evening under non-fasting conditions

**Regimen D** ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered in the morning under non-fasting conditions

**Regimen E** ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered in the morning under non-fasting conditions + LPV/r 800/200 mg QD administered in the evening under non-fasting conditions

**Regimen F** LPV/r 800/200 mg QD administered in the evening under non-fasting conditions

Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for the morning doses of all drugs and approximately 30 minutes after the start of the evening snack for the LPV/r, and the evening doses of ABT-333 as appropriate.

Subjects were confined to the study site and supervised for approximately 32 days in each study period. Confinement in each period began on Study Day -1 (1 day prior to the dosing day) and ended after the collection of the 72-hour blood samples and completion of the scheduled study procedures on Study Day 31. Subjects returned for an outpatient safety visit on Study Day 38 (a visit window of +2 days is allowed to accommodate subject scheduling). In each arm of the study, blood samples for pharmacokinetic analysis were collected as described in the protocol. Intensive pharmacokinetic sampling occurred on Study Days 14, 15 and 28 in Cohort 1 and on Study Days 13, 15 and 28 in Cohort 2.

#### **Number of Subjects (Planned and Analyzed):**

In Arm 1; Planned: 24, Entered: 24, Completed: 24, Evaluated for Safety: 24, Evaluated for Pharmacokinetics (PK): 24

In Arm 2; Planned: 24, Entered: 24, Completed: 23, Evaluated for Safety: 24, Evaluated for PK: 23 (except for Arm 2 [Cohort 2, Period 1], N = 23)

For the 48 subjects in Arm 1 and Arm 2, the mean age was 37.8 years (ranging from 23 to 54 years), the mean weight was 80.9 kg (ranging from 52.3 to 107.0 kg) and the mean height was 174.7 cm (ranging from 149.5 to 191.2 cm).

#### **Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers whose ages were between 18 and 55 years. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal for at least 2 years or surgically sterile, and were not pregnant or breastfeeding. Males were surgically sterile, sexually inactive or practiced birth control.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

	ABT-267	ABT-450/r	ABT-333	LPV/ritonavir
Dosage Form	Tablet	Tablet	Tablet	Tablet
Mode of Administration	Oral	Oral	Oral	Oral
Strength (mg)	25	75/50	400	200/50
Bulk Product Lot Number	11-002033	12-002722	12-001228	12-007812/21096AA
Potency (% of Label Claim)	NA	(b) (4)		NA
Manufacturing Site	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL
Manufacturing Date	(b) (4)	(b) (4)	(b) (4)	NA
Finishing Lot Number	12-007665	12-007666	12-007667	12-007668 and 12-008043
Expiration/Retest Date	(b) (4)			

NA = Not Available

**Duration of Treatment:**

Subjects in Arm 1 (Cohort 1: Regimens A and B; Cohort 2: Regimens C and B) were dosed between the dates of 09 January 2013 and 05 February 2013; Arm 2 (Cohort 1: Regimens D and E; Cohort 2: Regimens F and E) were dosed between the dates of 13 March 2013 and 09 April 2013.

**Criteria for Evaluation:**

**Pharmacokinetics:** The pharmacokinetic parameter values of ABT-333, ABT-333 M1, ABT-450, ritonavir, ABT-267, and lopinavir were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), time to  $C_{max}$  (peak time,  $T_{max}$ ), apparent terminal phase elimination rate constant ( $\beta$ ), terminal phase elimination half-life ( $t_{1/2}$ ), area under the plasma concentration-time curve (AUC) from time 0 to 12 hours ( $AUC_{12}$ , BID dosing only) and from time 0 to 24 hours ( $AUC_{24}$ , QD dosing only). Dose-normalized  $C_{max}$ ,  $AUC_{12}$  or  $AUC_{24}$ , and  $C_{12}$  or  $C_{24}$  values were calculated by dividing each of these pharmacokinetic parameters by the administered dose. For the ABT-333 M1 metabolite, the dose of ABT-333 was used to dose normalize the pharmacokinetic parameters.

**Safety Endpoints:** Safety was evaluated based on assessments of adverse events, vital signs, physical examinations, ECGs and laboratory tests.

**Statistical Methods:**

**Pharmacokinetic:** Pharmacokinetic:

Cohort 1: To assess the effect of LPV/r on ABT-450, ABT-333 (ABT-333 if applicable in an arm) and ABT-267, a repeated measure analysis was performed for the natural logarithms of ABT-450, ABT-333 (ABT-333 if applicable in an arm) and ABT-267.  $C_{max}$  and AUC utilizing data from Study Days 14 and 28 from Cohort 1 of each Arm. A separate analysis was performed for each arm. The model had day as a fixed effect and subject as a random effect. Additionally,



the ABT-450, ABT-333 (ABT-333 if applicable in an arm) and ABT-267  $C_{\max}$  and AUC ratios were estimated by taking the ratio of corresponding Study Day 28 versus Study Day 14 values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-measures analysis model.

Cohort 2: To assess the effect of ABT-450/r, ABT-333 (ABT-333 if applicable in an arm) and ABT-267 on LPV, a repeated measure analysis was performed for the natural logarithms of LPV  $C_{\max}$  and AUC utilizing data from Study Days 13 and 28 from Cohort 2 of each Arm. A separate analysis was performed for each Arm. The model had day as a fixed effect and subject as a random effect. Additionally, the LPV  $C_{\max}$  and AUC ratios were estimated by taking the ratio of corresponding Study Day 28 versus Study Day 13 values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-measures analysis model.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

## **Results:**

### **Pharmacokinetics:**

The effects of LPV/r on ABT-450, ABT-333 (ABT-333 if applicable in an arm) and ABT-267, a repeated measure analysis are summarized in Table 1-4. For the two one-sided tests based on the analysis of log-transformed PK parameters, the 90% confidence intervals and the corresponding point estimates of relative bioavailability are presented in the Tables.

The effects of LPV/r on ABT-450 with (Arm 1/Cohort 1) or without (Arm 2/Cohort 1) ABT-333 are summarized in Table 1. Following co-administration of LPV/r with ABT-450/r, ABT-267 and ABT-333, ABT-450  $AUC_{24}$  and  $C_{24}$  values were 1.9-fold and 8.2-fold, respectively, of those observed during administration of ABT-450/r, ABT-267 and ABT-333 without LPV/r ( $p < 0.05$ ). However, ABT-450  $C_{\max}$  values following co-administration of LPV/r with ABT-450/r, ABT-267 and ABT-333 were comparable to the administration of DAAs alone ( $p > 0.05$ ). Following co-administration of LPV/r with ABT-450/r and ABT-267 (i.e., without ABT-333 in Arm

2/Cohort 1), ABT-450  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  values were 1.8-fold, 3.5-fold and 14.8-fold, respectively, of those observed during administration of ABT-450/r and ABT-267 without LPV/r ( $p < 0.05$ ). The quantitative difference in the changes in ABT-450 exposure due to LPV/r with or without ABT-333 indicates that ABT-333 played a role in the interaction between ABT-450 and LPV/r.

**Table 1.** The effects of LPV/r 800/200 mg QD on ABT-450 with (Arm 1/Cohort 1) or without (Arm 2/Cohort 1) ABT-333

Arm/Cohort	ABT-450 Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values <sup>d</sup>	
		Study Day 28	Study Day 14	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
1/1 (N = 12)	$C_{\max}$	2050	2062	0.994	0.789 – 1.253
	$AUC_{24}$	21413	11424	1.874	1.397 – 2.515
	$C_{24}$	321	39	8.229	5.179 – 13.074
2/1 (N = 11)	$C_{\max}$	2348	1318	1.783	1.262 – 2.518
	$AUC_{24}$	21894	6172	3.547	2.366 – 5.319
	$C_{24}$	334	22.6	14.783	9.409 – 23.226

<sup>a</sup>. Exponentiation of the least squares means for logarithms.

<sup>b</sup>. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.

<sup>c</sup>. Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.

<sup>d</sup>. Study Day 28: Study Day 14.

The steady-state effect of LPV/r on the pharmacokinetics of ritonavir was evaluated by comparing ritonavir exposures on Study Day 28 and Study Day 14 in Cohort 1 and Study Day 28 and Study Day 13 in Cohort 2 in each Arm (Arm 1: with ABT-333 and Arm 2: without ABT-333). In Cohort 1, 300 mg dose of ritonavir on Study Day 28 was compared to 100 mg dose of ritonavir on Study Day 14. In Cohort 2, 300 mg dose of ritonavir on Study Day 28 was compared to 200 mg dose of ritonavir on Study Day 13. The ratio (Study Day 28/Study Day 14, Cohort 1 and Study Day 28/Study Day 13, Cohort 2) of central values for ritonavir  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  and the 90% confidence intervals are presented in Table 2.

Addition of LPV/r to the 3 DAA regimen or the 2 DAA regimen (Cohort 1) increased ritonavir  $C_{\max}$  and AUC values by up to 3.1-fold, while ritonavir  $C_{\text{trough}}$  values increased by 19-fold and 23-fold, respectively, compared to the co-administration of 3 DAAs and 2 DAAs without LPV/r. Following addition of the 3 DAA or 2 DAA regimens to steady-state LPV/r (Cohort 2), ritonavir  $C_{\max}$  and AUC were increased by approximately 20% to 60% and  $C_{24}$  increased by up to 8.4-fold. These changes are due to higher dose of ritonavir during co-administration of DAAs with LPV/r compared to the administration of DAAs (Cohort 1) or LPV/r (Cohort 2) alone.

**Table 2.** The steady-state effect of LPV/r 800/200 mg QD on the pharmacokinetics of ritonavir in Cohort 1 and Cohort 2 in each Arm (Arm 1: with ABT-333 and Arm 2: without ABT-333)

Arm/Cohort	Ritonavir Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values <sup>d</sup>	
		Study Day 28	Study Day 14	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>

1/1 (N = 12)	C <sub>max</sub>	2723	1740	1.565	1.336 – 1.833
	AUC <sub>24</sub>	28740	10951	2.624	2.319 – 2.970
	C <sub>24</sub>	703	36.1	19.460	15.934 – 23.767
1/2 (N = 12)	C <sub>max</sub>	2767	2363	1.171	1.010 – 1.358
	AUC <sub>24</sub>	27226	17739	1.535	1.363 – 1.728
	C <sub>24</sub>	294	35.1	8.389	6.829 – 10.305
2/1 (N = 11)	C <sub>max</sub>	2678	1492	1.795	1.300 – 2.479
	AUC <sub>24</sub>	26169	8463	3.092	2.356 – 4.059
	C <sub>24</sub>	668	28.9	23.161	15.545 – 34.507
2/2 (N = 12)	C <sub>max</sub>	3255	2466	1.320	1.163 – 1.498
	AUC <sub>24</sub>	30466	18884	1.613	1.482 – 1.757
	C <sub>24</sub>	222	31.1	7.132	5.702 – 8.921

- Exponentiation of the least squares means for logarithms.
- Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
- Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.
- Cohort 1 = Study Day 28:Study Day 14; Cohort 2 = Study Day 28:Study Day 13.

The effects of LPV/r 800/200 mg QD on ABT-267 with (Arm 1/Cohort 1) or without (Arm 2/Cohort 1) ABT-333 are summarized in Table 3. There were no clinically meaningful changes in ABT-267 due to the coadministration of LPV/r 800/200 mg QD regardless of ABT-333.

**Table 3.** The steady state effects of LPV/r 800/200 mg QD on ABT-267 with (Arm 1/Cohort 1) or without (Arm 2/Cohort 1) ABT-333

Arm/Cohort	ABT-267 Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values <sup>d</sup>	
		Study Day 28	Study Day 14	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
1/1 (N = 12)	C <sub>max</sub>	110	126	0.87	0.825 – 0.922
	AUC <sub>24</sub>	1384	1421	0.97	0.935 – 1.015
	C <sub>24</sub>	29.5	26.6	1.10	1.060 – 1.159
2/1 (N = 11)	C <sub>max</sub>	111	115	0.97	0.867 – 1.084
	AUC <sub>24</sub>	1390	1271	1.09	1.003 – 1.193
	C <sub>24</sub>	30.9	25.0	1.23	1.128 – 1.353

- Exponentiation of the least squares means for logarithms.
- Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
- Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.
- Study Day 28: Study Day 14.

The effects of LPV/r 800/200 mg QD on ABT-333 and its metabolite M1 are summarized in Table 4. Following co-administration of LPV/r with ABT-450/r, ABT-267 and ABT-333, ABT-333 C<sub>max</sub>, AUC<sub>12</sub> and C<sub>12</sub> were statistically significantly lower (p < 0.05) by 44%, 46% and 53%, respectively, compared to the co-administration of ABT-450/r, ABT-267 and ABT-333 without LPV/r. Similarly, following co-administration of LPV/r with ABT-450/r, ABT-267 and ABT-333, ABT-333 M1 C<sub>max</sub>, AUC<sub>12</sub> and C<sub>12</sub> were statistically significantly lower (p < 0.05) by 39%, 38% and 50%, respectively, compared to the co-administration of ABT-450/r, ABT-267 and ABT-333 without LPV/r.

**Table 4.** The steady-state effect of LPV/r 800/200 mg QD on the pharmacokinetics of ABT-333 and ABT-333 M1

Arm/Cohort	ABT-333 Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values <sup>d</sup>	
		Study Day28	Study Day 14	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
ABT-333					
1/1	C <sub>max</sub>	709	1270	0.558	0.474 – 0.658
(N = 12)	AUC <sub>12</sub>	4675	8586	0.544	0.459 – 0.645
	C <sub>12</sub>	165	349	0.473	0.389 – 0.575
ABT-333 M1 Metabolite					
1/1	C <sub>max</sub>	494	812	0.608	0.521 – 0.710
(N = 12)	AUC <sub>12</sub>	3129	5052	0.619	0.516 – 0.743
	C <sub>12</sub>	96	193	0.498	0.384 – 0.647

<sup>a</sup>. Exponentiation of the least squares means for logarithms.

<sup>b</sup>. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.

<sup>c</sup>. Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.

<sup>d</sup>. Study Day 28: Study Day 14.

The steady-state effect of ABT-450/r and ABT-267 with (Arm 1/Cohort 2) and without (Arm 2/Cohort 2) ABT-333 on the pharmacokinetics of lopinavir was evaluated by comparing ritonavir exposures on Study Day 28 and Study Day 13 (Table 5). Lopinavir exposures (C<sub>max</sub> and AUC) were comparable (up to ± 20% change) with and without co-administration of 3 DAAs and 2 DAAs. However, C<sub>trough</sub> (C<sub>24</sub>) was up to 3.5-fold higher during co-administration of DAA regimens with LPV/r.

**Table 5.** The steady effect of ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) on the PK of Lopinavir

Arm/Cohort	Lopinavir PK Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
		Study Day28	Study Day13	Point Estimate <sup>b</sup>	90% Confidence Interval <sup>c</sup>
1/2	C <sub>max</sub>	13457	15598	0.863	0.797 – 0.934
(N = 12)	AUC <sub>24</sub>	200027	213237	0.938	0.869 – 1.013
	C <sub>24</sub>	4742	1493	3.177	2.486 – 4.060
2/2	C <sub>max</sub>	16311	15515	1.051	0.949 – 1.165
(N = 12)	AUC <sub>24</sub>	245220	209688	1.169	1.086 – 1.260
	C <sub>24</sub>	5608	1601	3.503	2.690 – 4.563

<sup>a</sup>. Exponentiation of the least squares means for logarithms.

<sup>b</sup>. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.

<sup>c</sup>. Exponentiation of the endpoints of confidence intervals for the difference of logarithms means.

<sup>d</sup>. Study Day 28: Study Day 13.

## Safety Results:

The regimens were generally well tolerated. The majority of adverse events occurring in this study were mild in severity. Several of these adverse events were gastrointestinal or neurologic in nature, and were attributed to LPV/r. No new safety findings of concern occurred during this study, and there were no clinically significant abnormal vital signs, ECG, or laboratory measurements.

No deaths or other serious adverse events were reported in this study. One subject discontinued study drug due to elevations in ALT and AST which were assessed by the investigator as mild with a reasonable possibility of being related to LPV/r and resolved 13 days after discontinuation of study drug. Results of other safety analyses including individual subject changes, changes over time, and individual clinically significant values for vital signs, ECG, and laboratory measurements were unremarkable for each treatment group.

### **Conclusions:**

Co-administration of LPV/r with the 3 DAA regimen had minimal to moderate effect (up to  $\pm 50\%$  changes) on steady-state pharmacokinetics of the DAAs other than ABT-450. Overall, ABT-450 exposures (AUC and  $C_{\text{trough}}$ ) increased by 1.9-fold and by 8.2-fold, respectively, during co-administration with LPV/r QD compared to the administration of 3 DAAs alone.

Co-administration of LPV/r with the 2 DAA regimen of ABT-450/r and ABT-267 had minimal effect (up to  $\pm 24\%$  changes) on steady-state pharmacokinetics of ABT-267. However, ABT-450  $C_{\text{max}}$ , AUC and  $C_{24}$  values increased by 1.8-fold, 3.5-fold and 14.8-fold, respectively, during co-administration with LPV/r compared to the administration of 2 DAAs alone.

Addition of LPV/r to the 3 DAA regimen or the 2 DAA regimen (Cohort 1) increased ritonavir  $C_{\text{max}}$  and AUC values by up to 3.1-fold, while ritonavir  $C_{\text{trough}}$  values increased by 19-fold and 23-fold, respectively, compared to the co-administration of 3 DAAs and 2 DAAs without LPV/r. Following addition of the 3 DAA or 2 DAA regimens to steady-state LPV/r (Cohort 2), ritonavir  $C_{\text{max}}$  and AUC were increased by approximately 20% to 60% and  $C_{24}$  increased by up to 8.4-fold. These changes are due to higher dose of ritonavir during co-administration of DAAs with LPV/r compared to the administration of DAAs (Cohort 1) or LPV/r (Cohort 2) alone.

Addition of LPV/r to the 3 DAA regimen decreased ABT-333 and its metabolite M1 exposure by 40-50% compared to the administration of 3 DAA alone.

Lopinavir exposures ( $C_{\text{max}}$  and AUC) were comparable (up to  $\pm 20\%$  change) with and without co-administration of 3 DAAs and 2 DAAs. However,  $C_{\text{trough}}$  ( $C_{24}$ ) was up to 3.5-fold higher during co-administration of DAA regimens with LPV/r. However, despite up to 3.5-fold increase in lopinavir  $C_{\text{trough}}$  during co-administration of LPV/r 800/200 mg QD with DAAs, lopinavir  $C_{\text{trough}}$  values were comparable to those observed with the administration of LPV/r 400/100 mg BID alone. Hence, these changes in lopinavir exposures are not expected to have any adverse effects on the safety or efficacy of the LPV/r regimen.

The regimens were generally well tolerated. The majority of adverse events occurring in this study were mild in severity. One subject discontinued study drug due to elevations in ALT and AST which were assessed by the investigator as mild with a reasonable possibility of being

related to LPV/r and resolved 13 days after discontinuation of study drug. Several of these adverse events were gastrointestinal or neurologic in nature, and were attributed to LPV/r. No new safety findings of concern occurred during this study, and there were no other clinically significant abnormal vital signs, ECG, or laboratory measurements. No deaths or other serious adverse events were reported in this study. Results of other safety analyses including individual subject changes, changes over time, and individual clinically significant values for vital signs, ECG, and laboratory measurements were unremarkable for each treatment group.

*Reviewer's conclusion and labeling recommendation:*

*Based on the results of this study, the sponsor proposed that Lopinavir/ritonavir (800/200 mg once daily) should not be co-administered with 3 DAA (b) (4) regimens because of an increase in ABT-450 exposures ( $C_{max}$  and AUC increases up to 3.1-fold) and due to higher total doses of ritonavir (300 mg/day). The reviewer agreed with the sponsor's labeling proposal regarding the drug interaction between Lopinavir/ritonavir (800/200 mg once daily) and DAA regimens. It also should be noted that Lopinavir/ritonavir decreased ABT-333 and its metabolite M1 exposure by 40-50%.*

**Drug-Drug Interaction Trial with Lopinavir/Ritonavir**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Coadministration of Lopinavir/ritonavir (LPV/r) with ABT-450 Plus Ritonavir (ABT-450/r) and ABT-267 and/or ABT-333 in Healthy Adult Subjects (M13-492)**

**Study period:** 17 January 2012 to 19 March 2013

**Objectives:** The objectives of this study were:

- To determine the pharmacokinetics, safety and tolerability of the combination of ABT-450/r with ABT-267 and/or ABT-333 when dosed with LPV/r in healthy subjects.
- To determine the pharmacokinetics, safety and tolerability of LPV/r when coadministered with a combination of ABT-450/r with ABT-267 and/or ABT-333 in healthy subjects.

**Methodology:**

This was a Phase 1, single center, randomized, multiple-dose, non-fasting, open-label study which evaluated the combination of LPV/r and 2 or 3 Direct Acting Antivirals (DAA) (ABT-450/r and ABT-333, ABT-450/r and ABT-333 and ABT-267, or ABT-450/r and ABT-267, depending on the arm of the study). Adult male and female subjects in general good health were selected to participate in the study according to the selection criteria.

After meeting the selection criteria, 12 subjects in Arm 1, Arm 2, Arm 3 and 24 subjects in Arm 4 were randomly assigned in equal numbers to one of two treatment sequences. Arm 5 was not done.

Arm	Cohort	N	Regimens	
			Period 1	Period 2
Arm 1	1	12	A	B
	2	12	C	B
Arm 2 <sup>a</sup>	1	12	D	E
	2	12	F	E
Arm 3 <sup>a</sup>	1	12	G	H
	2	12	F	H
Arm 4 <sup>a</sup>	1	24	G	H
	2	24	F	E

- a. 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 (Arms 2, 3 or 4). Doses in Arm 2, Arm 3, and Arm 4 (Regimens D to H) could have been modified based on pharmacokinetic, safety, and tolerability results from previous arm(s). Doses in Arm 2, Arm 3 and Arm 4 could have been as low as 0 mg and did not exceed ABT-450/r 250/100 mg once daily (QD), ABT-333 800 mg twice daily (BID), ABT-267 100 mg QD, and LPV/r 800/200 mg QD or BID..

Study drugs were administered on Study Days 1 through 28 as shown in the following table:

**Regimen A** ABT-333 400 mg BID + ABT-450/r 150/100 mg QD administered under non-fasting conditions

- Regimen B** ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + LPV/r 400/100 mg BID administered under non-fasting conditions
- Regimen C** LPV/r 400/100 mg BID administered under non-fasting conditions
- Regimen D** ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD administered under non-fasting conditions
- Regimen E** ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + LPV/r 400/100 mg BID under non-fasting conditions
- Regimen F** LPV/r 400/100 mg BID administered under non-fasting conditions
- Regimen G** ABT-267 25 mg QD + ABT-450/r 150/100 mg QD administered under non-fasting conditions
- Regimen H** ABT-267 25 mg QD + ABT-450/r 150/100 mg QD + LPV/r 400/100 mg BID under non-fasting conditions

Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for the morning doses of all drugs and approximately 30 minutes after the start of the evening snack for the evening doses of ABT-333 and LPV/r, as appropriate.

Arms 2, 3 and 4 were conducted sequentially. Based on a review of the available pharmacokinetic, safety and tolerability results of the previous arm(s), a decision was made whether to conduct the next sequential arm (Arms 2, 3 or 4). An additional 12 subjects in equal numbers in Arm 2 and Arm 3 and an additional 24 subjects in Arm 4 were randomly assigned to the same study design as Arm 1. Doses in Arm 2, Arm 3 and Arm 4 (Regimens D to H) were modified based on pharmacokinetic, safety and tolerability results of the previous arm(s). Doses in Arm 2, Arm 3 and Arm 4 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 LPV/r 800/200 mg QD or BID.

Arm 4 was divided into 2 groups such that approximately half the subjects in each arm were dosed separately from the other half.

In each arm, subjects were confined to the study site and supervised for approximately 32 days. Confinement began on Study Day –1 (day prior to initial dosing day) and ended after the collection of the 72-hour blood sample and completion of the scheduled study procedures on Study Day 31. Subjects were to return for an outpatient safety visit on Study Day 38 (a visit window of +2 days was allowed to accommodate subject scheduling). In each arm of the study, blood samples for pharmacokinetic analysis were collected as described in the protocol.

Intensive pharmacokinetic sampling occurred on Study Days 14 and 28 in Arm 1 and on Study Days 14, 15 and 28 in Arm 2, Arm 3 and Arm 4.

Pharmacokinetics, safety, and tolerability were assessed throughout the study. A blood sample was collected from each subject to obtain a sample of genetic material deoxyribonucleic acid/ribonucleic acid (DNA/RNA).

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir ABT-267, ABT-333 and ABT-333 M1 metabolite were established at 0.513 ng/mL, 5.19 ng/mL, 1.26 ng/mL, 1.06 ng/mL and 2.14 ng/mL, respectively.



Plasma concentrations of lopinavir were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The LLOQ for lopinavir was established at 19.6 ng/mL and 18.7 ng/mL.

**Number of Subjects (Planned and Analyzed):**

Planned: 84, Entered: 60, Completed: 60, Evaluated for Safety: 60, Evaluated for Pharmacokinetics: 60

For the 60 subjects who participated in the study, the mean age was 38.6 years (ranging from 20 to 55 years), the mean weight was 79.0 kg (ranging from 54 to 103 kg) and the mean height was 175 cm (ranging from 155 to 192 cm).

**Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers whose ages were between 18 and 55 years. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG). Females were postmenopausal for at least 2 years or surgically sterile, and were not pregnant or breastfeeding. Males were surgically sterile, sexually inactive or practiced birth control.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

	ABT-267	ABT-450	Ritonavir	ABT-333	Lopinavir/ritonavir
Dosage Form	(b) (4) Tablet	(b) (4) Tablet	Soft Gelatin Capsule	Tablet	Tablet
Strength (mg)	25	50	100	400	200/50
Bulk Product Lot Number	11-002033	11-000781	11-005635	11-000511	11-005630
Manufacturing Site	AbbVie Inc, (b) (4)	AbbVie Inc, Lake County, IL	AbbVie Inc, Lake County, IL	AbbVie Inc, Lake County, IL	AbbVie Inc, Barceloneta, PR
Finishing Lot Number – Arms 1 and 2	11-005455	11-005537	11-005539	11-005536	11-005538
Expiration/Retest Date – Arms 1 and 2	(b) (4)				
Finishing Lot Number – Arms 3 and 4	12-003254	12-003260	12-003261	--	12-003262
Expiration/Retest Date – Arms 3 and 4	(b) (4)				

**Duration of Treatment:**

Subjects received study drugs for 28 continuous days.

**Criteria for Evaluation:**

Pharmacokinetics: Values for the pharmacokinetic parameters of ABT-333, ABT-333 M1, ABT-450, ritonavir, ABT-267 and lopinavir including the maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  ( $T_{max}$ ), pre-dose trough plasma concentration ( $C_{trough}$ ,  $C_{12}$ ,  $C_{24}$ ), and the area under the plasma concentration-time curve (AUC) were determined using noncompartmental methods. The terminal phase elimination rate constant ( $\beta$ ) and terminal elimination half-life ( $t_{1/2}$ ) were calculated using noncompartmental methods on Day 28 only.

Safety Endpoints: Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead ECGs, and vital signs.

## Statistical Methods:

Pharmacokinetic: Plasma concentrations and pharmacokinetic parameters values of ABT-267, ABT-450, ritonavir, lopinavir, ABT-333 and ABT-333 M1 were tabulated for each subject and for each of the regimens containing administrations of the respective compounds, and summary statistics were computed for each sampling time and each parameter.

A repeated measures analysis were used to assess the steady-state of each analyte (when applicable) on the  $C_{trough}$  value (prior to the morning dose for all analytes with exception of prior to evening dose for lopinavir if lopinavir is dosed QD in the evening) utilizing corresponding data from Study Days 6, 8, 11, 13, 14, 15, 20, 22, 25, 27, 28, and 29 for Arm 1 and data from Study Days 8, 11, 13, 14, 15, 16, 20, 25, 27, 28, and 29 for Arms 2, 3 and 4.

A separate analysis was performed for each cohort in each Arm. Arms 3 and 4  $C_{trough}$  data from Study Days 6 (Study Day 6 for Arm 1 only), 8, 11, 13, 14 and 15 will be used to assess the steady-state of DAAs in Cohort 1 and LPV/r in Cohort 2, while  $C_{trough}$  data from Study Days 16 (Day 16 for Arms 2, 3 and 4), 20, 22 (Day 22 for Arm 1 only), 25, 27, 28 and 29 will be used to assess the steady-state of DAAs and LPV/r during coadministration in both Cohorts 1 and 2 of each arm.

For the pharmacokinetic parameters,  $C_{max}$  and AUC, repeated measure analyses was performed to assess the effect of LPV/r on ABT-450, ABT-333 (ABT-333 if applicable in an arm) and ABT-267 (ABT-267 if applicable in an arm) and to assess the effect of ABT-450/r, ABT-333 and/or ABT-267 on lopinavir.

A separate analysis was performed for each arm. The logarithmic transformation was used for  $C_{max}$  and AUC unless the data show that the logarithm had substantial non-symmetry. Since Arms 3 and 4 had exactly the same design and regimen, an analysis was also performed by combining data of Arms 3 and 4.

## Results:

### Pharmacokinetics:

The steady-state effects of LPV/r on the PK of ABT-450, ABT-333 and ABT-267 in different arms, a repeated measure analysis, are summarized in Table 1. The steady state effects of 3 DAA and 2 DAA (either 'ABT-450/r and ABT-333' or 'ABT-450/r and ABT-267') on the PK of LPV and ritonavir are also summarized in Table 1. For the two one-sided tests based on the analysis of log-transformed PK parameters, the 90% confidence intervals and the corresponding point estimates of relative bioavailability are presented in the Table.

### ABT-450:

During coadministration with LPV/r, ABT-450  $C_{max}$  and AUC were 2.3-fold and 3.0-fold, respectively, of those during the administration of ABT-450/r and ABT-333 without LPV/r (Arm 1). Similarly, ABT-450  $C_{24}$  values during coadministration with LPV/r were 6.3-fold ( $p < 0.05$ ) of those with ABT-450/r and ABT-333 administered without LPV/r.

ABT-450  $C_{max}$  and AUC increased statistically significantly ( $p < 0.05$ ) by 104% to 117% (ratios: 2.04 to 2.173) when 3 DAAs (ABT-450/r, ABT-267 and ABT-333) were coadministered with LPV/r compared to administration of the 3 DAAs without LPV/r (Arm 2). Similarly, ABT-450  $C_{24}$  values during coadministration of 3 DAAs with LPV/r were 2.4-fold of those during administration of 3 DAAs without LPV/r; however, this increase was not statistically significant ( $p > 0.05$ ).

There were statistically significant ( $p < 0.05$ ) increases in ABT-450 exposure ( $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$ ) when ABT-450/r and ABT-267 were coadministered with LPV/r (Arms 3 and 4). During coadministration of ABT-450/r and ABT-267 with LPV/r, ABT-450  $C_{\max}$  and AUC values were 4.8-fold and 6.1-fold, respectively, of those during the administration of ABT-450/r and ABT-267 without LPV/r. Similarly, ABT-450  $C_{24}$  values during coadministration of ABT-450/r and ABT-267 with LPV/r were 12.3-fold of those with ABT-450/r and ABT-267 without LPV/r.

*Reviewer's comments: The magnitude (i.e., fold difference) of interaction between lopinavir/r and ABT-450 was highest in the 2-DAA regimen of ABT-450/r + ABT-267. It should be noted that ABT-450 exposure is lower in 2-DDA regimen of ABT-450/r + ABT-267 compared with 3-DAA of ABT-450/r + ABT-267 + ABT-333 or 2-DAA of ABT-450/r + ABT-333. Thus, the interaction between lopinavir/r and ABT-450 appears to be affected by co-administration with ABT-267 and/or ABT-333.*

#### Ritonavir:

Overall, the ritonavir exposure was increased when 3 DDA and 2 DAA regimens were coadministered with LPV/r. The increases in ritonavir exposure are considered to be due to higher dose of ritonavir during co-administration of DAAs with LPV/r compared to the administration of DAAs alone.

#### ABT-267:

There were no clinically meaningful changes in the ABT-267 exposure by co-administration with LPV/r 400/100 mg BID.

#### ABT-333 and its metabolite, ABT-333 M1:

There were no clinically meaningful changes in the ABT-333 and ABT-333 M1 exposure by co-administration with 400/100 mg BID. It should be noted that ABT-333 and ABT-333 M1 exposure was decreased by approximately 50% when it was co-administered with LPV/r 800/200 mg QD (see the results of Study M13-013).

#### Lopinavir:

Lopinavir exposures ( $C_{\max}$ , AUC and  $C_{24}$ ) were comparable (up to  $\pm 20\%$  change) with and without co-administration of 3-DAA and 2-DAA regimens.

**Table 1.**

Analyte	Arm/Cohort	Pharmacokinetic Parameter	Ratio of Central Values <sup>a</sup>			
			Central Value <sup>b</sup>		Point Estimate <sup>c</sup>	90% Confidence Interval
			Day 28	Day 14		
ABT-450	1/1	$C_{\max}$ (ng/mL)	2460	1070	2.305	1.283 – 4.142
		$AUC_{24}$ (ng•h/mL)	18300	6130	2.984	1.323 – 6.729
		$C_{24}$ (ng/mL)	133	21.0	6.336	1.984 – 20.230
	2/1	$C_{\max}$ (ng/mL)	1740	854	2.040	1.299 – 3.204
		$AUC_{24}$ (ng•h/mL)	11000	5080	2.173	1.634 – 2.890
		$C_{24}$ (ng/mL)	48.8	20.7	2.358	1.003 – 5.546

Ritonavir	3 + 4/1	C <sub>max</sub> (ng/mL)	1830	385	4.760	3.544 – 6.393
		AUC <sub>24</sub> (ng•h/mL)	14200	2330	6.102	4.295 – 8.669
		C <sub>24</sub> (ng/mL)	104	8.46	12.331	7.298 – 20.835
	1/1	C <sub>max</sub> (ng/mL)	2760	1900	1.452	1.144 – 1.843
		AUC <sub>24</sub> (ng•h/mL)	27800	12400	2.247	1.937 – 2.607
		C <sub>24</sub> (ng/mL)	337	54.2	6.220	4.332 – 8.932
	1/2	C <sub>max</sub> (ng/mL)	1500	640	2.348	2.026 – 2.721
		AUC <sub>24</sub> (ng•h/mL)	18100	6810	2.659	2.330 – 3.034
		C <sub>24</sub> (ng/mL)	241	193	1.251	0.908 – 1.724
	2/1	C <sub>max</sub> (ng/mL)	1800	1160	1.554	1.157 – 2.089
		AUC <sub>24</sub> (ng•h/mL)	21100	10300	2.045	1.491 – 2.805
		C <sub>24</sub> (ng/mL)	324	61.7	5.254	3.334 – 8.279
	2/2	C <sub>max</sub> (ng/mL)	2040	930	2.196	1.558 – 3.096
		AUC <sub>24</sub> (ng•h/mL)	19700	10900	1.802	1.574 – 2.062
		C <sub>24</sub> (ng/mL)	277	205	1.350	1.025 – 1.778
	3 + 4/1	C <sub>max</sub> (ng/mL)	2410	1390	1.737	1.392 – 2.167
		AUC <sub>24</sub> (ng•h/mL)	23500	8420	2.784	2.423 – 3.200
		C <sub>24</sub> (ng/mL)	326	32.6	10.018	7.656 – 13.109
	3 + 4/2	C <sub>max</sub> (ng/mL)	2510	1110	2.255	1.947 – 2.613
		AUC <sub>24</sub> (ng•h/mL)	24700	12300	2.014	1.881 – 2.157
		C <sub>24</sub> (ng/mL)	331	237	1.398	1.228 – 1.591
ABT-267	2/1	C <sub>max</sub> (ng/mL)	147	129	1.139	1.010 – 1.284
		AUC <sub>24</sub> (ng•h/mL)	1970	1680	1.168	1.066 – 1.280
		C <sub>24</sub> (ng/mL)	46.3	37.5	1.236	1.140 – 1.339
	3 + 4/1	C <sub>max</sub> (ng/mL)	121	113	1.071	1.012 – 1.134
		AUC <sub>24</sub> (ng•h/mL)	1650	1320	1.252	1.188 – 1.319
		C <sub>24</sub> (ng/mL)	36.7	24.9	1.475	1.387 – 1.569
ABT-333	1/1	C <sub>max</sub> (ng/mL)	736	966	0.762	0.579 – 1.001
		AUC <sub>12</sub> (ng•h/mL)	4780	5930	0.805	0.594 – 1.090
		C <sub>12</sub> (ng/mL)	144	195	0.737	0.577 – 0.941
	2/1	C <sub>max</sub> (ng/mL)	873	879	0.993	0.754 – 1.309
		AUC <sub>12</sub> (ng•h/mL)	6220	6710	0.927	0.746 – 1.152
		C <sub>12</sub> (ng/mL)	226	334	0.677	0.571 – 0.802
ABT-333 M1	1/1	C <sub>max</sub> (ng/mL)	662	721	0.918	0.650 – 1.298
		AUC <sub>12</sub> (ng•h/mL)	4180	4250	0.983	0.647 – 1.492
		C <sub>12</sub> (ng/mL)	129	116	1.114	0.728 – 1.704
	2/1	C <sub>max</sub> (ng/mL)	594	503	1.179	0.823 – 1.689
		AUC <sub>12</sub> (ng•h/mL)	4030	3560	1.133	0.844 – 1.521
		C <sub>12</sub> (ng/mL)	134	164	0.813	0.687 – 0.963
Lopinavir	1/2	C <sub>max</sub> (ng/mL)	8790	10100	0.871	0.790 – 0.960
		AUC <sub>12</sub> (ng•h/mL)	87700	87500	1.003	0.943 – 1.066
		C <sub>12</sub> (ng/mL)	5900	4830	1.223	1.063 – 1.406

2/2	C <sub>max</sub> (ng/mL)	9410	10800	0.870	0.762 – 0.994
	AUC <sub>12</sub> (ng•h/mL)	90300	95800	0.942	0.810 – 1.096
	C <sub>12</sub> (ng/mL)	5930	5170	1.148	0.932 – 1.415
3 + 4/2	C <sub>max</sub> (ng/mL)	11200	10600	1.062	0.990 – 1.140
	AUC <sub>12</sub> (ng•h/mL)	108000	95700	1.132	1.091 – 1.174
	C <sub>12</sub> (ng/mL)	7250	5420	1.337	1.259 – 1.420

### **Safety Results:**

The regimens were generally well tolerated. The majority of adverse events occurring in this study were mild in severity. Events of diarrhea appeared to be more common with combination DAA + lopinavir/r dosing. Six subjects experienced low-grade elevations of ALT (maximum elevation 108 U/L) with DAAs or lopinavir/r alone, and with DAA + lopinavir/r combination dosing. The elevations were asymptomatic and resolved by the final study visit. Elevations of total bilirubin (primarily indirect) are consistent with inhibition of the bilirubin transporter, organic anion transporting polypeptide 1B1 (OATP1B1), by ABT-450. No new safety findings of concern occurred during this study, and there were no clinically significant abnormal vital signs, ECG, or laboratory measurements. No deaths or other serious adverse events were reported in this study. Results of other safety analyses including individual subject changes, changes over time, and individually clinically significant values for vital signs, ECG, and laboratory measurements were unremarkable for each treatment group.

### **Conclusions:**

Coadministration of lopinavir/r with the 3-DAA regimen had no clinically relevant effect (up to ± 30% change) on steady-state pharmacokinetics of the DAAs other than ABT-450. Overall, ABT-450 exposures (C<sub>max</sub>, AUC and C<sub>trough</sub>) increased by up to 135% during coadministration compared to the administration of DAAs alone.

Coadministration of lopinavir/r with the 2-DAA regimen of ABT-450/r and ABT-333 had no clinically relevant effect (up to ± 25% change) on steady-state pharmacokinetics of ABT-333 and ABT-333 M1; however, ABT-450 C<sub>max</sub>, AUC and C<sub>24</sub> values were about 2.3-fold, 3.0 and 6.3-fold, respectively, of those during the administration of ABT-450/r and ABT-333 alone. Coadministration of lopinavir/r with the 2-DAA regimen of ABT-450/r and ABT-267 had no clinically relevant effect (up to ± 50% increase) on steady-state pharmacokinetics of ABT-267; however, the magnitude of interaction between lopinavir/r and ABT-450 was highest in the 2-DAA regimen of ABT-450/r + ABT-267. ABT 450 C<sub>max</sub>, AUC and C<sub>trough</sub> were 4.8-fold, 6.1-fold, and 12.3-fold, respectively, of those during the coadministration of the 2-DAA regimen without lopinavir/r.

### *Reviewer's conclusion and labeling recommendation:*

*Based on the results of this study and Study M13-013, the sponsor proposed that Lopinavir/ritonavir (both 400/100 mg BID and 800/200 mg once daily) should not be co-administered with 3 DAA (b) (4) regimens because of an increase in ABT-450 exposures and due to higher total doses of ritonavir (300 mg/day). The reviewer agreed with the sponsor's labeling proposal regarding the drug interaction between Lopinavir/ritonavir (both 400/100 mg BID and 800/200 mg once daily) and DAA regimens. Unlike the results of Study M13-013, Lopinavir/ritonavir 400/100 mg BID did not affect ABT-333 and its metabolite M1 exposure.*

**Drug-Drug Interaction Trial with Ketoconazole**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**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, ABT-333 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), ABT-267 (25 mg) and ABT-333 (250 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	Mylan Pharmaceuticals Morgantown, WV
Finishing Lot Number	12-008101	12-008102	12-008103
Retest Date	(b) (4)		

Ketoconazole, 200 mg tablets were manufactured by Mylan Pharmaceuticals, Morgantown, WV, as Lot 3036319, NDC 0378-0261-01.

## Sample Collection

Blood samples for measurement of the concentrations of ABT-450, ritonavir, ABT-333, ABT-333 M1, 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, ABT-333, 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 %
ABT-333	4.39-3150	4.39	11.7, 195, 2430	11.3 % to 12.1 %	2.1 % to 9.9 %
ABT-333 M1	4.58-3290	4.58	12, 199, 2490	9.8 % to 10.3 %	4 % to 6 %
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 1)**

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 1.

ABT-450 Pharmacokinetic Parameters		<u>Regimen A</u> Study Day 1 (N = 12)	<u>Regimen B</u> Study Day 10 (N = 12)
	(Units)		
C <sub>max</sub>	(ng/mL)	2000 ± 1200	2420 ± 838
T <sub>max</sub>	(h)	4.3 ± 1.4	4.3 ± 1.1
t <sub>1/2</sub> <sup>a</sup>	(h)	5.5 ± 1.4	13.7 ± 3.6
AUC <sub>t</sub>	(ng•h/mL)	9480 ± 4350	17400 ± 3850
AUC <sub>∞</sub>	(ng•h/mL)	9500 ± 4350	17500 ± 3850

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.

a. Harmonic mean ± pseudo-standard deviation.

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 1.

<b>Ritonavir Pharmacokinetic Parameters</b>	<b>(Units)</b>	<b><u>Regimen A</u> Study Day 1 (N = 12)</b>	<b><u>Regimen B</u> Study Day 10 (N = 12)</b>
$C_{\max}$	(ng/mL)	1710 $\pm$ 770	2100 $\pm$ 640
$T_{\max}$	(h)	4.1 $\pm$ 1.0	3.9 $\pm$ 0.3
$t_{1/2}^a$	(h)	3.7 $\pm$ 0.9	5.5 $\pm$ 1.2
$AUC_t$	(ng•h/mL)	10300 $\pm$ 4680	15600 $\pm$ 5200
$AUC_{\infty}$	(ng•h/mL)	10300 $\pm$ 4680	15700 $\pm$ 5200

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.

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

### ABT-267 (Arm 1)

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

<b>ABT-267 Pharmacokinetic Parameters</b>	<b>(Units)</b>	<b><u>Regimen A</u> Study Day 1 (N = 12)</b>	<b><u>Regimen B</u> Study Day 10 (N = 12)</b>
$C_{\max}$	(ng/mL)	138 $\pm$ 29.9	135 $\pm$ 25.1
$T_{\max}$	(h)	4.8 $\pm$ 1.3	5.3 $\pm$ 1.1
$t_{1/2}^a$	(h)	23.5 $\pm$ 7.5	36.0 $\pm$ 13.1
$AUC_t$	(ng•h/mL)	1890 $\pm$ 458	2150 $\pm$ 475
$AUC_{\infty}$	(ng•h/mL)	2080 $\pm$ 542	2430 $\pm$ 624

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.

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

### ABT-333 and ABT-333 M1 metabolite (Arm 1)

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 metabolite in Arm 1.

Pharmacokinetic Parameters	(Units)	<u>Regimen A</u> Study Day 1 (N = 12)	<u>Regimen B</u> Study Day 10 (N = 12)
		ABT-333	
C <sub>max</sub>	(ng/mL)	1470 ± 431	1700 ± 427
T <sub>max</sub>	(h)	3.7 ± 1.4	3.6 ± 0.7
t <sub>1/2</sub> <sup>a</sup>	(h)	5.5 ± 0.9	6.9 ± 1.4
AUC <sub>t</sub>	(ng•h/mL)	12100 ± 4540	16800 ± 4750
AUC <sub>∞</sub>	(ng•h/mL)	12100 ± 4540	16900 ± 4750
ABT-333 M1 Metabolite			
C <sub>max</sub>	(ng/mL)	899 ± 226	742 ± 141
T <sub>max</sub>	(h)	4.3 ± 1.3	4.6 ± 1.1
t <sub>1/2</sub> <sup>a</sup>	(h)	4.3 ± 0.3	5.8 ± 0.7
AUC <sub>t</sub>	(ng•h/mL)	6720 ± 1940	7130 ± 1160
AUC <sub>∞</sub>	(ng•h/mL)	6800 ± 1920	7200 ± 1160

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.

a. Harmonic mean ± pseudo-standard deviation.

### Ketoconazole (Arm 1)

Table 9 shows the mean pharmacokinetic parameters of ketoconazole in Arm 1.

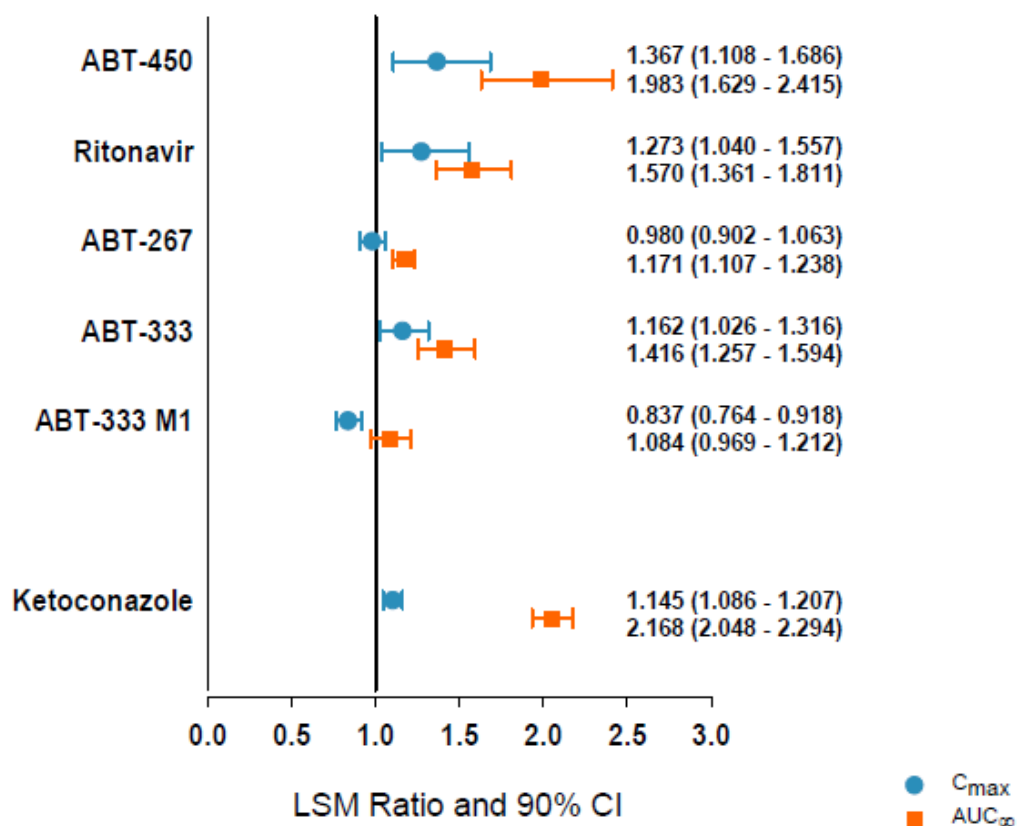
Ketoconazole Pharmacokinetic Parameters	(Units)	<u>Regimen B</u> Study Day 9 (N = 12)	<u>Regimen B</u> Study Day 10 (N = 12)
C <sub>max</sub>	(µg/mL)	12.1 ± 2.1	13.7 ± 1.9
T <sub>max</sub>	(h)	3.0 ± 0.9	4.2 ± 1.6
t <sub>1/2</sub> <sup>a</sup>	(h)	3.3 ± 1.2	15.7 ± 4.9
AUC <sub>24</sub>	(µg•h/mL)	88.2 ± 19.7	190 ± 36.4

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.

a. Harmonic mean ± 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, ABT-333, ABT-333 M1 metabolite and 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<sub>max</sub> and AUC increased by 1.6- to 2-fold, respectively, but the ABT-450 mean t<sub>1/2</sub> did not appear to change with ritonavir dose..*
- *Ritonavir, ABT-333, and ABT-267 are substrates of P-gp (ABT-267 is also a substrate of BCRP); hence, the increase in exposures of ABT-333, 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>	<i>3.12</i>	<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>	<i>3.04</i>	<i>Higher doses of ketoconazole (greater than 200 mg per day) are not recommended</i>
<i>Saquinavir/ritonavir (1000/100 mg BID)</i>	<i>2.68 (168 % higher)</i>	<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>	<i>2.69 (169 % higher)</i>	<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 and ABT-333 with ketoconazole:

- Increased the mean  $C_{max}$  and AUC of ABT-450 by 37 % and 98 % , respectively.
- Increased the mean  $C_{max}$  and AUC of ritonavir by 27 % and 57 % , respectively.
- Decreased the mean  $C_{max}$  of ABT-267 by 2 % and increased ABT-267 AUC by 17 %.
- Increased the mean  $C_{max}$  and AUC of ABT-333 by 16 % and 41 % , respectively.
- Decreased the mean  $C_{max}$  of ABT-333 M1 metabolite by 17 % and increased M1 metabolite AUC by 8 %.
- Increased the mean  $C_{max}$  and AUC of ketoconazole by 14 % and 117 % , respectively.

## Conclusion

When ABT-450/ritonavir/ABT-267 and ABT-333 is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg/day.

**Drug-Drug Interaction Trial with Digoxin**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with the 3 DAAs.***

**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:

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.

Table 2.	Dosing Regimens
<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 evening dose was administered approximately 30 minutes after the start of an evening snack. 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), ABT-267 (25 mg) and ABT-333 (400 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	(b) (4)		
	<b>ABT-333</b>	<b>Lanoxin<sup>®</sup> (Digoxin)</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	GlaxoSmithKline Research Triangle Park, NC	--
Finishing Lot Number	12-005622	12-005626	--
Expiration Date	(b) (4)		

## 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, ABT-267, ABT-333, ABT-333 M1 and digoxin were estimated using non-compartmental methods.

## Results

### *Bioanalytical methods*

The concentrations of ABT-450, ritonavir, ABT-267, ABT-333 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 %
ABT-333	4.39-3150	4.39	11.7,195, 2430	3.4 % to 11.6%	2.1 % to 4.3 %
ABT-333 M1	4.58-3290	4.58	12,199,2490	2.7 % to 5.4 %	4.2 % to 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 demographic summary of all subjects enrolled in the trial.

	Arm 1		Arm 2		Overall	
	Mean $\pm$ SD (N = 12)	Min – Max	Mean $\pm$ SD (N = 12)	Min – Max	Mean $\pm$ SD (N = 24)	Min – Max
Age (years)	35.3 $\pm$ 11.2	21 – 55	30.3 $\pm$ 7.41	21 – 45	32.8 $\pm$ 9.61	21 – 55
Weight (kg)	76.8 $\pm$ 12.7	60 – 100	74.8 $\pm$ 10.5	60 – 100	75.8 $\pm$ 11.4	60 – 100
Height (cm)	171 $\pm$ 12.4	154 – 188	172 $\pm$ 10.1	163 – 195	172 $\pm$ 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 1 are presented in this review.*

#### **ABT-450 (Arm 1)**

Table 5 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-450 in Arm 1.

Parameter (Unit)	Day 14, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	Day 15, Period 2 ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + digoxin 0.5 mg
	N	N
C <sub>max</sub> (ng/mL)	1680 $\pm$ 1060	1590 $\pm$ 1030
T <sub>max</sub> (h)	4.0 $\pm$ 1.0	4.1 $\pm$ 0.9
AUC <sub>24</sub> (ng•h/mL)	7550 $\pm$ 3840	7310 $\pm$ 4150
C <sub>24</sub> (ng/mL)	24.6 $\pm$ 13.3	22.1 $\pm$ 11.4

#### **Ritonavir (Arm 1)**

Table 6 shows the mean  $\pm$  SD pharmacokinetic parameters of ritonavir in Arm 1.

Parameter (Unit)	Day 14, Period 2	Day 15, Period 2
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + digoxin 0.5 mg
N	12	12
C <sub>max</sub> (ng/mL)	2200 ± 802	2190 ± 695
T <sub>max</sub> (h)	4.2 ± 0.8	3.9 ± 0.9
AUC <sub>24</sub> (ng•h/mL)	13500 ± 3880	13200 ± 3610
C <sub>24</sub> (ng/mL)	61.7 ± 21.8	60.2 ± 24.6

### ABT-267 (Arm 1)

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

Parameter (Unit)	Day 14, Period 2	Day 15, Period 2
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + digoxin 0.5 mg
N	12	12
C <sub>max</sub> (ng/mL)	132 ± 49.7	133 ± 42.6
T <sub>max</sub> (h)	4.8 ± 0.7	4.7 ± 0.7
AUC <sub>24</sub> (ng•h/mL)	1460 ± 459	1460 ± 450
C <sub>24</sub> (ng/mL)	31.0 ± 9.25	30.9 ± 10.2

### ABT-333 (Arm 1)

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 in Arm 1.

Parameter (Unit)	Day 14, Period 2	Day 15, Period 2
	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID	ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + digoxin 0.5 mg
<b>ABT-333</b>		
N	12	12
C <sub>max</sub> (ng/mL)	1140 ± 438	1120 ± 371
T <sub>max</sub> (h)	3.3 ± 0.9	3.3 ± 0.5
AUC <sub>12</sub> (ng•h/mL)	7620 ± 2610	7250 ± 2130
C <sub>12</sub> (ng/mL)	250 ± 68.7	247 ± 58.3
<b>ABT-333 M1</b>		
N	12	12
C <sub>max</sub> (ng/mL)	827 ± 368	803 ± 321
T <sub>max</sub> (h)	3.7 ± 1.0	3.7 ± 0.7
AUC <sub>12</sub> (ng•h/mL)	4920 ± 1980	4780 ± 1670
C <sub>12</sub> (ng/mL)	145 ± 45.2	142 ± 44.7

## Digoxin (Arm 1)

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

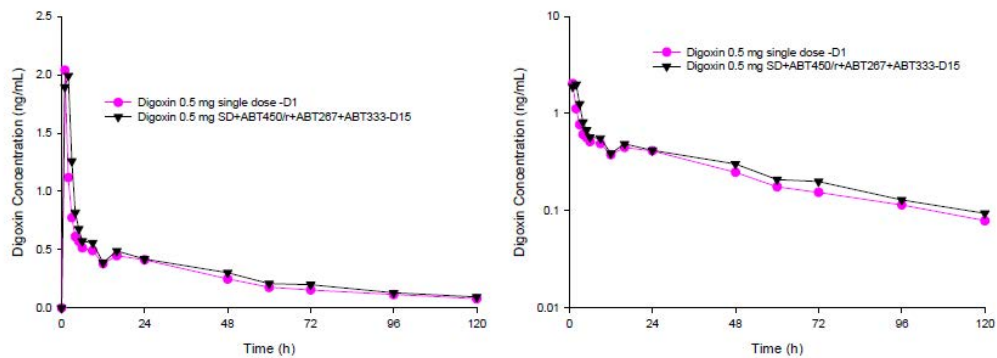


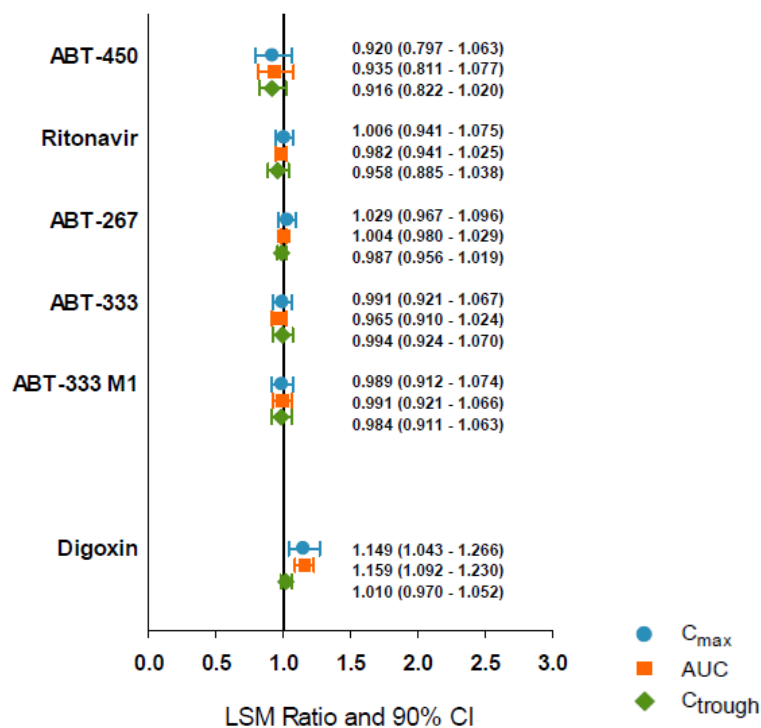
Table 9 shows the mean  $\pm$  SD pharmacokinetic parameters of digoxin in Arm 1.

Parameter (Unit)	Day 1, Period 1 digoxin 0.5 mg	Day 15, Period 2
		ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + digoxin 0.5 mg
N	12	12
C <sub>max</sub> (ng/mL)	2.04 $\pm$ 0.54	2.32 $\pm$ 0.45
T <sub>max</sub> (h)	0.9 $\pm$ 0.1	1.6 $\pm$ 0.5
AUC <sub>t</sub> (ng•mL)	31.4 $\pm$ 5.69	36.3 $\pm$ 6.09
AUC <sub>inf</sub> (ng•mL)	36.7 $\pm$ 6.94	42.5 $\pm$ 8.09
t <sub>1/2</sub> <sup>a</sup> (h)	43.9 $\pm$ 8.08	42.7 $\pm$ 8.82
C <sub>24</sub> (ng/mL)	0.41 $\pm$ 0.08	0.42 $\pm$ 0.08
f <sub>e</sub> (%)	45.0 $\pm$ 10.0	44.3 $\pm$ 6.76
CL <sub>ren</sub> (L/h)	7.41 $\pm$ 2.09	6.29 $\pm$ 1.35

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

## Statistical Evaluation of the Pharmacokinetic Parameters

Fig 3 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite and digoxin in Arm 1.



## Safety

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

## Results

Co-administration of ABT-450/r, ABT-267 and ABT-333 with digoxin:

- Increased the mean C<sub>max</sub> and AUC of digoxin by 15 % and 16 %, respectively.
- Did not significantly alter the mean C<sub>max</sub> and AUC of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333M1.

## Conclusion

The 3-DAA regimen (ABT-450/ritonavir, ABT-267, and ABT-333) can be co-administered with digoxin without any dose adjustments.

**Drug-Drug Interaction Trial with Warfarin**  
**Reviewer: Seong Jang, Ph.D.**

**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, Safety and Tolerability of Warfarin Sodium in Healthy Subjects (M12-198)**

**Study period:** 05 October 2012 to 30 May 2013

**Objectives:** The objectives of this study were:

- To evaluate the pharmacokinetics, safety and tolerability of a single dose of warfarin sodium 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.
- 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 warfarin sodium in healthy subjects.

*Reviewer's comments: The effect of single dose of warfarin on the steady state exposure of 2 or 3 DAAs was not reviewed because it is not clinically meaningful (note that warfarin is a drug has long half-life [3- 5 days] and is mostly given as multiple dose in clinical settings) and not the purpose of the study.*

**Methodology:**

This was a Phase 1, single-center, open-label, sequential, multiple-dose study. Adult male and female subjects in general good health were selected to participate in the study according to the selection criteria. Arms were enrolled sequentially; 12 subjects were enrolled per arm, each arm consisting of two periods. Subjects in each arm were to complete both Period 1 and Period 2. Arm 3 was not conducted.

Study drug was administered as follows:

- Regimen A:** Warfarin sodium 5 mg single dose + 10 mg single dose Vitamin K<sub>1</sub> on Study Day 1 followed by a washout interval of at least 14 days.
- Regimen B:** ABT-450/r 150/100 mg once daily (QD) + ABT-267 25 mg QD + ABT-333 400 mg twice daily (BID) from Study Days 1 to 24, warfarin sodium 5 mg single dose + 10 mg single dose Vitamin K<sub>1</sub> on Study Day 15 in Period 2.
- Regimen C:** Warfarin sodium 5 mg single dose + 10 mg single dose Vitamin K<sub>1</sub> on Study Day 1 followed by a washout interval of at least 14 days.
- Regimen D:** ABT-450/r 150/100 mg QD + ABT-267 25 mg QD on from Study Days 1 to 24, warfarin sodium 5 mg single dose + 10 mg single dose Vitamin K<sub>1</sub> on Study Day 15 in Period 2.

In Period 1, single doses of warfarin sodium 5 mg and Vitamin K<sub>1</sub> 10 mg were administered on Study Day 1 under non-fasting conditions. In Period 2, all study drugs were taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast in the morning. In Arm 1, the evening ABT-333 dose was taken orally with approximately 240 mL of

water approximately 30 minutes after the start of the evening snack. A washout period of at least 14 days separated the two periods. Blood samples for R- and S-warfarin were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, 20, 24, 48, 60, 72, 96, 120, 144, 168, 192, 216 and 240 hours after dosing in Period 1, Study Day 1 and prior to dose (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, 20, 24, 48, 60, 72, 96, 120, 144, 168, 192, 216 and 240 hours in Period 2, Study 15. Blood samples for ABT-267, ABT-450, ritonavir, ABT-333 and ABT-333 M1 metabolite (ABT-333 M1) were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12 and 16 hours after dosing on Study Day 14 and prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12 and 16 hours after dosing on Study Day 15. Trough samples were collected prior to morning direct-acting antiviral agent (DAA) doses on Days 9, 13, 16, 18, 20, 22 and 25. Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were determined using a validated protein precipitation and on-line solid phase extraction method with liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). No metabolites for ABT-450, ritonavir, ABT-267 and ABT-333 were assayed for this study, except ABT-333 M1. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were established at 0.595 ng/mL, 4.71 ng/mL, 0.417 ng/mL, 4.39 ng/mL and 4.58 ng/mL, respectively, using a 100 µL plasma sample.

Plasma concentrations of R- and S-warfarin were determined using a validated extraction and high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQ for R- and S-warfarin in plasma was established at 5 ng/mL.

#### Number of Subjects (Planned and Analyzed):

Planned: 36; Entered: 24 (Arm 3 was not conducted); Completed: 23; Evaluated for Safety: 24; Evaluated for Pharmacokinetics: 23

For the 24 subjects who participated in the study, the mean age was 36.9 years (ranging from 20 to 55 years), the mean weight was 78.4 kg (ranging from 66 to 96 kg) and the mean height was 175 cm (ranging from 160 to 193 cm).

#### Diagnosis and Main Criteria for Inclusion:

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram (ECG). Females were either postmenopausal for at least 2 years or surgically sterile and were not pregnant. Males were either surgically sterile or practicing at least one of the acceptable methods of birth control.

#### Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

	<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
Manufacturing Site	AbbVie North Chicago, IL	AbbVie North Chicago, IL	AbbVie North Chicago, IL
Finishing Lot Number	12-006142	12-006227	12-006141
Expiration Date	(b) (4)		
	<b>ABT-333</b>	<b>Warfarin sodium</b>	<b>Vitamin K<sub>1</sub></b>
Dosage Form	Tablet	Tablet	Tablet
Strength (mg)	400 mg	5 mg	5 mg

Manufacturing Site	AbbVie North Chicago, IL	Barr Laboratories	Aton, Pharm, Inc.
Finishing Lot Number	12-006143	12-006296	12-006298
Expiration Date	(b) (4)		

**Duration of Treatment:** Dosing for Arm 1 began on 05 October 2012 and ended on 07 December 2012. Dosing for Arm 2 began on 22 March 2013 and ended on 30 May 2013.

### Criteria for Evaluation:

**Pharmacokinetic:** Values for the pharmacokinetic parameters of ABT-267, ABT-450, ritonavir, ABT-333, ABT-333 M1 and R- and S-warfarin were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  ( $T_{max}$ ), and the pre-dose plasma concentration ( $C_{trough}$ ,  $C_{24}$ ,  $C_{12}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ( $AUC_{24}$ ) for ABT-450, ritonavir and ABT-267, the AUC from time 0 to 12 hours ( $AUC_{12}$ ) for ABT-333 and ABT-333 M1, the AUC from time 0 to the last measureable concentration ( $AUC_t$ ), and AUC from time 0 to infinity ( $AUC_{inf}$ ) for R- and S-warfarin, the apparent terminal phase elimination rate constant ( $\beta$ ), and the terminal phase elimination half-life ( $t_{1/2}$ ) for R- and S-warfarin. Dose-normalized parameters were also calculated  $C_{max}$ ,  $C_{24}$ ,  $C_{12}$ ,  $AUC_t$ ,  $AUC_{inf}$ ,  $AUC_{24}$  and  $AUC_{12}$ .

The effect of single dose of warfarin on the steady state exposures of 2 or 3 DAAs was evaluated by comparing the 2-DAA or 3-DAA exposures (Study Day 15) when the 2 DAAs or 3 DAAs were administered in the presence of warfarin to the 2 DAAs or 3 DAAs steady-state exposures (Study Day 14) where the 2 DAAs or 3 DAAs were administered without warfarin. The effect of steady state 2 DAAs or 3 DAAs on the single dose of warfarin was evaluated by comparing Study Day 15 (Period 2) R- and S-warfarin exposures when warfarin was administered with 2 or 3 DAAs to Study Day 1 (Period 1) exposures when warfarin was administered alone.

**Safety Endpoints:** Safety was evaluated based on assessments of adverse events, vital signs, physical examinations, ECGs and laboratory tests.

### Statistical Methods:

**Pharmacokinetic:** To assess the effect of ABT-450/r, ABT-333 and ABT-267 on R-warfarin and S-warfarin, a repeated-measures analysis was performed for the natural logarithms of  $C_{max}$ , AUC and  $C_{trough}$  utilizing data from Period 1, Study Day 1 and Period 2, Study Day 15. A separate analysis was performed for R-warfarin and S-warfarin and for each arm. The model had day as a fixed effect with two levels (Period 1, Study Day 1 and Period 2, Study Day 15) and subject as a random effect. Additionally, the  $C_{max}$ , AUC and  $C_{trough}$  ratios were estimated by taking the ratio of Period 2, Study Day 15 versus Period 1, Study Day 1 values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of



subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

## Results:

**Pharmacokinetics:** The effect of steady-state ABT-450, ritonavir, ABT-267 and ABT-333 (i.e., 3 DAAs) on a single dose of warfarin was evaluated by comparing Study Day 15 (Period 2) R- and S-warfarin exposures when warfarin was administered with ABT-450, ritonavir, ABT-267 and ABT-333 to Study Day 1 (Period 1) exposures when warfarin was administered alone (Arm 1). R- and S-warfarin  $T_{max}$  values increased slightly from 1.9 to 2.9 hours (R-) and from 1.6 to 2.3 hours (S-). R- and S-warfarin  $t_{1/2}$  values did not change in the presence of the DAAs. Compared to the R- and S-warfarin exposures when warfarin was administered alone, both R- and S-warfarin  $AUC_{inf}$  showed a statistically significant decrease of 12% ( $p < 0.05$ ), in the presence of steady state ABT-450/r, ABT-267 and ABT-333 (Table 1). R- and S-warfarin  $C_{max}$  and  $C_{24}$  values were not statistically significantly different ( $p > 0.05$ ) in the presence of the DAAs (Table 1).

**Table 1.** The effect of steady-state ABT-450, ritonavir, ABT-267 and ABT-333 on a single dose of warfarin (Arm 1)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% Confidence Interval
<b>R-Warfarin</b>				
$C_{max}$ (ng/mL)	237	249	1.053	0.945 – 1.174
$AUC_{inf}$ (ng•h/mL)	18200	15900	0.877	0.811 – 0.948
$C_{24}$ (ng/mL)	151	142	0.939	0.836 – 1.054
<b>S-Warfarin</b>				
$C_{max}$ (ng/mL)	266	255	0.959	0.854 – 1.076
$AUC_{inf}$ (ng•h/mL)	9730	8570	0.880	0.805 – 0.962
$C_{24}$ (ng/mL)	87.7	83.2	0.949	0.883 – 1.020

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Period 1, Study Day 1 (P1D1): Warfarin 5 mg single dose + Vitamin K1 10 mg single dose.

<sup>c</sup>. P2D15: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + warfarin 5 mg single dose + Vitamin K1 10 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The effect of steady-state ABT-450, ritonavir and ABT-267 (i.e., 2 DAAs) on a single dose of warfarin was evaluated by comparing Study Day 15 (Period 2) R- and S-warfarin exposures when warfarin was administered with ABT-450, ritonavir and ABT-267 to Study Day 1

(Period 1) exposures when warfarin was administered alone (Arm 2). R- and S-warfarin  $T_{\max}$  increased slightly from 2.1 to 3.6 hours and 1.8 to 2.8 hours, respectively. R- and S-warfarin  $t_{1/2}$  values did not change in the presence of the DAAs. Compared to the R- and S-warfarin exposure when warfarin was administered alone, R- and S-warfarin showed statistically significant ( $p < 0.05$ ) decreases of 13% to 16% for  $AUC_{\text{inf}}$  and of 11% to 13% for  $C_{24}$  in the presence of steady state ABT-450/r and ABT-267 (Table 2). R- and S-warfarin  $C_{\max}$  were not statistically significantly different ( $p > 0.05$ ) in the presence of the DAAs (Table 2).

**Table 2.** The effect of steady-state ABT-450, ritonavir, and ABT-267 on a single dose of warfarin (Arm 2)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% Confidence Interval
<b>R-Warfarin</b>				
$C_{\max}$ (ng/mL)	265	255	0.960	0.878 – 1.051
$AUC_{\text{inf}}$ (ng•h/mL)	19300	16700	0.866	0.823 – 0.911
$C_{24}$ (ng/mL)	175	153	0.872	0.836 – 0.910
<b>S-Warfarin</b>				
$C_{\max}$ (ng/mL)	267	240	0.900	0.818 – 0.991
$AUC_{\text{inf}}$ (ng•h/mL)	13000	11000	0.845	0.755 – 0.947
$C_{24}$ (ng/mL)	105	93.5	0.888	0.844 – 0.933

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. P1D1: Warfarin 5 mg single dose + Vitamin K<sub>1</sub> 10 mg single dose.

<sup>c</sup>. P2D15: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + warfarin 5 mg single dose + Vitamin K<sub>1</sub> 10 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Safety:** The DAAs co-administered with warfarin sodium in all the arms of this study were generally well tolerated by the subjects. One subject was discontinued from the study due to an adverse event of rhabdomyolysis, which was assessed by the investigator as being severe and having a reasonable possibility of being related to the DAAs. In this subject, the CPK had never been within normal limits since screening and was significantly elevated prior to initiation of the DAA regimen. CPK declined once the DAAs were started, but again increased significantly, which led to study drug discontinuation. Elevation/fluctuation of CPK before DAA administration suggests causes other than DAA therapy may have precipitated the event. The remaining treatment-emergent adverse events having a reasonable possibility of being related to the DAAs were self-limited and mild in severity.

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

There were no clinically meaningful or significant trends noted among the potentially clinically significant laboratory values in this study. No new safety signals or unexpected toxicities were observed when the DAAs were co-administered with warfarin sodium.

## Conclusions:

### Three DAA Combination + Warfarin

Following co-administration with the 3-DAA regimen at steady state (ABT-450/r QD + ABT-267 QD + ABT-333 BID), R- and S-warfarin  $AUC_{inf}$  decreased slightly ( $\leq 12\%$ ) compared to when warfarin was administered alone, while R- and S-warfarin  $C_{max}$  and  $C_{24}$  were not affected.

#### Two DAA Combination + Warfarin

Following co-administration with the 2-DAA regimen at steady state (ABT-450/r QD + ABT-267 QD), R- and S-warfarin  $AUC_{inf}$  and  $C_{24}$  decreased slightly ( $\leq 16\%$ ) compared to when warfarin was administered alone, while R- and S-warfarin  $C_{max}$  was not affected.

However, these small changes in exposure may be clinically significant for a narrow therapeutic index drug such as warfarin. The current study did not evaluate the effects of DAAs on the pharmacodynamics of warfarin as determined by parameters such as INR, and it is recommended that INR be monitored when warfarin is co-administered with 2- and 3-DAA combinations.

*Reviewer's comments: We agree with the sponsor's conclusion. In this study, the effects of DAAs on the protein binding of warfarin as well as the effects of DAAs on the INR changes have not been evaluated. Thus, although the changes in exposure of warfarin due to the co-administration with DAAs are small, it is recommended that INR be monitored when warfarin is co-administered with 2- and 3-DAA combinations.*

(b) (4)

*Reviewer's comments: We do not agree*

(b) (4)

*Accordingly, based on this study, we can conclude that the 2- and 3-DAA combination is not expected to affect the PK of other CYP2C9 substrates when other CYP2C9 substrates are co-administered with 2- and 3-DAA combinations. It should be noted that it is not known whether (or how much) the PK of DAAs are affected by co-administration with warfarin in a clinical setting.*

(b) (4)

*Reviewer's comments:*

(b) (4)

**Drug-Drug Interaction Trial with Furosemide or Amlodipine Besylate**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-administration of Furosemide or Amlodipine Besylate with Combination of ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) and ABT-333 in Healthy Adult Volunteers (M14-325)**

**Study period:** 16 September 2013 to 25 November 2013

**Objectives:** The objective of this study was to determine the effect of steady-state ABT-450/r/ABT-267 and ABT-333 on the pharmacokinetics, safety and tolerability of a single dose of furosemide or amlodipine besylate in healthy subjects. In addition, the effect of a single dose of furosemide or amlodipine besylate on the pharmacokinetics, safety and tolerability of steady-state ABT-450/r/ABT-267 and ABT-333 was also determined.

*Reviewer's comments: The effect of a single dose of amlodipine on the PK of ABT-450/r, ABT-267 and ABT-333 is not clinically meaningful because the PK of steady state amlodipine would not be similar to that of a single dose. The half-life of amlodipine is approximately 30-60 hours. Thus, the results of this study (i.e., the effect of a single dose of amlodipine on the PK of ABT-450/r, ABT-267 and ABT-333) are not informative to predict the clinically relevant effect of amlodipine on the PK of ABT-450/r, ABT-267 and ABT-333 unless the PK of ABT-450/r, ABT-267 and ABT-333 were affected substantially due to the single dose of amlodipine so that it is obvious to recommend a contraindication of DAAs with amlodipine (this is not the case based on the sponsor's study report). Thus, the effect of a single dose of amlodipine on the PK of ABT-450/r, ABT-267 and ABT-333 was not reviewed. However, the half-life of furosemide is approximately 2 hours so that the effects of a single dose of furosemide on the PK of ABT-450/r, ABT-267 and ABT-333 are considered to be similar to those of steady state furosemide. Accordingly, the effect of a single dose of furosemide on the PK of ABT-450/r, ABT-267 and ABT-333 in this study was reviewed.*

**Methodology:**

This was a Phase 1, single-center, open-label, sequential, multiple-dose study. Adult male and female subjects in general good health were selected to participate in the study according to the selection criteria. The study consisted of two independent parts, Part I and Part II. Enrolled subjects were assigned into either Part I or Part II so that 12 subjects were enrolled in Part I and 14 subjects were enrolled in Part II.

Part	Treatment	Subjects	Single Dose of Furosemide and Potassium Bicarbonate (Part I) OR Single Dose of Amlodipine Besylate (Part II)	ABT-450/r/ABT-267 (QD) and ABT-333 (BID)
I	Furosemide	12	Study Day 1 and Study Day 17	Study Days 3 – 18
II	Amlodipine Besylate	14	Study Day 1 and Study Day 25	Study Days 11 – 34

In Part I, a single dose of furosemide 20 mg with 20 mEq oral potassium bicarbonate was administered in the morning on Study Day 1 followed by a washout period for 2 days (through morning of Study Day 3). Starting on Study Day 3, ABT-450/r/ABT-267 150/100/25 mg was administered once daily (QD) in the morning and ABT-333 250 mg was administered twice daily (BID) for 16 days (Study Days 3 through 18). On Study Day 17, a single dose of furosemide 20 mg was administered with 20 mEq oral potassium bicarbonate.

In Part II, a single dose of amlodipine besylate 5 mg was administered in the morning on Study Day 1 followed by a washout period for 10 days (through morning of Study Day 11). Starting on Study Day 11, ABT-450/r/ABT-267 150/100/25 mg was administered QD in the morning and ABT-333 250 mg was administered BID for 24 days (Study Days 11 through 34). On Study Day 25, a single dose of amlodipine besylate 5 mg was administered. Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for all morning doses and approximately 30 minutes after the start of the evening snack for the evening dose of ABT-333.

Blood samples for furosemide were collected by venipuncture prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing in Part I, Study Day 1 and prior to dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing in Part I, Study Day 17. Blood samples amlodipine were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120, 168, and 240 hours after dosing in Part II, Study Day 1 and prior to dose (0 hour) and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 120, 168, and 240 hours after dosing in Part II, Study Day 25. Blood samples for ABT-267, ABT-450, ritonavir, ABT-333 and ABT-333 M1 metabolite (ABT-333 M1) were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 hours after dosing in Part I on Study Day 16 and in Part II on Study Day 24 and prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 hours after dosing in Part I on Study Day 17 and in Part II on Study Day 25.

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were determined using a validated protein precipitation and on-line solid phase extraction method with liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). No metabolites for ABT-450, ritonavir, ABT-267 and ABT-333 were assayed for this study, except ABT-333 M1. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were established at 0.590 ng/mL, 5.04 ng/mL, 0.446 ng/mL, 4.77 ng/mL and 4.75 ng/mL, respectively, using a 100 µL plasma sample.

Plasma concentrations of furosemide were determined using a validated extraction and high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQ for furosemide in plasma was established at 5 ng/mL.

Plasma concentrations of amlodipine were determined using a validated extraction and high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQ for amlodipine in plasma was established at 50 pg/mL using a 0.500 mL plasma sample.

**Number of Subjects (Planned and Analyzed):**

Planned: 26; Entered: 26; Completed: 26; Evaluated for Safety: 26; Evaluated for Pharmacokinetics: 26.

For the 26 subjects who participated in the study, the mean age was 38.5 years (ranging from 22 to 55 years), the mean weight was 76.6 kg (ranging from 57 to 96 kg) and the mean height was 173 cm (ranging from 153 to 192 cm).

#### Diagnosis and Main Criteria for Inclusion:

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram (ECG). Females were either postmenopausal for at least 2 years or surgically sterile or practicing protocol defined birth control and were not pregnant. Males were either surgically sterile or practicing at least one of the acceptable methods of birth control.

#### Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Products	ABT-450/ Ritonavir/ ABT-267	ABT-333	Furosemide	Amlodipine Besylate	Potassium Bicarbonate
Dosage Form	Tablet	Tablet	Tablet	Tablet	Tablet
Strength (mg)	75/50/12.5	250	20	5	2000 (20 mEq)
Bulk Product Lot Number	12-008149	13-000242	13-004117	13-004089	13-004433
Manufacturing Site	AbbVie, Cork, Ireland	AbbVie, North Chicago, IL	Sanofi Aventis	Pfizer	Nomax Inc.
Finishing Lot Number	13-004143	13-004144	13-004145	13-004146	13-004491
Expiration Date	(b) (4)				

#### Duration of Treatment:

Dosing for Part I began on 15 October 2013 and ended on 01 November 2013. Dosing for Part II began on 08 October 2013 and ended on 10 November 2013.

#### Criteria for Evaluation:

**Pharmacokinetic:** Values for the pharmacokinetic parameters of ABT-267, ABT-450, ritonavir, ABT-333, ABT-333 M1, furosemide and amlodipine were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  ( $T_{max}$ ), and the pre-dose plasma concentration ( $C_{trough}$ ,  $C_{24}$ ,  $C_{12}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ( $AUC_{24}$ ) for ABT-450, ritonavir and ABT-267, the AUC from time 0 to 12 hours ( $AUC_{12}$ ) for ABT-333 and ABT-333 M1, the AUC from time 0 to the last measureable concentration ( $AUC_t$ ), and AUC from time 0 to infinity ( $AUC_{inf}$ ) for furosemide and amlodipine, the apparent terminal phase elimination rate constant ( $\beta$ ), and the terminal phase elimination half-life ( $t_{1/2}$ ) the apparent oral clearance value ( $CL/F$ ) and the apparent volume of distribution ( $V_{d\beta/F}$ ) for furosemide and amlodipine.

In Part I, the effect of single dose of furosemide on the steady state exposures of 3 DAAs was evaluated by comparing the 3-DAA exposures (Study Day 17) when the 3 DAAs were administered in the presence of furosemide to the 3 DAAs steady-state exposures (Study Day 16) where the 3 DAAs were administered without furosemide. The effect of steady state 3 DAAs on

the single dose of furosemide was evaluated by comparing Study Day 17 exposures when furosemide was administered with 3 DAAs to Study Day 1 exposures when furosemide was administered alone.

In Part II, the effect of single dose of amlodipine besylate on the steady state exposures of 3 DAAs was evaluated by comparing the 3-DAA exposures (Study Day 25) when the 3 DAAs were administered in the presence of amlodipine besylate to the 3 DAAs steady-state exposures (Study Day 24) where the 3 DAAs were administered without amlodipine besylate. The effect of steady state 3 DAAs on the single dose of amlodipine was evaluated by comparing Study Day 25 exposures when amlodipine besylate was administered with 3 DAAs to Study Day 1 exposures when amlodipine besylate was administered alone.

**Safety Endpoints:** The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, ECG and laboratory tests.

### **Statistical Methods:**

**Pharmacokinetic:** To assess the effect of a single dose furosemide or amlodipine on steady-state ABT-450, ritonavir, ABT-267, and ABT-333, a repeated measure analysis was performed for the natural logarithms of ABT-450, ritonavir, ABT-267, and ABT-333 and ABT-333 M1  $C_{max}$ , AUC,  $C_{24}$  and  $C_{12}$  values utilizing data from Study Days 16 and 17 for Part I, and 24 and 25 for Part II. A separate analysis was performed for each part. The model had day as a fixed effect and subject as a random effect. Additionally, ratios of the ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1  $C_{max}$  and AUC when administered with furosemide or amlodipine besylate to that of administered without furosemide or amlodipine besylate were estimated by taking the ratio of corresponding Study Day 17 versus Study Day 16 values for furosemide, and Study Day 25 versus Study Day 24 for amlodipine besylate, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

To assess the effect of steady-state DAAs on a single dose of furosemide or amlodipine besylate, a repeated measure analysis was performed for the natural logarithms of the  $C_{max}$  and AUC values of furosemide or amlodipine, utilizing data from Study Days 1 and 17 for furosemide and Study Days 1 and 25 for amlodipine. A separate analysis was performed for each part. The model had day as a fixed effect and subject as a random effect. Additionally, the ratio of furosemide and or amlodipine  $C_{max}$  and AUC when administered with DAAs to that of administered without DAAs was estimated by taking the ratio of Study Day 17 versus Study Day 1 values for furosemide and Study Day 25 versus Study Day 1 for amlodipine, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

To assess steady state of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 when dosed without furosemide or amlodipine besylate, a repeated measures analysis were performed on the trough concentration measurements of Days 10, 13, 16 and 17 for Part I and Days 18, 21, 24 and 25 for Part II. A separate analysis was performed for each part. Within the framework of repeated measure analysis, pair-wise tests and trend analyses were performed on the contrasts in

the study day effects to determine the earliest day after which there was no statistically significant change.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

## Results:

### Pharmacokinetics:

**Part 1 (Furosemide):** The effect of a single dose of furosemide on the PK of ABT-450/r/ABT-267 + ABT-333 was summarized in Table 1. No clinically meaningful changes in the PK parameters of ABT-450/r/ABT-267 + ABT-333 were observed when co-administered with a single dose of furosemide.

**Table 1.** Effect of a single dose of furosemide on the PK of ABT-450/r/ABT-267 + ABT-333

Pharmacokinetic Parameter		Central Value <sup>a</sup>		Ratio of Central Values	
		Day 16 <sup>b</sup>	Day 17 <sup>c</sup>	Point Estimate <sup>d</sup>	90% Confidence Interval
ABT-450	C <sub>max</sub> (ng/mL)	1440	1330	0.925	0.628 – 1.360
	AUC <sub>24</sub> (ng•h/mL)	6390	5860	0.916	0.695 – 1.208
	C <sub>24</sub> (ng/mL)	15.2	19.3	1.264	1.159 – 1.379
Ritonavir	C <sub>max</sub> (ng/mL)	1460	1610	1.101	0.957 – 1.266
	AUC <sub>24</sub> (ng•h/mL)	9070	9460	1.043	0.919 – 1.183
	C <sub>24</sub> (ng/mL)	34.6	37.0	1.072	0.985 – 1.167
ABT-267	C <sub>max</sub> (ng/mL)	136	155	1.136	1.025 – 1.260
	AUC <sub>24</sub> (ng•h/mL)	1490	1590	1.065	1.009 – 1.124
	C <sub>24</sub> (ng/mL)	29.3	32.7	1.115	1.076 – 1.155
ABT-333	C <sub>max</sub> (ng/mL)	1130	1270	1.122	0.962 – 1.308
	AUC <sub>24</sub> (ng•h/mL)	7600	8260	1.087	0.961 – 1.230
	C <sub>24</sub> (ng/mL)	313	330	1.055	0.979 – 1.137
ABT-333	C <sub>max</sub> (ng/mL)	669	741	1.109	0.902 – 1.362
M1	AUC <sub>24</sub> (ng•h/mL)	4000	4110	1.027	0.862 – 1.223



C <sub>24</sub> (ng/mL)	126	125	0.992	0.916 – 1.075
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<sup>a</sup>. Antilogarithm of the least squares means for logarithms.  
<sup>b</sup>. Part I Study Day 16: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID.  
<sup>c</sup>. Part I Study Day 17: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + furosemide 20 mg single dose + oral potassium bicarbonate 20 mEq single dose.  
<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The effects of the combination of ABT-450/r/ABT-267 and ABT-333 (3 DAAs) on the pharmacokinetics of furosemide administered as a single dose in healthy subjects are summarized in Table 2. Co-administration with the ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID regimen increased furosemide C<sub>max</sub> and AUC by 42% and 11%, respectively.

**Table 2.** The effect ABT-450/r/ABT-267 and ABT-333 on the pharmacokinetics of furosemide administered as a single dose in healthy subjects

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Day 1 <sup>b</sup>	Day 17 <sup>c</sup>	Point Estimate <sup>d</sup>	90% Confidence Interval
C <sub>max</sub> (ng/mL)	156	222	1.419	1.168 – 1.724
AUC <sub>24</sub> (ng•h/mL)	742	821	1.107	1.037 – 1.181
AUC <sub>inf</sub> (ng•h /mL)	795	862	1.083	1.004 – 1.169

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.  
<sup>b</sup>. Part I Study Day 1: Furosemide 20 mg single dose + oral potassium bicarbonate 20 mEq single dose.  
<sup>c</sup>. Part I Study Day 17: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + furosemide 20 mg single dose + oral potassium bicarbonate 20 mEq single dose.  
<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: Based on the results of this study, the sponsor proposed the following labeling recommendation regarding the co-administration of 3 DAAs with furosemide.*

*"Clinical monitoring of patients is recommended (b) (4) "*

*The sponsor did not evaluate the urinary excretion of furosemide in this study. The diuretic effect of furosemide is related to the urinary excretion rate, but not to its plasma concentration. Although the co-administration of 3 DAAs increased the C<sub>max</sub> value by 42%, it is not known whether (or how much) the urinary excretion of furosemide is changed by the co-administration with 3 DAAs. Because 3 DAAs is most likely to interact with furosemide through renal active secretion mechanism (e.g., inhibition of renal active secretion of furosemide, resulting in C<sub>max</sub> of furosemide), the renal clearance of furosemide may be decreased when co-administered with 3 DAAs. (b) (4)*

*Without knowing the quantitative change in the urinary excretion of furosemide by the co-administration with 3 DAAs, the sponsor's recommendation (b) (4) may not be reasonable. It is strongly recommended to conduct an additional study to evaluate the change in the urinary excretion rate of furosemide when co-administered with 3 DAAs. At this time, we recommend that the labeling be revised as follows.*

**Part 2 (Amlodipine):** The effects of the combination of ABT-450/r/ABT-267 and ABT-333 on the pharmacokinetics of amlodipine administered as a single dose in healthy subjects are summarized in Table 3. Co-administration with the ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID regimen increased amlodipine  $C_{max}$  and  $AUC_{inf}$  by 26% and 2.57-fold, respectively.

**Table 3.** The effect of ABT-450/r/ABT-267 and ABT-333 on the pharmacokinetics of amlodipine administered as a single dose in healthy subjects

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Day 1 <sup>b</sup>	Day 17 <sup>c</sup>	Point Estimate <sup>d</sup>	90% Confidence Interval
$C_{max}$ (ng/mL)	2.98	3.76	1.262	1.110 – 1.436
$AUC_t$ (ng•h/mL)	169	357	2.109	1.921 – 2.317
$AUC_{inf}$ (ng•h/mL)	175	450	2.572	2.312 – 2.862

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Part II Study Day 1: Amlodipine besylate 5 mg single dose.

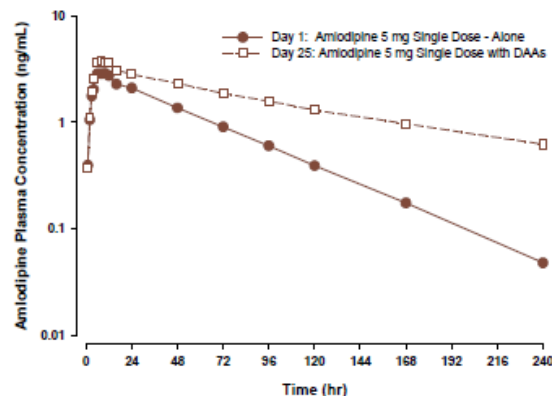
<sup>c</sup>. Part II Study Day 25: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + amlodipine besylate 5 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: As mentioned above, the effects of a single dose of amlodipine on the PK of DAAs are not clinically relevant because the half-life of amlodipine is 30 – 60 hours. It should not be presumed that the effect of steady state amlodipine similar to that of a single dose amlodipine.* (b) (4)

*It should be noted that the co-administration with amlodipine administered as a single dose decreased the  $C_{max}$  and AUC by 23% and 22%, respectively.*

*It should be also noted that the harmonic mean half-life increased of amlodipine from 42±6.7 hours to 104±18 hours when co-administered with 3 DAAs (see Figure 1). Because the increase in the amlodipine  $C_{max}$  was substantially smaller than the increase in the amlodipine AUC (probably due to increase in half-life), an increase in dosing interval of amlodipine (e.g., from QD to every other day) should be considered rather than a decrease of amlodipine daily dose. In addition, the sponsor proposed that amlodipine dose should be decreased (b) (4) when co-administered with 3 DAAs. However, the mean increase in AUC was 2.57-fold, meaning that an additional decrease in amlodipine dose may be needed. Thus, an increase in dosing interval of amlodipine should be considered to reduce the exposure of amlodipine when co-administered with 3 DAAs.*



**Figure 1.** Mean amlodipine concentration-time profiles in Part 2 (Amlodipine besylate with and without ABT-450/r/ABT-267+ABT-333)

#### Safety Results:

The DAAs co-administered with furosemide and potassium bicarbonate in Part I and with amlodipine besylate in Part II of this study were well tolerated by the subjects. Adverse events were all mild, with no apparent pattern in their nature or frequency. No adverse events were considered to be related to any of the study drugs.

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

There were no clinically meaningful or significant trends noted among the potentially clinically significant laboratory values in this study. No new safety signals or unexpected toxicities were observed when the DAAs were co-administered with either furosemide and potassium bicarbonate or amlodipine besylate.

#### **Conclusions:**

##### Part 1: Furosemide

When the 3-DAA regimen (ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID) was co-dosed with a single 20 mg oral dose of furosemide steady-state exposures of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were minimally affected, except for a 26% increase in ABT-450  $C_{trough}$ . Co-administration with the ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID regimen had minimal impact on furosemide AUC values (up to 11% increase), but increased furosemide  $C_{max}$  by 42%. Caution is warranted when co-administering furosemide with the 3-DAA regimen and monitoring of the clinical response is recommended.

##### Part 2: Amlodipine

Co-administration with the ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID regimen increased amlodipine  $C_{max}$  and AUC by 26% and 157%, respectively. When co-administering amlodipine with the 3-DAA regimen, caution is warranted and <sup>(b) (4)</sup> reduction in the dose of amlodipine should be considered.

#### Safety:

The safety profile of the DAAs co-administered with furosemide and potassium bicarbonate in Part I and amlodipine besylate in Part II in this study administered as a single dose was comparable to that of the DAAs administered alone.

*Reviewer's conclusion and labeling recommendation:*

- *It is strongly recommended to conduct an additional study to evaluate the change in the urinary excretion rate of furosemide when co-administered with 3 DAAs. At this time, we recommend that the labeling be revised as follows.*

(b) (4)

- *We agreed that amlodipine dose should be reduced and clinical monitoring of patients is recommended when co-administered with ABT-450/r/ABT-267+ABT-333. However, as mentioned above, an increase in dosing interval of amlodipine appears relevant rather than a decrease in daily dose. Thus, we recommend that the labeling should be revised as follows.*

(b) (4)

- *It is not known whether dose adjustment of ABT-450/r/ABT-267+ABT-333 is required or not when amlodipine is co-administered with ABT-450/r/ABT-267+ABT-333.*

**Drug-Drug Interaction Trial with Alprazolam or Zolpidem Tartrate**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-administration of Alprazolam or Zolpidem Tartrate with Combination of ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) and ABT-333 in Healthy Adult Volunteers (M14-324)**

**Study period:** 30 September 2013 to 06 December 2013

**Objectives:** The objective of this study was to determine the effect of steady-state ABT-450/r/ABT-267 and ABT-333 on the pharmacokinetics, safety and tolerability of single dose alprazolam or zolpidem tartrate in healthy subjects. In addition, the effect of single dose alprazolam or zolpidem tartrate on the pharmacokinetics, safety and tolerability of steady-state ABT-450/r/ABT-267 and ABT-333 was also determined.

**Methodology:**

This was a Phase 1, single center, multiple-dose, open-label study to evaluate the pharmacokinetics, safety and tolerability of a three direct-acting antiviral agent (DAA) combination (ABT-450/r/ABT-267 + ABT-333) and alprazolam or zolpidem tartrate when given alone and in combination. This study consisted of two independent parts (Part I and Part II). Adult male and female subjects (N = 24) in general good health were selected to participate in the study according to the selection criteria. Having met the selection criteria, subjects were assigned to Part I or Part II of the study as shown in the following table.

Part	N	Study Drug Regimens	
		Interacting Drug	DAAs
I	12	Alprazolam 0.5 mg: Study Days 1 and 18	ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID: Study Days 4 to 21
II	12	Zolpidem tartrate 5 mg: Study Days 1 and 17	ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID: Study Days 3 to 18

DAAs = Direct-acting antiviral agents; QD = Once daily; BID = Twice daily

Part I: A single dose of alprazolam 0.5 mg was administered in the morning of Study Day 1 followed by a washout period for 3 days (through morning of Study Day 4). Starting on Study Day 4, ABT-450/r/ABT-267 150/100/25 mg was administered once daily (QD) in the morning and ABT-333 250 mg was administered twice daily (BID) for 18 days (Study Days 4 through 21). On Study Day 18, a single dose of alprazolam 0.5 mg was administered.

Part II: A single dose of zolpidem tartrate 5 mg was administered in the morning of Study Day 1 followed by a washout period for 2 days (through morning of Study Day 3). Starting on Study Day 3, ABT-450/r/ABT-267 150/100/25 mg was administered QD in the morning and ABT-333 250 mg was administered BID for 16 days (Study Days 3 through 18). On Study Day 17, a single dose of zolpidem tartrate 5 mg was administered.

Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for all morning doses and approximately 30 minutes after the

start of the evening snack for the evening dose of ABT-333. The dose of alprazolam on Study Day 18 (Part I) and the dose of zolpidem tartrate on Study Day 17 (Part II) were administered in the morning at the same time as the direct-acting antiviral agents (DAAs).

Subjects were confined to the study site and supervised for approximately 23 days for Part I and 20 days for Part II. Confinement began on Study Day -1 (one day prior to initial dosing day) for both study parts and ended after the collection of the 96-hour alprazolam blood sample and completion of the scheduled study procedures on Study Day 22 for Part I, or after the collection of the 48-hour zolpidem tartrate blood sample and completion of the scheduled study procedures on Study Day 19 for Part II. Subjects returned for an outpatient safety visit on Study Day 31 for Part I or Study Day 28 for Part II (a visit window of  $\pm 2$  days was allowed to accommodate subject scheduling).

In Part I, blood samples for assay of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were collected by venipuncture on the following days: Prior to the morning dose on Study Days 11 and 14; prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 hours after the morning dose on Study Day 17; prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 (Study Day 19) hours after the morning dose on Study Day 18, or upon subject discontinuation due to an adverse event.

Blood samples for assay of alprazolam were collected by venipuncture on the following days: Prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 (Study Day 2), 36 (Study Day 2), 48 (Study Day 3), and 72 (Study Day 4) hours after the morning dose on Study Day 1; prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 (Study Day 19), 36 (Study Day 19), 48 (Study Day 20), 72 (Study Day 21), and 96 (Study Day 22) hours after the morning dose on Study Day 18, or upon subject discontinuation due to an adverse event. In Part II, blood samples for assay of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were collected by venipuncture on the following days: Prior to the morning dose on Study Days 10 and 13; prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 hours after the morning dose on Study Day 16; prior to dosing (0-hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 (Study Day 18) hours after the morning dose on Study Day 17, or upon subject discontinuation due to an adverse event.

Blood samples for assay of zolpidem were collected by venipuncture on the following days: Prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 (Study Day 2) hours after the morning dose on Study Day 1; prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 (Study Day 18), 36 (Study Day 18) and 48 (Study Day 19) hours after the morning dose on Study Day 17, or upon subject discontinuation due to an adverse event.

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were established 0.590 ng/mL, 5.04 ng/mL, 0.446 ng/mL, 4.77 ng/mL and 4.75 ng/mL, respectively.

Plasma concentrations of alprazolam were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The LLOQ for alprazolam was established at 0.100 ng/mL. Plasma concentrations of zolpidem were determined using a validated liquid

chromatography method with tandem mass spectrometric detection. The LLOQ for zolpidem was established at 0.25 ng/mL.

**Number of Subjects (Planned and Analyzed):**

Planned: 24, Entered: 24, Completed: 24, Evaluated for Safety: 24, Evaluated for Pharmacokinetics: 24

For the 24 subjects who participated in the study, the mean age was 37.4 years (ranging from 22 to 55 years), the mean weight was 79.8 kg (ranging from 52 to 101 kg) and the mean height was 174 cm (ranging from 154 to 184 cm).

**Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers whose ages were between 18 and 55 years. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal for at least 2 years, surgically sterile or practice birth control, and were not pregnant or breastfeeding. Males were surgically sterile or practiced birth control.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

	ABT-450/ritonavir/ ABT-267	ABT-333	Xanax® (alprazolam)	Ambien® (zolpidem tartrate)
Dosage Form	Tablet	Tablet	Tablet	Tablet
Strength	75/50/12.5 mg	250 mg	0.5 mg	5 mg
Bulk Product Lot Number	12-008149	13-000242	13-004390	13-004389
Manufacturing Site	AbbVie, Inc. Cork, Ireland	AbbVie, Inc. North Chicago, IL	Pfizer New York, NY	Sanofi Aventis Bridgewater, NJ
Finishing Sublot Number	13-004139	13-004140	13-004141	13-00414

**Duration of Treatment:**

In Part I, twelve subjects received alprazolam 0.5 mg on Study Days 1 and 18, and ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID on Study Days 4 to 21. In Part II, twelve subjects received zolpidem tartrate 5 mg on Study Days 1 and 17, and ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID on Study Days 3 to 18.

**Criteria for Evaluation:**

Pharmacokinetics: The pharmacokinetic parameter values of were estimated using noncompartmental methods. For ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite: the maximum observed plasma concentration ( $C_{max}$ ), time to  $C_{max}$  (peak time,  $T_{max}$ ), plasma trough concentration ( $C_{trough}$ :  $C_{12}$  or  $C_{24}$ ), and area under the plasma concentration-time curve during a dosing interval ( $AUC_{tau}$ :  $AUC_{0-12}$  or  $AUC_{0-24}$ ). For alprazolam and zolpidem tartrate:  $C_{max}$ ,  $T_{max}$ , apparent terminal phase elimination rate constant ( $\beta$ ), terminal phase elimination half-life ( $t_{1/2}$ ), area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration ( $AUC_t$ ), AUC from time 0 to infinite time ( $AUC_{\infty}$ ), apparent oral clearance value ( $CL/F$ ) and apparent volume of distribution ( $V_{d\beta}/F$ ).

Safety Endpoints: Safety was evaluated based on assessments of adverse events, vital signs, physical examinations, ECGs and laboratory tests.

### **Statistical Methods:**

Pharmacokinetic: To assess the effect of a single dose alprazolam or zolpidem tartrate on steady-state ABT-450, ritonavir, ABT-267 and ABT-333, a repeated measure analysis was performed for the natural logarithms of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 C<sub>max</sub> and AUC values utilizing data from Study Days 17 and 18 for Part I (alprazolam part) and Study Days 16 and 17 for Part II (zolpidem tartrate part). Additionally, ratios of the ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 C<sub>max</sub> and AUC were estimated by taking the ratio of corresponding Study Day 18 versus Study Day 17 values for Part I (alprazolam part) and Study Day 17 versus Study Day 16 values for Part II (zolpidem tartrate part), obtained from the repeated measures analysis of the difference of mean logarithms.

To assess the effect of steady-state DAAs on a single dose of alprazolam or zolpidem tartrate, a repeated measure analysis was performed for the natural logarithms of alprazolam or zolpidem C<sub>max</sub> and AUC values utilizing data from Study Days 1 and 18 for Part I (alprazolam part), and Study Days 1 and 17 for Part II (zolpidem tartrate part). Additionally, the ratio of alprazolam or zolpidem C<sub>max</sub> and AUC was estimated by taking the ratio of corresponding Study Day 18 versus Study Day 1 values for Part I (alprazolam part), and Study Day 17 versus Study Day 1 values for Part II (zolpidem tartrate part), obtained from the repeated measures analysis of the difference of mean logarithms.

To assess steady state of ABT-450, ritonavir, ABT-267 and ABT-333, a repeated measures analysis was performed on the logarithmic transformed pre-dose concentration measurements of Study Days 11, 14, 17 and 18 in Part I and Study Days 10, 13, 16 and 17 in Part II. Within the framework of the repeated measures analysis, the hypothesis of no difference between Study Day 18 and each of Study Days 17, 14 and 11 in Part I or between Study Day 17 and each of Study Days 16, 13 and 10 for Part II was tested with a significance level of 0.05 for each test to determine the earliest day after which there was not a statistically significant change. In addition, a test was performed on a contrast in the means chosen to be sensitive to a linear trend across all days to determine whether there was a linear trend from Study Day 11 to Study Day 18 for Part I or from Study Day 10 to Study Day 17 for Part II.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who had treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by the following study time segments within each part of the study. The tabulation of the number of subjects with treatment-emergent adverse events was also provided with further breakdowns by severity rating and relationship to study drug. Laboratory test values, vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

### **Results:**

#### Pharmacokinetics:

##### Part I: Interaction with alprazolam



The effect of a single dose of alprazolam on the PK of DAAs was evaluated by comparing the exposures on Study Day 18 to Study Day 17. The  $C_{\max}$ ,  $AUC_{\tau}$  and  $C_{\text{trough}}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 1. The PK of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were minimally affected by a single dose of alprazolam.

**Table 1.** Effect of a single dose of alprazolam (0.5 mg) on the PK of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite.

Analyte	Pharmacokinetic Parameter	Central Value		Ratio of Central Values <sup>a</sup>	
		Day 18	Day 17	Point Estimate	90% Confidence Interval
ABT-450	$C_{\max}$ (ng/mL)	626	686	0.913	0.636 – 1.310
	$AUC_{0-24}$ (ng•h/mL)	3630	3765	0.964	0.734 – 1.267
	$C_{24}$ (ng/mL)	15.6	13.9	1.120	1.022 – 1.228
Ritonavir	$C_{\max}$ (ng/mL)	1095	1187	0.923	0.838 – 1.017
	$AUC_{0-24}$ (ng•h/mL)	6957	7273	0.957	0.887 – 1.031
	$C_{24}$ (ng/mL)	31.0	30.6	1.013	0.942 – 1.090
ABT-267	$C_{\max}$ (ng/mL)	140	143	0.983	0.928 – 1.040
	$AUC_{0-24}$ (ng•h/mL)	1584	1587	0.998	0.960 – 1.037
	$C_{24}$ (ng/mL)	33.2	33.8	0.982	0.933 – 1.035
ABT-333	$C_{\max}$ (ng/mL)	789	850	0.928	0.825 – 1.044
	$AUC_{0-24}$ (ng•h/mL)	5430	5539	0.980	0.866 – 1.110
	$C_{24}$ (ng/mL)	229	229	1.001	0.869 – 1.154
ABT-333	$C_{\max}$ (ng/mL)	485	517	0.937	0.770 – 1.140
M1 Metabolite	$AUC_{0-24}$ (ng•h/mL)	3032	3075	0.986	0.822 – 1.182
	$C_{24}$ (ng/mL)	110	105	1.053	0.942 – 1.177

Study Day 17: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID

Study Day 18: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + alprazolam 0.5 mg

<sup>a</sup>. Study Day 18:Study Day 17.

The steady-state effect of ABT-450/r/ABT-267 and ABT-333 on alprazolam was evaluated by comparing the exposures on Study Day 18 to Study Day 1. The  $C_{\max}$ ,  $AUC_t$  and  $AUC_{\infty}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 2. The alprazolam AUC value was increased by 34% due to the co-administration of 3-DAAs.

**Table 2.** The steady-state effect of ABT-450/r/ABT-267 and ABT-333 on the PK of alprazolam

Analyte	Pharmacokinetic Parameter	Central Value		Ratio of Central Values <sup>a</sup>	
		Day 18	Day 1	Point Estimate	90% Confidence Interval
Alprazolam	$C_{\max}$ (ng/mL)	7.09	6.52	1.086	1.030 – 1.145
	$AUC_t$ (ng•h/mL)	174	131	1.326	1.156 – 1.521
	$AUC_{\infty}$ (ng•h/mL)	184	137	1.336	1.151 – 1.550

Study Day 1: Alprazolam 0.5 mg

Study Day 18: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + alprazolam 0.5 mg

<sup>a</sup>. Study Day 18:Study Day 1.

*Reviewer's comments: The sponsor proposed that caution is warranted and clinical monitoring is recommended when alprazolam administered with the 3-DAA regimen. We agreed with the sponsor's labeling proposal related to the interaction between alprazolam and 3-DAA regimen.*

## Part II: Interaction with zolpidem

The effect of zolpidem tartrate on DAAs at steady state was evaluated by comparing the exposures on Study Day 17 to Study Day 16. The  $C_{\max}$ ,  $AUC_{\tau}$  and  $C_{\text{trough}}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 3. There were no clinically meaningful changes (<50% decrease or <2-fold increase) in the PK of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite when zolpidem was administered with 3 DAAs.

**Table 3.** Effect of a single dose of zolpidem (5 mg) on the PK of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite.

Analyte	Pharmacokinetic Parameter	Central Value		Ratio of Central Values <sup>a</sup>	
		Day 18	Day 17	Point Estimate	90% Confidence Interval
ABT-450	$C_{\max}$ (ng/mL)	1446	2295	0.630	0.463 – 0.857
	$AUC_{0-24}$ (ng•h/mL)	6284	9240	0.680	0.546 – 0.848
	$C_{24}$ (ng/mL)	20.0	16.3	1.228	1.095 – 1.377
Ritonavir	$C_{\max}$ (ng/mL)	1813	1849	0.981	0.884 – 1.088
	$AUC_{0-24}$ (ng•h/mL)	10248	10587	0.968	0.882 – 1.063
	$C_{24}$ (ng/mL)	37.6	36.5	1.029	0.966 – 1.097
ABT-267	$C_{\max}$ (ng/mL)	149	139	1.071	0.998 – 1.149
	$AUC_{0-24}$ (ng•h/mL)	1549	1498	1.034	1.000 – 1.069
	$C_{24}$ (ng/mL)	32.8	31.4	1.043	1.004 – 1.084
ABT-333	$C_{\max}$ (ng/mL)	1095	1180	0.928	0.838 – 1.028
	$AUC_{0-24}$ (ng•h/mL)	6948	7291	0.953	0.843 – 1.077
	$C_{24}$ (ng/mL)	238	259	0.919	0.834 – 1.014
ABT-333	$C_{\max}$ (ng/mL)	716	851	0.842	0.706 – 1.004
M1 Metabolite	$AUC_{0-24}$ (ng•h/mL)	3928	4722	0.832	0.709 – 0.976
	$C_{24}$ (ng/mL)	104	121	0.855	0.761 – 0.959

Study Day 16: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID

Study Day 17: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + zolpidem tartrate 5 mg

a. Study Day 17: Study Day 16.

The steady-state effect of ABT-450/r/ABT-267 and ABT-333 on zolpidem was evaluated by comparing the exposures on Study Day 17 to Study Day 1. The  $C_{\max}$ ,  $AUC_t$  and  $AUC_{\infty}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 4. The zolpidem exposure ( $C_{\max}$  and AUC) was not affected by the co-administration of 3-DAAs.

**Table 4.** The steady-state effect of ABT-450/r/ABT-267 and ABT-333 on the PK of zolpidem

Central Value	Ratio of Central Values <sup>a</sup>

Analyte	Pharmacokinetic Parameter	Day 17	Day 1	Point Estimate	90% Confidence Interval
Alprazolam	C <sub>max</sub> (ng/mL)	57.8	61.7	0.937	0.755 – 1.163
	AUC <sub>t</sub> (ng•h/mL)	318	328	0.968	0.757 – 1.238
	AUC <sub>∞</sub> (ng•h/mL)	321	337	0.953	0.742 – 1.225

Study Day 1: Zolpidem tartrate 5 mg

Study Day 17: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + zolpidem tartrate 5 mg

a. Study Day 17: Study Day 1.

**Safety Results:** The regimens tested were generally well tolerated by the subjects. The only adverse event experienced by more than one subject in this study was somnolence, which in most instances appeared to be related to zolpidem tartrate administration when administered alone. Somnolence was an expected observation because zolpidem tartrate is prescribed as a sleep-aid, and it was administered in the morning in this study. All remaining adverse events were reported by a maximum of one subject. No deaths, serious adverse events or other significant adverse events were reported during the study. The majority of the treatment-emergent adverse events were mild in severity and assessed by the investigator as having "no reasonable possibility" of being related to ABT-450/r/ABT-267 and ABT-333, but having "reasonable possibility" of being related to alprazolam or zolpidem tartrate. No clinically significant vital signs or laboratory measurements were observed during the course of the study. No new safety issues were identified.

## Conclusions:

### Part I: DAAs + Alprazolam

When the 3-DAA regimen (ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID) was coadministered with a single oral dose of alprazolam 0.5 mg, steady-state exposures of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were minimally affected ( $\leq 12\%$  change). Co-administration with ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID had minimal impact on alprazolam C<sub>max</sub> (up to 9% increase), but increased the alprazolam AUC values by 34%. Caution is warranted and clinical monitoring is recommended when alprazolam is administered with the 3-DAA regimen.

### Part II: DAAs + Zolpidem Tartrate

When the 3-DAA regimen (ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID) was coadministered with a single oral dose of zolpidem tartrate 5 mg, steady-state exposures of ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were minimally affected ( $\leq 17\%$  change). However, the ABT-450 C<sub>max</sub> and AUC<sub>0-24</sub> values were decreased by up to 37% and 32%, respectively. Co-administration with ABT-450/r/ABT-267 150/100/25 mg QD and ABT-333 250 mg BID had minimal impact on zolpidem tartrate C<sub>max</sub> and AUC values (up to 6% decrease). No dose adjustment is needed for zolpidem tartrate when it is administered with the 3-DAA regimen.

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs or laboratory measurements were observed during the course of the study. No deaths or other serious adverse events were reported. No new safety issues were identified from this study.

*Reviewer's conclusion and labeling recommendation:*

*We recommend that clinical monitoring be conducted when alprazolam administered with the 3-DAA regimen as the sponsor proposed. Based on the results of this study, zolpidem may be administered with 3 DAAs without dose adjustment.*

**Drug-Drug Interaction Trial with Rosuvastatin or Pravastatin**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-administration of Rosuvastatin or Pravastatin with Combination of ABT-450 with Ritonavir (ABT-450 /r), with ABT-267 and/or ABT-333 in Healthy Adult Subjects (M12-200)**

**Study period:** 02 July 2012 to 25 October 2012

**Objectives:** The objectives of the study were as follows: to determine the pharmacokinetics, safety and tolerability of the combination of ABT-450 with ritonavir (ABT-450/r), with ABT-267 and/or ABT-333 when dosed with rosuvastatin or pravastatin in healthy subjects; and to determine the pharmacokinetics, safety and tolerability of rosuvastatin or pravastatin when co-administered with a combination of ABT-450 with ritonavir (ABT-450/r), with ABT-267 and/or ABT-333 in healthy subjects.

**Methodology:**

This Phase 1, single-center, multiple-dose, sequential, open-label study was designed to evaluate the co-administration of rosuvastatin or pravastatin with two and three direct-acting antiviral agents (DAAs) (Arm 1: ABT-450/r, ABT-267 and ABT-333 with pravastatin [Cohort 1] or rosuvastatin [Cohort 2]) or with 2 DAAs (Arm 2: ABT-450/r and ABT-267 with pravastatin [Cohort 1] or rosuvastatin [Cohort 2]). Adult male and female subjects (N = 48) in general good health were selected to participate in the study according to the selection criteria. Arms 1 and 2 were sequential and each consisted of 24 subjects. Each arm was further divided into Cohort 1 and Cohort 2, which each consisted of 12 subjects. There were two periods in each arm.

After meeting the selection criteria, subjects were enrolled sequentially to each arm. In both arms, study drugs were administered starting on Day 1 of Period 1 and Day 1 of Period 2. A 14-day washout separated Period 1 and Period 2 in both arms.

Period 1

Arm 1, Cohorts 1 and 2: Single doses of ABT-450/r 150/100 mg, ABT-267 25 mg and ABT 333 400 mg were administered on Day 1 under non-fasting conditions.

Arm 2, Cohorts 1 and 2: Single doses of ABT-450/r 150/100 mg and ABT-267 25 mg were administered on Day 1 under non-fasting conditions.

Period 2

Arm 1, Cohort 1: Pravastatin 10 mg was administered QD on Days 1 to 3. ABT 450/r 150/100 mg QD, ABT-267 25 mg QD, ABT-333 400 mg BID were co-administered along with pravastatin 10 mg QD on Days 4 to 17 under non fasting conditions.

Arm 1, Cohort 2: Rosuvastatin 5 mg was administered QD on Days 1 to 7. ABT 450/r 150/100 mg QD, ABT-267 25 mg QD, ABT-333 400 mg BID were co-administered along with rosuvastatin 5 mg QD on Days 8 to 21 under non fasting conditions.

Arm 2, Cohort 1: Pravastatin 10 mg was administered QD on Days 1 to 3. ABT 450/r 150/100 mg QD and ABT-267 25 mg QD were co-administered along with pravastatin 10 mg QD on Days 4 to 17 under non-fasting conditions.

Arm 2, Cohort 2: Rosuvastatin 5 mg was administered QD on Days 1 to 7. ABT 450/r 150/100 mg QD and ABT-267 25 mg QD were co-administered along with rosuvastatin 5 mg QD on Days 8 to 21 under non-fasting conditions.

Blood samples for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite (A-1041392) were collected by venipuncture in 3 mL evacuated potassium ethylenediaminetetraacetic acid (K2 EDTA)-containing collection tubes. Sufficient blood was collected to provide approximately 1.3 mL plasma from each sample. Samples were collected on the following days in Arms 1 and 2:

#### Period 1, Cohorts 1 and 2

Day 1: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, and 72 hours after dosing on Day 1

#### Period 2, Cohort 1

Day 4: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after the morning dose administered on Day 4

Day 17: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, and 72 hours after the morning dose administered on Day 17

Trough samples: prior to morning dose on Days 5, 9, 13, and 15

#### Period 2, Cohort 2

Day 8: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after the morning dose administered on Day 8

Day 21: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, and 72 hours after the morning dose administered on Day 21

Trough samples: prior to morning dose on Days 9, 13, 15 and 19

Blood samples for pravastatin were collected in 4 mL sodium Heparin-containing collection tubes in Cohort 1 only. Sufficient blood was collected to provide approximately 1.6 mL plasma from each sample. Blood samples for rosuvastatin were collected in 2 mL K2 EDTA-containing collection tubes in Cohort 2 only. Sufficient blood was collected to provide approximately 0.9 mL plasma from each sample.

Samples for pravastatin and rosuvastatin were collected on the following days in Period 2 of Arms 1 and 2:

Period 2, Cohort 1 (Pravastatin)

Days 1, 3 and 4: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after the morning dose administered on Days 1, 3 and 4

Day 17: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, and 72 hours after the morning dose administered on Day 17

Trough samples: prior to morning dose on Days 2, 5, 9, 13, and 15

Period 2, Cohort 2 (Rosuvastatin)

Days 1, 7 and 8: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after the morning dose administered on Days 1, 7 and 8

Day 21: prior to dosing (0 hour), 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, and 72 hours after the morning dose administered on Day 21

Trough samples: prior to morning dose on Days 2, 5, 9, 13, 15 and 19

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite were determined using a validated protein precipitation and on-line solid phase extraction method with liquid chromatography and tandem mass spectrometric detection (LCMS/MS). The lower limit of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were established at 0.595 ng/mL, 4.71 ng/mL, 0.460 ng/mL, 4.53 ng/mL and 4.50 ng/mL, respectively.

Plasma concentrations of pravastatin were determined using a validated LCMS/MS method. The LLOQ for pravastatin was established at 0.500 ng/mL.

Plasma concentrations of rosuvastatin were determined using a validated LCMS/MS method. The LLOQ for rosuvastatin was established at 0.100 ng/mL.

**Number of Subjects (Planned and Analyzed):**

Planned: 48 (for Arms 1 and 2; Arm 3 was not conducted); Entered: 48; Completed: 45; Evaluated for Safety: 48; Evaluated for Pharmacokinetics: 48

Arm 1 Cohort 1: For the 12 subjects who participated in Arm 1 Cohort 1, the mean age was 34.3 years (ranging from 21 to 49 years), the mean weight was 76.7 kg (ranging from 61 to 90 kg) and the mean height was 172 cm (ranging from 161 to 186 cm).

Arm 1 Cohort 2: For the 12 subjects who participated in Arm 1 Cohort 2, the mean age was 33.8 years (ranging from 20 to 47 years), the mean weight was 81.0 kg (ranging from 67 to 102 kg) and the mean height was 175 cm (ranging from 156 to 193 cm).

Arm 2 Cohort 1: For the 12 subjects who participated in Arm 2 Cohort 1, the mean age was 32.3 years (ranging from 22 to 55 years), the mean weight was 79.9 kg (ranging from 63 to 100 kg) and the mean height was 175 cm (ranging from 156 to 195 cm).

Arm 2 Cohort 2: For the 12 subjects who participated in Arm 2 Cohort 2, the mean age was 32.1 years (ranging from 22 to 50 years), the mean weight was 77.1 kg (ranging from 55 to 95 kg) and the mean height was 173 cm (ranging from 163 to 181 cm).

### Diagnosis and Main Criteria for Inclusion:

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal for at least 2 years, surgically sterile and were not pregnant or breast-feeding. Males were surgically sterile or were practicing at least one of the acceptable methods of birth control specified in the protocol.

### Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Products	ABT-267	ABT-450	Ritonavir	ABT-333	Pravastatin	Rosuvastatin
Dosage Form	Tablet	Tablet	Soft Gelatin Capsule	Tablet	Tablet	Tablet
Strength (mg)	25 mg	50 mg	100 mg	400 mg	10 mg	5 mg
Bulk Product Lot Number	11-002033	10-003507	11-005635	11-002720	12-004051	12-003992
Potency (% of Lable Claim)	(b) (4)				Unknown	Unknown
Manufacturing Site	AbbVie (b) (4)	AbbVie LC <sup>b</sup>	AbbVie LC <sup>b</sup>	AbbVie LC <sup>b</sup>	Glenmark Generics	Astra Zeneca
Finishing Lot Number	12-003825	12-003826	12-003828	12-003827	12-004049	12-003829
Retest Date	(b) (4)					

a. AbbVie, (b) (4)

b. AbbVie, Lake County, USA

**Duration of Treatment:** Dosing for Arm 1 began on 20 July 2012 and ended on 23 August 2012. Dosing for Arm 2 began on 14 September 2012 and ended on 18 October 2012.

### Criteria for Evaluation:

**Pharmacokinetic:** The pharmacokinetic parameter values of ABT-267, ABT-450, ritonavir, ABT-333, ABT-333 M1, pravastatin and rosuvastatin were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), plasma trough concentration ( $C_{trough}$ ) [plasma concentration at 24 hours after dosing ( $C_{24}$ ) for ABT-267, ABT-450, ritonavir, pravastatin and rosuvastatin or plasma concentration at 12 hours after dosing ( $C_{12}$ ) for ABT333 and ABT-333 M1], the apparent terminal phase elimination rate constant ( $\beta$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to time of the last measurable concentration ( $AUC_l$ ), the AUC from time 0 to infinity ( $AUC_{\infty}$ ) and the AUC from time 0 to 24 hours ( $AUC_{24}$ ).



for ABT-267, ABT-450, ritonavir, pravastatin and rosuvastatin and the AUC from time 0 to 12 hours (AUC<sub>12</sub>) for ABT-333 and ABT-333 M1.

Safety Endpoints: Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECGs and laboratory tests.

### **Statistical Methods:**

Pharmacokinetic: Repeated measures analysis was used to assess the steady-state of each analyte (when applicable) on the C<sub>trough</sub> values (prior to the morning dose). A separate analysis was performed for each period of each cohort in each Arm (as appropriate). C<sub>trough</sub> data from Study Days 5, 9, 13, 15, 17, 18 for Cohort 1, and Study Days 9, 13, 15, 19, 21, 22 for Cohort 2 were used to assess the steady-state of DAAs in each arm. For rosuvastatin we had two terms within Period 2 Cohort 2 of each arm. For term 1, C<sub>trough</sub> data from Study Days 2, 5, 7 and 8; and for term 2, C<sub>trough</sub> data from Study Days 9, 13, 15, 19, 21, 22 were used to assess the steady state of rosuvastatin. The model had day as a fixed effect and subject as a random effect. Within the framework of the repeated measures analysis, pair-wise tests and trend analyses were performed on the contrasts in the study day effects to determine the earliest day after which there was no statistically significant change. No steady state analysis was performed for pravastatin since all the C<sub>trough</sub> values were below the limit of quantitation for all but one day for one subject.

Safety: All adverse events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by the following study time segments within each cohort of each arm:

**Arm 1, Cohort 1:** Three study time segments (Period 1 for ABT-450/r + ABT-333 + ABT-267, Period 2 Days 1-3 for pravastatin and Period 2 Days 4 through study completion for ABT-450/r + ABT-333 + ABT-267 + pravastatin).

**Arm 1, Cohort 2:** Three study time segments (Period 1 for ABT-450/r + ABT-333 + ABT-267, Period 2 Days 1-7 for rosuvastatin and Period 2 Days 8 through study completion for ABT-450/r + ABT-333 + ABT-267 + rosuvastatin).

**Arm 2, Cohort 1:** Three study time segments (Period 1 for ABT-450/r + ABT-267, Period 2, Days 1-3 for pravastatin and Period 2, Days 4 through study completion for ABT-450/r + ABT-267 + pravastatin).

**Arm 2, Cohort 2:** Three study time segments (Period 1 for ABT-450/r + ABT-267, Period 2, Days 1-7 for rosuvastatin and Period 2, Days 8 through study completion for ABT-450/r + ABT-267 + rosuvastatin).

The tabulation of the number of subjects with treatment-emergent adverse events was also provided with further breakdowns by severity rating and relationship to study drug. Within each study time segment, subjects reporting more than one adverse event for a given MedDRA Preferred Term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that were very high or very low, according to predefined criteria, were identified.

## Results:

### Pharmacokinetics:

#### Arm 1 Cohort 1

The steady-state effect of pravastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (i.e., 3 DAAs) was evaluated by comparing the exposures on Day 4 Period 2 to Day 1 Period 1. Repeated measures analyses were performed for the natural logarithms of  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  to assess the effect of pravastatin on ABT-450/ritonavir/ABT-267 and ABY-333. The  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 1. There were no clinically significant changes (i.e., <50% decrease or <2-fold increase) in the PK of DAAs by the coadministration with pravastatin.

**Table 1.** The steady-state effect of pravastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (Arm 1 Cohort 1)

Analyte	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
		Period 2 Day 4	Period 1 Day 1	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	$C_{max}$	720	752	0.957	0.692 – 1.322
	$AUC_{24}$	4403	3909	1.126	0.917 – 1.384
	$C_{24}$	30.7	22.1	1.389	1.214 – 1.590
Ritonavir	$C_{max}$	1343	1506	0.892	0.730 – 1.089
	$AUC_{24}$	7635	8029	0.951	0.860 – 1.051
	$C_{24}$	35.6	33.0	1.081	0.982 – 1.189
ABT-267	$C_{max}$	132	139	0.951	0.888 – 1.018
	$AUC_{24}$	1114	1186	0.939	0.891 – 0.989
	$C_{24}$	16.1	17.2	0.936	0.886 – 0.990
ABT-333	$C_{max}$	1148	1153	0.995	0.868 – 1.141
	$AUC_{24}$	7372	7652	0.963	0.850 – 1.092
	$C_{24}$	330	322	1.025	0.911 – 1.153
ABT-333 M1 Metabolite	$C_{max}$	702	680	1.032	0.862 – 1.235
	$AUC_{24}$	4207	4096	1.027	0.883 – 1.195
	$C_{24}$	188	164	1.146	1.020 – 1.288

Period 1 Day 1: ABT-450/r + ABT-267 + ABT-333

Period 2 Day 4: ABT-450/r + ABT-267 + ABT-333 + Pravastatin

<sup>a</sup> Antilogarithm of the least squares means for logarithms.

<sup>b</sup> Antilogarithm of the difference of the least squares means for logarithms.

The steady-state effect of ABT-450/r, ABT-267 and ABT-333 on pravastatin was evaluated by comparing the exposures of pravastatin on Day 17 Period 2 to Day 3 Period 2. Repeated measures analyses were performed for the natural logarithms of  $C_{max}$  and  $AUC_{24}$  to assess the effect of DAAs on pravastatin. Statistical analysis was not performed on pravastatin  $C_{24}$  as

pravastatin concentrations at 24 hours post-dose were below the lower limit of quantitation for all but one subject on Day 4 due to its very short half-life of less than 2 hours. The  $C_{\max}$  and  $AUC_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 2.

**Table 2.** Pravastatin  $C_{\max}$  and  $AUC_{24}$  Ratios (90% Confidence Intervals) of the Central Values (Arm 1 Cohort 1)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Period 2 Day 17	Period 2 Day 3	Point Estimate <sup>b</sup>	90% Confidence Interval
$C_{\max}$	25.5	18.7	1.366	1.105 – 1.690
$AUC_{24}$	88.7	48.7	1.821	1.595 – 2.078

Period 2 Day 3: Pravastatin alone

Period 2 Day 17: ABT-450/r + ABT-267 + ABT-333 + Pravastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: The increases of pravastatin  $C_{\max}$  and  $AUC_{24}$  due to co-administration with 3-DAA's appear to be clinically significant. However, the approved doses of pravastatin for adults are 40 mg QD and 80 mg QD (only for patients not reaching LDL-C goal with 40 mg). Thus, as the sponsor proposed, the pravastatin dose should not exceed 40 mg per day when it is co-administered with 3-DAA's. Similarly, the pravastatin doses should not exceed the recommended starting dose for other special population [e.g., 10 mg per day for patients with renal impairment, 20 mg per day for children (ages 8 to 13 years, inclusive) and 40 mg per day for adolescents]. The PK of pravastatin is directly proportional to the dose. Accordingly, it is acceptable the results of this study (10 mg per day of pravastatin) to extrapolate the interaction at the approved doses (40 mg per day of pravastatin).*

### Arm 1 Cohort 2

The steady-state effect of rosuvastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (i.e., 3 DAAs) was evaluated by comparing the exposures on Day 8 Period 2 to Day 1 Period 1. Repeated measures analyses were performed for the natural logarithms of  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  to assess the effect of rosuvastatin on ABT-450/ritonavir/ABT-267 and ABY-333. The  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 3. There were no clinically significant changes (i.e., <50% decrease or <2-fold increase) in the PK of DAAs by the co-administration with rosuvastatin.

**Table 3.** The steady-state effect of rosuvastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (Arm 1 Cohort 2)

Analyte	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
		Period 2 Day 4	Period 1 Day 1	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	$C_{\max}$	700	440	1.590	1.133 – 2.232
	$AUC_{24}$	4009	2631	1.524	1.225 – 1.895

	C <sub>24</sub>	29.3	20.5	1.430	1.219 – 1.676
Ritonavir	C <sub>max</sub>	1402	1432	0.979	0.836 – 1.147
	AUC <sub>24</sub>	8392	8229	1.020	0.927 – 1.121
	C <sub>24</sub>	40.3	40.3	1.000	0.895 – 1.118
ABT-267	C <sub>max</sub>	118	128	0.923	0.820 – 1.039
	AUC <sub>24</sub>	979	1105	0.886	0.829 – 0.948
	C <sub>24</sub>	14.2	16.1	0.881	0.830 – 0.936
ABT-333	C <sub>max</sub>	1096	1027	1.067	0.920 – 1.236
	AUC <sub>24</sub>	7092	6562	1.081	0.924 – 1.264
	C <sub>24</sub>	307	267	1.149	1.054 – 1.253
ABT-333 M1 metabolite	C <sub>max</sub>	740	639	1.158	0.962 – 1.394
	AUC <sub>24</sub>	4281	3674	1.165	0.986 – 1.376
	C <sub>24</sub>	180	144	1.253	1.132 – 1.385

Period 1 Day 1: ABT-450/r + ABT-267 + ABT-333

Period 2 Day 4: ABT-450/r + ABT-267 + ABT-333+ Pravastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The steady-state effect of ABT-450/r, ABT-267 and ABT-333 on rosuvastatin was evaluated by comparing the exposures of rosuvastatin on Day 21 Period 2 to Day 7 Period 2. Repeated measures analyses were performed for the natural logarithms of C<sub>max</sub>, AUC<sub>24</sub> and C<sub>24</sub> to assess the effect of DAAs on rosuvastatin. The C<sub>max</sub>, AUC<sub>24</sub> and C<sub>24</sub> ratios of central values and 90% confidence intervals for the comparison are presented in Table 4.

**Table 4.** Rosuvastatin C<sub>max</sub>, AUC<sub>24</sub>, and C<sub>24</sub> ratios (90% Confidence Intervals) of the Central Values (Arm 1 Cohort 2)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Period 2 Day 21	Period 2 Day 7	Point Estimate <sup>b</sup>	90% Confidence Interval
C <sub>max</sub>	13.8	1.93	7.133	5.107 – 9.962
AUC <sub>24</sub>	51.1	19.7	2.593	2.094 – 3.212
C <sub>24</sub>	0.243	0.411	0.590	0.505 – 0.690

Period 2 Day 7: Rosuvastatin alone

Period 2 Day 21: ABT-450/r + ABT-267 + ABT-333+ Rosuvastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: The increases of rosuvastatin C<sub>max</sub> and AUC<sub>24</sub> due to co-administration with 3-DAAs appear to be clinically significant. However, the approved doses of rosuvastatin for adults and pediatric patients 10 to 17 years of age are 5-40 mg QD and 5-20 mg QD, respectively. Thus, as the sponsor proposed, the rosuvastatin dose should not exceed 10 mg per day when it is co-administered with 3 DAAs in adults. The sponsor did not propose the rosuvastatin dose adjustment for pediatric patients 10 to 17 years of age. In pediatric patients 10 to 17 years of age, rosuvastatin dose should not exceed 5 mg per day when co-administered with 3 DAAs.*

### Arm 2 Cohort 1

The steady-state effect of pravastatin on single dose of ABT-450/ritonavir/ABT-267 (i.e., 2 DAAs) was evaluated by comparing the exposures on Day 4 Period 2 to Day 1 Period 1. Repeated measures analyses were performed for the natural logarithms of  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  to assess the effect of pravastatin on ABT-450/ritonavir/ABT-267. The  $C_{\max}$ ,  $AUC_{24}$  and  $C_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 5. There were no clinically significant changes (i.e., <50% decrease or <2-fold increase) in the PK of DAAs by the co-administration with pravastatin.

**Table 5.** The steady-state effect of pravastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (Arm 2 Cohort 1)

Analyte	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
		Period 2 Day 4	Period 1 Day 1	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	$C_{\max}$	284	197	1.441	1.149 – 1.807
	$AUC_{24}$	2005	1509	1.329	1.091 – 1.618
	$C_{24}$	21.1	16.5	1.277	0.830 – 1.964
Ritonavir	$C_{\max}$	814	594	1.371	1.052 – 1.786
	$AUC_{24}$	5384	3919	1.374	0.841 – 2.243
	$C_{24}$	43.6	51.2	0.852	0.760 – 0.955
ABT-267	$C_{\max}$	124	127	0.975	0.898 – 1.058
	$AUC_{24}$	1007	1066	0.944	0.878 – 1.016
	$C_{24}$	14.7	15.2	0.966	0.904 – 1.032

Period 1 Day 1: ABT-450/r + ABT-267

Period 2 Day 4: ABT-450/r + ABT-267 + Pravastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The steady-state effect of ABT-450/r and ABT-267 on pravastatin was evaluated by comparing the exposures of pravastatin on Day 17 Period 2 to Day 3 Period 2. Repeated measures analyses were performed for the natural logarithms of  $C_{\max}$  and  $AUC_{24}$  to assess the effect of DAAs on pravastatin. Statistical analysis was not performed on pravastatin  $C_{24}$  as pravastatin concentrations at 24 hours post-dose were below the lower limit of quantitation for all but one subject on Day 4 due to its very short half-life of less than 2 hours. The  $C_{\max}$  and  $AUC_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 6.

**Table 6.** Pravastatin  $C_{\max}$  and  $AUC_{24}$  Ratios (90% Confidence Intervals) of the Central Values (Arm 1 Cohort 1)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Period 2 Day 17	Period 2 Day 3	Point Estimate <sup>b</sup>	90% Confidence Interval
$C_{\max}$	26.3	18.4	1.428	1.086 – 1.876
$AUC_{24}$	86.0	48.8	1.763	1.456 – 2.134

Period 2 Day 3: Pravastatin alone

Period 2 Day 17: ABT-450/r + ABT-267 + ABT-333 + Pravastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: The increase of pravastatin  $C_{max}$  and  $AUC_{24}$  due to co-administration with 2-DAAs are similar to those due to co-administration with 3-DAAs.* (b) (4)

## Arm 2 Cohort 2

The steady-state effect of rosuvastatin on single dose of ABT-450/ritonavir/ABT (i.e., 2 DAAs) was evaluated by comparing the exposures on Day 8 Period 2 to Day 1 Period 1. Repeated measures analyses were performed for the natural logarithms of  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  to assess the effect of rosuvastatin on ABT-450/ritonavir/ABT-267. The  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 7. There were no clinically significant changes (i.e., <50% decrease or <2-fold increase) in the PK of DAAs by the co-administration with rosuvastatin.

**Table 7.** The steady-state effect of rosuvastatin on single dose of ABT-450/ritonavir/ABT-267 and ABY-333 (Arm 2 Cohort 2)

Analyte	Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
		Period 2 Day 8	Period 1 Day 1	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	$C_{max}$	413	296	1.396	1.122 – 1.737
	$AUC_{24}$	2448	2010	1.218	1.052 – 1.410
	$C_{24}$	15.9	15.0	1.063	0.854 – 1.323
Ritonavir	$C_{max}$	1169	1110	1.054	0.908 – 1.222
	$AUC_{24}$	6783	7243	0.936	0.839 – 1.045
	$C_{24}$	31.1	40.4	0.770	0.592 – 1.002
ABT-267	$C_{max}$	110	123	0.888	0.812 – 1.971
	$AUC_{24}$	897	1023	0.876	0.832 – 0.923
	$C_{24}$	13.0	14.9	0.869	0.827 – 0.913

Period 1 Day 1: ABT-450/r + ABT-267

Period 2 Day 4: ABT-450/r + ABT-267 + Rosuvastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The steady-state effect of ABT-450/r and ABT-267 on rosuvastatin was evaluated by comparing the exposures of rosuvastatin on Day 21 Period 2 to Day 7 Period 2. Repeated measures analyses were performed for the natural logarithms of  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  to assess the effect of DAAs on rosuvastatin. The  $C_{max}$ ,  $AUC_{24}$  and  $C_{24}$  ratios of central values and 90% confidence intervals for the comparison are presented in Table 8.

**Table 8.** Rosuvastatin  $C_{max}$ ,  $AUC_{24}$ , and  $C_{24}$  ratios (90% Confidence Intervals) of the Central Values (Arm 2 Cohort 2)

Pharmacokinetic Parameter	Central Value <sup>a</sup>		Ratio of Central Values	
	Period 2 Day 21	Period 2 Day 7	Point Estimate <sup>b</sup>	90% Confidence Interval
$C_{max}$	6.088	2.33	2.611	2.014 – 3.386
$AUC_{24}$	30.7	23.0	1.334	1.142 – 1.557
$C_{24}$	0.327	0.502	0.650	0.570 – 0.742

Period 2 Day 7: Rosuvastatin alone

Period 2 Day 21: ABT-450/r + ABT-267 + ABT-333+ Rosuvastatin

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: The increases of rosvastatin  $C_{max}$  and  $AUC_{24}$  due to co-administration with 2-DAA are quantitatively different from that due to co-administration with 2-DAA, indicating that ABT-333 plays a major role in the interaction between rosvastatin and 3 DAAs.*

**Safety:** The regimens tested were generally well tolerated by the subjects. No deaths or other serious adverse events were reported in this study. One subject in Arm 2 discontinued from the study due to an adverse event of vomiting after receiving ABT-450/r 150/100 mg QD + ABT-267 25 mg QD+pravastatin 10 mg QD. There was no pattern to the adverse events which were reported. Dermatitis contact, headache, nausea and oropharyngeal pain were the only treatment-emergent adverse events reported by more than one subject for the study in any given regimen. There were no clinically meaningful or significant trends noted among the potentially clinically significant vital signs or laboratory values in this study.

### Conclusions:

Following steady-state dosing with the 3-DAA combination of ABT-450/r 150/100 mg, ABT-267 25 mg and ABT-333 400 mg, the steady state  $C_{max}$  and AUC of pravastatin were about 40% and 80% higher, respectively; while those of rosvastatin were about 7.1-fold and 2.6-fold of those without DAAs.

Following co-administration of single dose of the 3-DAA combination of ABT-450/r, ABT-267 and ABT-333 with steady state of pravastatin or rosvastatin, the exposures ( $C_{max}$  and AUC) of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite and ritonavir were similar (only up to  $\pm$  20% change) to those achieved with single dose of the 3-DAA combination alone, except for ABT-450 exposures being 40% to 60% higher during co-administration with rosvastatin.

Following steady-state dosing with the 2-DAA combination of ABT-450/r 150/100 mg and ABT-267 25 mg, the steady state  $C_{max}$  and AUC of pravastatin were about 40% and 80% higher, respectively; while those of rosvastatin were about 160% and 30% higher, respectively.

Following co-administration of single dose of the 2-DAA combination of ABT-450/r and ABT-267 with steady state of pravastatin, the exposures ( $C_{max}$  and AUC) of ABT-267 were similar (only up to 6% lower), while those of ABT-450 and ritonavir were 30% to 45% higher than those achieved with single dose of the 2-DAA combination alone. Following co-administration of single dose of the 2-DAA combination of ABT-450/r and ABT-267 with steady state of rosvastatin, the exposures ( $C_{max}$  and AUC) of ABT-267 and ritonavir were similar (only up to  $\pm$

15% change), while those of ABT-450 were 20% to 40% higher than those achieved with single dose of the 2-DAA combination alone.

The regimens tested were generally well tolerated by the subjects. There was no pattern to the adverse events which were reported.

There were no clinically meaningful or significant trends noted among the vital signs or laboratory values in this study.

*Labeling recommendations: The proposed labeling in Section 7.3 is acceptable.*



**Drug-Drug Interaction Trial with Buprenorphine/Naloxone**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**Trial Design**

Phase 1, single-center, open-label, sequential, multiple-dose study to evaluate the coadministration of buprenorphine/naloxone with DAAs. Arm 1 included administration of the 3-DAA regimen of ABT-450/r, ABT-267 and ABT-333 with buprenorphine/naloxone (BUP/NAL). The DAAs and buprenorphine/naloxone were administered at the same time in Arm 1. Arm 2 included administration of the 3-DAA regimen which included a co-formulated tablet of ABT-450, ABT-267 and ritonavir (ABT-450/r/ABT-267) and ABT-333 followed by the administration of buprenorphine/naloxone, as a formulated film, approximately 4 hours after administration of the 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). For Arm 2, BUP/NAL was administered approximately 30 minutes after the start of a standardized lunch, which was approximately 4 hours following the administration of the DAAs.

### DAA Dosing:

For drugs dosed once daily and the morning dose of ABT-333, DAAs were administered approximately 30 minutes after the start of a standardized breakfast. For ABT-333, the evening dose was administered approximately 30 minutes after the start of an evening snack.

Two different ABT-450, ritonavir, and ABT-267 formulations were used in the study. Arm 1 was dosed with the (b) (4) tablet of ABT-450, ritonavir soft gelatin capsules (SGC) and the (b) (4) tablet of ABT-267. Arms 2 and 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 <sup>c</sup> , 1004, 1005, 1006, 1007, 1008 <sup>a</sup> , 1009 <sup>e</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-333 and 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, ABT-333, and ABT-267.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), ABT-267 (25 mg) and ABT-333 (400 mg twice daily) 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 (or doses that provided comparable systemic exposures) were also evaluated in the 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 (b) (4)
Potency (% of Label Claim)					
Manufacturing Site	AbbVie (b) (4)	(b) (4)	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL
Manufacturing Date					(b) (4)
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 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, ABT-333, ABT-333 M1, 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 %
ABT-333	5-3080	5	11.4,190, 2370	2 % to 3.9 %	-2.1 % to 0 %
ABT-333 M1	5.15-3180	5.15	11.7,195, 2440	2 % to 3.8 %	0.9 %-2.5 %
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.

	Mean ± SD (N = 36)	Min – Max
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 1:

#### ABT-450

Table 5 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 1.

ABT-450 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	530 ± 655	1230 ± 2250
T <sub>max</sub> (h)	5.6 ± 1.2	5.1 ± 0.32
AUC <sub>24</sub> (ng•h/mL)	2860 ± 3010	5880 ± 10200
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	8.62 ± 2.73
C <sub>24</sub> (ng/mL)	23.3 ± 25.6	37.0 ± 63.8

Formulation: ABT-450 SDD tablet, ritonavir SGC, ABT-267 HME tablet and ABT-333 tablet.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 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-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	1360 ± 876	1650 ± 639
T <sub>max</sub> (h)	4.8 ± 0.72	4.6 ± 0.70
AUC <sub>24</sub> (ng•h/mL)	7960 ± 5150	11300 ± 6460
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.58 ± 3.11
C <sub>24</sub> (ng/mL)	68.3 ± 57.7	90.0 ± 85.2

Formulation: ABT-450 (b) (4) tablet, ritonavir SGC, ABT-267 (b) (4) tablet and ABT-333 tablet.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-67 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 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-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	79.2 ± 19.7	83.2 ± 23.0
T <sub>max</sub> (h)	4.9 ± 0.79	4.9 ± 0.74
AUC <sub>24</sub> (ng•h/mL)	713 ± 161	989 ± 330
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	27.4 ± 9.43
C <sub>24</sub> (ng/mL)	11.2 ± 2.78	22.5 ± 10.7

Formulation: ABT-450 (b) (4) tablet, ritonavir SGC, ABT-267 (b) (4) tablet and ABT-333 tablet.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 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.

## ABT-333 and ABT-333 M1

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 in Arm1.



Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
<b>ABT-333</b>		
C <sub>max</sub> (ng/mL)	851 ± 312	953 ± 337
T <sub>max</sub> (h)	4.3 ± 1.1	4.0 ± 0.94
AUC <sub>12</sub> (ng•h/mL)	5500 ± 2100	6250 ± 2480
C <sub>12</sub> (ng/mL)	243 ± 128	231 ± 97.2
C <sub>24</sub> (ng/mL)	221 ± 91.8	261 ± 143
<b>ABT-333 M1</b>		
C <sub>max</sub> (ng/mL)	536 ± 268	541 ± 316
T <sub>max</sub> (h)	4.9 ± 0.79	5.0 ± 0.47
AUC <sub>12</sub> (ng•h/mL)	3000 ± 1590	3070 ± 1720
C <sub>12</sub> (ng/mL)	130 ± 76.0	95.2 ± 47.3
C <sub>24</sub> (ng/mL)	96.5 ± 26.1	100 ± 44.8

Formulation: ABT-450 (b) (4) tablet, ritonavir SGC, ABT-267 (b) (4) tablet and ABT-333 tablet.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 and buprenorphine/naloxone.

Note: t<sub>1/2</sub> could not be determined for ABT-333 or ABT-333 M1 because there were less than three time-points in the terminal phase with plasma concentrations of ABT-333 or ABT-333 M1 below the LLOQ.

ABT-333 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-333 with multiple dosing.

BUP and nor-BUP (Arm 1)

Table 9 shows the mean ± SD pharmacokinetic parameters of BUP and nor-BUP in Arm 1.



Pharmacokinetic Parameter (Unit)	Day 8	Day 9	Day 22
	Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
<b>Buprenorphine</b>			
C <sub>max</sub> (pg/mL)	12000 ± 10700	13600 ± 17300	15300 ± 17100
C <sub>max</sub> /Dose (pg/mL/mg)	700 ± 443	769 ± 688	882 ± 676
T <sub>max</sub> (h)	1.8 ± 0.72	1.6 ± 0.43	1.9 ± 0.53
AUC <sub>24</sub> (pg•h/mL)	82800 ± 64900	112000 ± 128000	136000 ± 167000
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	4940 ± 2750	6440 ± 5060	7790 ± 6670
C <sub>24</sub> (pg/mL)	1920 ± 1980	2650 ± 2300	3630 ± 4270
C <sub>24</sub> /Dose (pg/mL/mg)	111 ± 79.2	158 ± 95.1	213 ± 174
<b>Norbuprenorphine</b>			
C <sub>max</sub> (pg/mL)	10600 ± 14100	16100 ± 25800	16000 ± 29400
C <sub>max</sub> /Dose (pg/mL/mg)	606 ± 575	881 ± 1040	834 ± 1180
T <sub>max</sub> (h)	3.8 ± 6.4	9.5 ± 7.8	6.9 ± 7.2
AUC <sub>24</sub> (pg•h/mL)	168000 ± 226000	276000 ± 397000	296000 ± 552000
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	9510 ± 9090	15500 ± 16100	15400 ± 22100
C <sub>24</sub> (pg/mL)	7580 ± 10600	10700 ± 11900	10700 ± 17100
C <sub>24</sub> /Dose (pg/mL/mg)	426 ± 430	624 ± 493	583 ± 675

Formulation: ABT-450 (b) (4) tablet, ritonavir SGC, ABT-267 (b) (4) tablet and ABT-333 tablet.

Arm 1: Day 8: Daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 and buprenorphine/naloxone.

Buprenorphine dose in Arm 1, median (min – max): 16 (8 – 24) mg.

Norbuprenorphine was dose-normalized using buprenorphine dose.

Plasma concentrations of buprenorphine in one subject (1009) on study day 22 were 2 to 3 times higher than other subjects in Arm 1 and plasma concentrations of norbuprenorphine in the same subject were up to 10 times higher (on study days 8 and 9). This may explain, in part, the high % CV in the mean BUP pharmacokinetic parameters on day 22 (% CV was 77 % and 86 % for dose normalized C<sub>max</sub> and AUC, respectively) and in the mean nor-BUP pharmacokinetic parameters on day 8 (% CV was 95 % and 96 % for dose normalized C<sub>max</sub> and AUC, respectively) and day 9 (% CV was 118 % and 104 % for dose normalized C<sub>max</sub> and AUC, respectively).

NAL (Arm 1)

Table 10 shows the mean ± SD pharmacokinetic parameters of NAL in Arm 1.

Naloxone Pharmacokinetic Parameter (Unit)	Day 8	Day 9	Day 22
	Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (pg/mL)	312 ± 277	330 ± 357	329 ± 319
C <sub>max</sub> /Dose (pg/mL/mg)	73.0 ± 46.0	74.0 ± 57.1	77.0 ± 55.8
T <sub>max</sub> (h)	1.1 ± 0.42	1.0 ± 0.26	1.2 ± 0.41
AUC <sub>t</sub> (pg·h/mL)	738 ± 628	811 ± 839	827 ± 731
AUC <sub>t</sub> /Dose (pg·h/mL/mg)	174 ± 119	184 ± 140	205 ± 164

Formulation: ABT-450 (b) (4) tablet, ritonavir SGC, ABT-267 (b) (4) tablet and ABT-333 tablet.

Arm 1: Day 8: Daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 9: First day of dosing ABT-450/r + ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 1: Day 22: Steady-state dosing of ABT-450/r + ABT-267 + ABT-333 and buprenorphine/naloxone.

Naloxone dose in Arm 1, median (min – max): 4 (2 – 6) mg.

Note: AUC<sub>t</sub> was calculated instead of AUC<sub>24</sub> because the last time point with measurable concentration varied between subjects and study days. AUC<sub>t</sub> is the most accurate estimate of the total exposure of naloxone within 24 hours.

## Arm 2

## ABT-450

Table 11 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 2.

ABT-450 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	1270 ± 1300	2690 ± 3040
T <sub>max</sub> (h)	4.7 ± 0.90	4.2 ± 0.92
AUC <sub>24</sub> (ng·h/mL)	4800 ± 4210	15500 ± 28100
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.27 ± 1.79
C <sub>24</sub> (ng/mL)	24.7 ± 25.2	54.9 ± 128

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 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 suggests accumulation of ABT-450 following multiple doses.

## Ritonavir

Table 12 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 2.

Ritonavir Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	1170 ± 526	1670 ± 505
T <sub>max</sub> (h)	4.6 ± 0.93	4.2 ± 0.79
AUC <sub>24</sub> (ng•h/mL)	7350 ± 4000	10500 ± 4560
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.13 ± 1.57
C <sub>24</sub> (ng/mL)	46.0 ± 40.3	47.0 ± 23.4

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 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 ritonavir exposures on Day 22 compared to Day 9 suggests accumulation of ritonavir following multiple doses.

## ABT-267

Table 13 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 2.

ABT-267 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (ng/mL)	90.2 ± 26.9	106 ± 27.9
T <sub>max</sub> (h)	5.3 ± 0.65	4.6 ± 0.70
AUC <sub>24</sub> (ng•h/mL)	776 ± 200	973 ± 203
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	22.1 ± 6.28
C <sub>24</sub> (ng/mL)	14.3 ± 4.09	18.8 ± 5.33

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 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.

## ABT-333 and ABT-333 M1 Metabolite

Table 14 shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 in Arm 2.

Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
<b>ABT-333</b>		
C <sub>max</sub> (ng/mL)	1350 ± 487	1640 ± 518
T <sub>max</sub> (h)	4.0 ± 1.2	3.3 ± 0.95
AUC <sub>12</sub> (ng•h/mL)	8420 ± 2880	10100 ± 3450
C <sub>12</sub> (ng/mL)	310 ± 124	323 ± 144
C <sub>24</sub> (ng/mL)	310 ± 147	248 ± 151
<b>ABT-333 M1</b>		
C <sub>max</sub> (ng/mL)	914 ± 423	1020 ± 434
T <sub>max</sub> (h)	4.7 ± 1.0	4.3 ± 1.1
AUC <sub>12</sub> (ng•h/mL)	5220 ± 2770	6310 ± 3640
C <sub>12</sub> (ng/mL)	216 ± 156	210 ± 201
C <sub>24</sub> (ng/mL)	190 ± 144	130 ± 124

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 and buprenorphine/naloxone.

Note: t<sub>1/2</sub> could not be determined for ABT-333 or ABT-333 M1 because there were less than three time-points in the terminal phase with plasma concentrations of ABT-333 or ABT-333 M1 above the LLOQ.

ABT-333 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-333 with multiple dosing.

BUP and nor-BUP (Arm 2)

Table 15 shows the mean ± SD pharmacokinetic parameters of BUP and nor-BUP in Arm 2.

Pharmacokinetic Parameter (Unit)	Day 8 Buprenorphine/naloxone QD (N = 11)	Day 9	Day 22
		ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
Buprenorphine			
C <sub>max</sub> (pg/mL)	5020 ± 3290	12600 ± 7840	10000 ± 5090
C <sub>max</sub> /Dose (pg/mL/mg)	341 ± 232	816 ± 439	681 ± 323
T <sub>max</sub> (h)	1.9 ± 1.1	1.7 ± 0.40	1.6 ± 0.64
AUC <sub>24</sub> (pg•h/mL)	39300 ± 21500	80500 ± 47000	80800 ± 40800
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	2720 ± 1600	5300 ± 2710	5570 ± 2930
C <sub>24</sub> (pg/mL)	705 ± 443	1640 ± 1140	2280 ± 1500
C <sub>24</sub> /Dose (pg/mL/mg)	49.3 ± 32.0	110 ± 65.5	162 ± 103
Norbuprenorphine			
C <sub>max</sub> (pg/mL)	4550 ± 3260	9460 ± 7040	8000 ± 4840
C <sub>max</sub> /Dose (pg/mL/mg)	296 ± 195	603 ± 420	540 ± 307
T <sub>max</sub> (h)	3.5 ± 2.2	2.9 ± 1.3	2.8 ± 0.72
AUC <sub>24</sub> (pg•h/mL)	78700 ± 53000	159000 ± 115000	131000 ± 83300
AUC <sub>24</sub> /Dose (pg•h/mL/mg)	5160 ± 3360	10300 ± 7280	8950 ± 5520
C <sub>24</sub> (pg/mL)	2890 ± 2020	6350 ± 4740	5930 ± 4250
C <sub>24</sub> /Dose (pg/mL/mg)	194 ± 133	412 ± 292	404 ± 262

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Day 8 and Day 22: C<sub>24</sub> = C<sub>0</sub>.

Arm 2: Day 8: Daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 and buprenorphine/naloxone.

Buprenorphine dose in Arm 2, median (min – max): 16 (4 – 24) mg.

Norbuprenorphine was dose-normalized using buprenorphine dose.

NAL (Arm 2)

Table 16 shows the mean ± SD pharmacokinetic parameters of NAL in Arm 2.

Naloxone Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD		
	Day 8 Buprenorphine/naloxone QD (N = 11)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 11)	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Buprenorphine/naloxone QD (N = 10)
C <sub>max</sub> (pg/mL)	293 ± 239	325 ± 204	328 ± 251
C <sub>max</sub> /Dose (pg/mL/mg)	75.2 ± 55.4	87.9 ± 57.4	93.6 ± 76.6
T <sub>max</sub> (h)	0.66 ± 0.23	0.86 ± 0.32	0.75 ± 0.35
AUC <sub>t</sub> (pg•h/mL)	555 ± 383	667 ± 398	670 ± 510
AUC <sub>t</sub> /Dose (pg•h/mL/mg)	139 ± 99.5	171 ± 90.6	180 ± 154

Formulation: ABT-450/r/ABT-267 co-formulated tablet and ABT-333 tablet.

Day 8 and Day 22: C<sub>24</sub> = C<sub>0</sub>.

Arm 2: Day 8: Daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 9: First day of dosing ABT-450/r/ABT-267 + ABT-333 with daily dosing of buprenorphine/naloxone at steady state.

Arm 2: Day 22: Steady-state dosing of ABT-450/r/ABT-267 + ABT-333 and buprenorphine/naloxone.

Naloxone dose in Arm 2, median (min – max): 4 (1 – 6) mg.

Note: AUC<sub>t</sub> was calculated instead of AUC<sub>24</sub> because the last time point with measurable concentration varied between subjects and study days. AUC<sub>t</sub> is the most accurate estimate of the total exposure of naloxone within 24 hours.

## Statistical Evaluation of the Pharmacokinetic Parameters

### Buprenorphine

Fig 1 shows the least squares mean (LSM) ratios and 90 % confidence intervals (CI) for Buprenorphine (dose normalized C<sub>max</sub>, AUC, and C<sub>24</sub>)

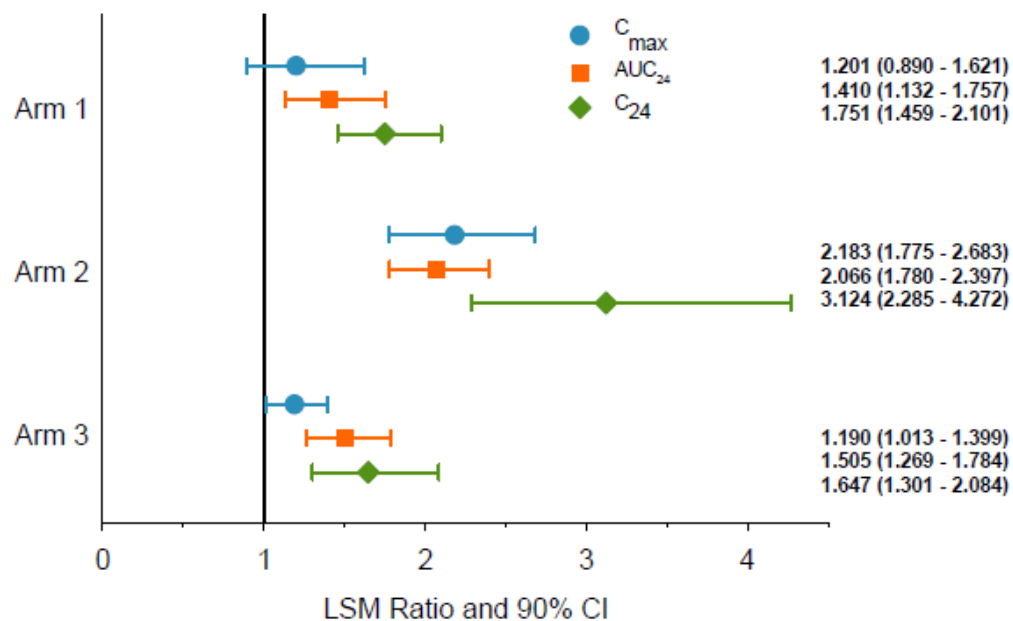
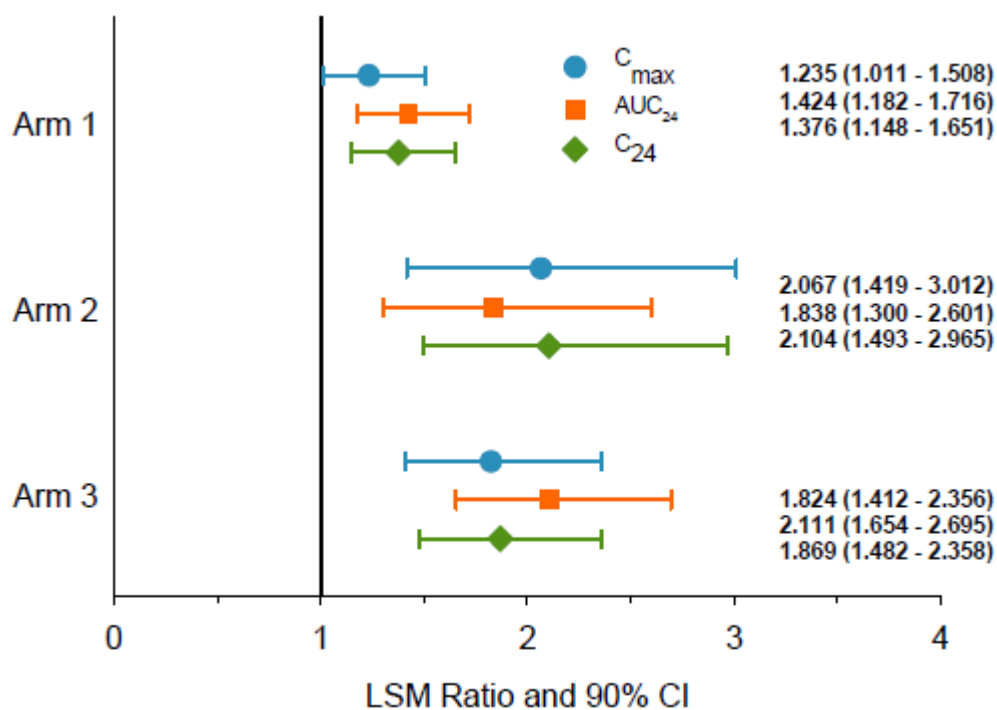


Fig 2 shows the least squares mean (LSM) ratios and 90 % confidence intervals (CI) for Nor-BUP (dose normalized  $C_{max}$ , AUC, and  $C_{24}$ )



## Pharmacodynamic Assessments

Overall, there were no changes in the pupil response, SOWS response, and the DDQ response after administration of the 3-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 ABT-333 (Arm 2) and buprenorphine/naloxone:

- Increased the mean  $C_{max}$  and AUC of buprenorphine by 118 % and 106 %, respectively.
- Increased the mean  $C_{max}$  and AUC of norbuprenorphine by 106 % and 84 %, respectively.
- Cross study comparison of ABT-450, ABT-267, ABT-333, and ABT-333 M1 exposures suggested no impact of BUP/NAL on the pharmacokinetics of the individual components of the 3-DAA regimen.

## Conclusion

When the 3-DAA regimen is co-administered with buprenorphine/naloxone, clinical monitoring for sedation and cognitive effects is recommended and dose reduction of buprenorphine may be considered.



**Drug-Drug Interaction Trial with Cyclosporine**  
**Reviewer: Seong Jang, Ph.D.**

**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, Safety and Tolerability of Cyclosporine in Healthy Subjects (M13-103)**

**Study period:** 27 February 2012 to 27 August 2012

**Objectives:** The objectives of this study were:

- To evaluate the effect of the combination of ABT-450/r and ABT-333 and/or ABT-267 on the pharmacokinetics of cyclosporine (CsA) administered as a single dose in healthy subjects.
- To determine safety and tolerability of a single dose of cyclosporine when administered with ABT-450/r and ABT-333 and/or ABT-267 at steady state.
- To determine the effect of a single dose of cyclosporine on the pharmacokinetics of ABT-450/r and ABT-333 and/or ABT-267 at steady state.

*Reviewer's comments: The effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267 is not clinically meaningful because the PK of steady state CsA (i.e., multiple dose) is substantially different from that of a single dose CsA. In addition, the CsA dose (30 mg) is not clinically relevant; the recommended dose is 300 mg BID as an initial dose. Thus, the results of this study (i.e., the effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267) are not informative to predict the effect of clinically relevant CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267 unless the PK of ABT-450/r and ABT-333 and/or ABT-267 were affected substantially due to the single dose of CsA so that it is obvious to recommend a contraindication with tacrolimus and DAAs. Thus, the effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267 was not reviewed. In this study, a single dose of CsA 30 mg increased the AUC of ABT-450 by 72 % and decreased the AUC of ABT-333 by 30%.*

**Methodology:**

This was a Phase 1, single center, open-label, sequential, multiple-dose. Adult male and female subjects in general good health were selected to participate in the study according to the selection criteria. Arms were enrolled sequentially; 12 subjects were enrolled per arm, each arm consisting of two periods. Subjects in each arm were to complete both Period 1 and Period 2.

Study drug was administered as follows:

- Regimen A** Cyclosporine 100 mg single dose
- Regimen B** Cyclosporine 10 mg on Study Days 1 and 15. ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) from Study Days 1 through 21
- Regimen C** Cyclosporine 100 mg single dose
- Regimen D** Cyclosporine 10 mg on Study Days 1 and 15. ABT-267 25 mg QD + ABT-450/r 150/100 mg QD from Study Days 1 through 21
- Regimen E** Cyclosporine 100 mg single dose

**Regimen F** Cyclosporine 30 mg on Study Days 1 and 15. ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + ABT-267 25 mg QD from Study Days 1 through 21

In Period 1 of each arm, each dose of cyclosporine tablet was taken orally with approximately 240 mL of water following a minimum 10-hour fast and approximately 4 hours before lunch. On Study Days 1 and 15 of Period 2 of each arm, cyclosporine suspension was prepared and administered. All other doses of study drug were taken orally with approximately 200 mL of water approximately 30 minutes after the start of breakfast for all morning doses and orally with approximately 240 mL of water approximately 30 minutes after the start of the evening snack for the evening doses.

Blood samples for cyclosporine were collected by venipuncture prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 18, 24, and 48 after dosing in Period 1, Study Day 1 and prior to dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 18, 24, 48, 72, 96, 120, and 144 hours in Period 2, Study Day 1 and 15. Blood samples for ABT-267, ABT-450, ritonavir, and ABT-333, ABT-333 M1 were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 15, 18, and 24 hours after dosing on Study Day 14 and 15. Trough samples were collected prior to morning DAA doses on Days 9, 12, 17, 19, 21 and 24 hours after DAA dosing (Day 22).

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were determined using a validated protein precipitation and on-line solid phase extraction method with liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). No metabolites for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were assayed for this study. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were established at 0.595, ng/mL 4.91 ng/mL, 0.424 ng/mL, 4.53 ng/mL and 4.72 ng/mL, respectively, using a 100 µL plasma sample.

Blood concentrations of CsA were determined using a validated liquid chromatography method with liquid/liquid extraction with LC-MS/MS. The LLOQ for CsA was established at 5.0 ng/mL using a 200 µL blood sample.

**Number of Subjects (Planned and Analyzed):**

Planned: 48; Entered: 36; Completed: 35; Evaluated for Safety: 36; Evaluated for Pharmacokinetics: 34.

For the 36 subjects who participated in the study, the mean age was 31.1 years (ranging from 20 to 54 years), the mean weight was 79.5 kg (ranging from 56 to 103 kg) and the mean height was 174 cm (ranging from 158 to 190 cm).

**Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram (ECG). Females were either postmenopausal for at least 2 years or surgically sterile and were not pregnant. Males were either surgically sterile or practicing at least one of the acceptable methods of birth control. The subject's Body Mass Index (BMI) was  $\geq 18$  to  $< 30$  kg/m<sup>2</sup>.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

	ABT-267	ABT-450	Ritonavir	ABT-333	Cyclosporine (Neoral)	Cyclosporine (Neoral)
Dosage Form	(b) (4) Tablet	(b) (4) Tablet	SGC	Tablet	SGC	Solution
Strength (mg)	25 mg	50 mg	100 mg	400 mg	100 mg	100 mg/mL of solution
Bulk Product Lot Number	11-002033	11-000781	11-005635	11-002720	12-001335 & 12-003897	12-001330
Potency (% of Label Claim)	(b) (4)				Unknown	Unknown
Manufacturing Site	AbbVie (b) (4)	AbbVie LC	AbbVie LC	AbbVie LC	Manufactured for/by Novartis	Manufactured for/by Novartis
Manufacturing Date	(b) (4)				Unknown	Unknown
Finishing Lot Number:	12-000519 & 12-003621	12-000521 & 12-003622	12-000524 & 12-003623	12-000522	12-000938 & 12-003832	12-000936 & 12-003830
Expiration/Retest Date:	(b) (4)					

(b) (4) SGC = soft gelatin capsule

. AbbVie, (b) (4)  
 b. AbbVie, Lake County, USA.

**Duration of Treatment:**

Dosing for Arm 1 began on 15 March 2012 and ended on 11 April 2012. Dosing for Arm 2 began on 17 May 2012 and ended on 13 June 2012. Dosing for Arm 3 began on 19 July 2012 and ended on 15 August 2012.

**Criteria for Evaluation:**

**Pharmacokinetic:** Values for the pharmacokinetic parameters of ABT-267, ABT-450, ritonavir, ABT-333, ABT-333 M1 and CsA were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  ( $T_{max}$ ), and the pre-dose plasma concentration ( $C_{trough}$ ,  $C_{24}$ ,  $C_{12}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ( $AUC_{24}$ ), the AUC from time 0 to 12 hours ( $AUC_{12}$ ), for ABT-333 and ABT-333 M1, the AUC from time 0 to the last measureable concentration ( $AUC_t$ ), and AUC from time 0 to infinity ( $AUC_{inf}$ ,  $AUC_{\infty}$ ) for CsA, the dose-normalized  $C_{max}$ ,  $C_{24}$ ,  $C_{12}$ ,  $AUC_t$ , and  $AUC_{inf}$ , the apparent terminal phase elimination rate constant ( $\beta$ ), and the terminal phase elimination half-life ( $t_{1/2}$ ) for CsA.

The effect of single dose of CsA on the steady state exposures of 2 DAAs or 3 DAAs was evaluated by comparing the 2-DAA or 3-DAA exposures (Study Day 15) when the 2 DAAs or 3 DAAs in the presence of CsA to the 2 DAAs or 3 DAAs steady state exposures (Study Day 14) where the the 2 DAAs or 3 DAAs without CsA. The effect of single doses of 2 DAAs or 3 DAAs on the single dose of CsA was evaluated by comparing Study Day 1 (Period 2) dose-normalized CsA exposures when CsA was administered with 2 DAAs or 3 DAAs to Study Day 1 (Period 1)

dose-normalized exposures when CsA was administered alone. The effect of steady state 2 DAAs or 3 DAAs on the single dose of CsA was evaluated by comparing Study Day 15 (Period 2) dose-normalized CsA exposures when CsA was administered with 2 DAAs or 3 DAAs to Study Day 1 (Period 1) dose-normalized exposures when CsA was administered alone.

**Safety Endpoints:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECG and laboratory tests..

### **Statistical Methods:**

**Pharmacokinetic:** To assess the effect of ABT-450/r, ABT-333 and ABT-267 on cyclosporine, a repeated measure analysis was performed for the natural logarithms of cyclosporine  $C_{max}$ , AUC and  $C_{trough}$  utilizing data from Period 1 Study Day 1, and Period 2 Study Days 1 and 15 from Arms 1, 2, and 3. Arm 4 was not run. A separate analysis was performed for Arms 1, 2, and 3. The model had day as a fixed effect with three levels ('Period 1 study day 1', 'Period 2 study day 1' and 'Period 2 study day 15') and subject as a random effect.  $C_{max}$ , AUC and  $C_{trough}$  ratios were estimated by taking the ratio of 'Period 2 Study Day 1' and 'Period 1 Study Day 1' and the ratio of 'period 2 Study Day 15' and 'Period 1 Study Day 1' values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

To assess the effect of cyclosporine on ABT-450/r, ABT-333 and ABT-267, a repeated measure analysis was performed for the natural logarithms of ABT-450/r, ABT-333 and ABT-267  $C_{max}$ , AUC and  $C_{trough}$  utilizing data from Period 2 Study Days 14 and 15 from Arms 1, 2, and 3. A separate analysis was performed for Arms 1, 2, and 3. The model had day as a fixed effect with two levels ('period 2 study day 14' and 'period 2 study day 15') and subject as a random effect. Additionally,  $C_{max}$ , AUC and  $C_{trough}$  ratios were estimated by taking the ratio of 'period 2 study day 15' and 'period 2 study day 14' values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

## Results:

### Pharmacokinetics:

The effects of the combination of ABT-450/r and ABT-333 and/or ABT-267 on the pharmacokinetics of cyclosporine (CsA) administered as a single dose in healthy subjects are summarized in Tables 1-3. Repeated measures analyses were performed for the natural logarithm of dose-normalized CsA  $C_{\max}$ ,  $C_{24}$ , and AUC to assess the effect of DAAs on CsA.

**Table 1.** The effect of ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) on the PK of CsA administered as a single dose in healthy subjects (Arm 1)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
$C_{\max}/D$ (ng/mL/mg)	6.23	5.71	0.92	0.79 – 1.07
$AUC_t/D$ (ng•h/mL/mg)	19.0	73.3	3.86	3.34 – 4.48
$AUC_{inf}/D$ (ng•h/mL/mg)	20.1	90.0	4.49	3.93 – 5.12
$C_{24}/D$ (ng/mL/mg)	0.09	1.20	13.5	12.1 – 15.0

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Period 1, Day 1 (P1D1): CsA 100 mg single dose.

<sup>c</sup>. Period 2, Day 15 (P2D15): CsA 10 mg single dose + steady-state DAAs (ABT-450/r 150/100 mg QD + ABT-333 400 mg BID).

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Table 2.** The effect of ABT-267 25 mg QD + ABT-450/r 150/100 mg QD on the PK of CsA administered as a single dose in healthy subjects (Arm 2)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
$C_{\max}/D$ (ng/mL/mg)	5.90	4.87	0.83	0.72 – 0.94
$AUC_t/D$ (ng•h/mL/mg)	17.2	64.2	3.74	3.19 – 4.39
$AUC_{inf}/D$ (ng•h/mL/mg)	18.1	77.5	4.28	3.66 – 5.01
$C_{24}/D$ (ng/mL/mg)	0.08	1.00	12.8	10.6 – 15.6

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Period 1, Day 1 (P1D1): CsA 100 mg single dose.

<sup>c</sup>. Period 2, Day 15 (P2D15): CsA 10 mg single dose + steady state DAAs (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD).

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Table 3.** The effect of ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + ABT-267 25 mg QD on the PK of CsA administered as a single dose in healthy subjects (Arm 3)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
$C_{\max}/D$ (ng/mL/mg)	6.22	6.29	1.01	0.85 – 1.20
$AUC_t/D$ (ng•h/mL/mg)	19.7	112	5.69	4.67 – 6.93
$AUC_{inf}/D$ (ng•h/mL/mg)	20.7	120	5.82	4.73 – 7.14
$C_{24}/D$ (ng/mL/mg)	0.082	1.29	15.8	13.8 – 18.1

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Period 1, Day 1 (P1D1): CsA 100 mg single dose.

<sup>c</sup>. Period 2, Day 15 (P2D15): CsA 30 mg single dose + steady state DAAs (ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID).

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: Regardless of combination of DAAs (two or three), the  $C_{24}$  and AUC of CsA increased approximately 13- to 14-fold and 4- to 6-fold, respectively, indicating that ABT-450 and ritonavir may play major role in interacting with CsA (i.e., probably by inhibiting the CYP 3A4-mediated metabolism of CsA). It should be noted that the fold-changes in  $C_{24}$  and AUC are not similar so that the recommended target range of  $C_{24}$  for therapeutic monitoring of CsA cannot be used when CsA is co-administered with DAAs. Accordingly, it is recommended that the coadministration of DAAs with CsA be contraindicated. However, if unmet medical needs to use DAAs in organ transplant patients are justified, then we recommend* (b) (4)

#### Safety Results:

The DAAs coadministered with CsA in all the arms of this study were well tolerated by the subjects. Adverse events were infrequent and mostly mild and self-limited, with no pattern observed to the adverse events which were reported. Headache, somnolence, and insomnia were the only treatment-emergent adverse event reported in more than one subject for the study. No deaths or other serious adverse events were reported in this study. There were no clinically meaningful or significant trends noted among the potentially clinically significant laboratory values in this study.

#### **Conclusions:**

##### Two DAA Combination + CsA

Dose-normalized CsA  $C_{24}$ ,  $AUC_t$  and  $AUC_{inf}$  in the presence of the 2-DAA combination (either ABT-450/r/ABT-333 or ABT-450/r/ABT-267) at steady state were 13- to 14-fold, 3.7- to 3.9-fold and 4.3- to 4.5-fold, respectively, of CsA exposures when administered alone.

##### Three DAA Combination + CsA

Dose-normalized CsA  $C_{24}$ ,  $AUC_t$  and  $AUC_{inf}$  in the presence of 3-DAA combination at steady state were 15.7-fold, 5.6-fold and 5.8-fold of the CsA exposures when administered alone, respectively.

The DAAs co-administered with CsA in all the arms of this study were well tolerated by the subjects. Adverse events were infrequent and mostly mild and self-limited: there was no pattern observed in the adverse events or the laboratory abnormalities reported. No deaths or other serious adverse events were reported in this study.

The sponsor made the following conclusion and labeling recommendation regarding co-administration of DAAs with CsA.

(b) (4)

(b) (4)

Sponsor's labeling recommendation:

(b) (4)

*Reviewer's conclusion and labeling recommendation:*

*As mentioned above, the fold-change in the  $C_{24}$  of CsA due to co-administration with DAAs are not similar to that in the AUC so that the recommended target range of  $C_{24}$  for therapeutic monitoring of CsA cannot be used when CsA is co-administered with DAAs. Although  $C_{24}$  of CsA is attained within the recommended concentration range, the AUC of CsA would be much lower when CsA is co-administered with DAAs compared with when CsA is administered alone. Accordingly, it is recommended that the co-administration of DAAs with CsA be contraindicated. However, if unmet medical needs to use DAAs in organ transplant patients are justified, then we recommend that*

(b) (4)

*The effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267 is not clinically meaningful because the PK of steady state CsA (i.e., multiple dose) is substantially different from that of a single dose CsA. In addition, the CsA dose (100 mg) in this study is not clinically relevant; the recommended dose is 300 mg BID as an initial dose. Thus, the results of this study (i.e., the effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267) are not informative to predict the effect of clinically relevant CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267. Thus, the effect of a single dose of CsA on the PK of ABT-450/r and ABT-333 and/or ABT-267 in this study do not support the sponsor's conclusion*

(b) (4)

**Drug-Drug Interaction Trial with Tacrolimus**  
**Reviewer: Seong Jang, Ph.D.**

**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, Safety and Tolerability of Tacrolimus in Healthy Subjects (M13-491)**

**Study period:** 01 March 2012 to 19 October 2012

**Objectives:** The objectives of this study were:

- To evaluate the effect of the combination of ABT-450/r and ABT-333 and/or ABT-267 on the pharmacokinetics of tacrolimus administered as a single dose in healthy subjects.
- To determine safety and tolerability of a single dose of tacrolimus when administered with ABT-450/r and ABT-333 and/or ABT-267 at steady state.
- To determine the effect of a single dose of tacrolimus on the pharmacokinetics of ABT-450/r and ABT-333 and/or ABT-267 at steady state.

*Reviewer's comments: The effect of a single dose of tacrolimus on the PK of ABT-450/r and ABT-333 and/or ABT-267 is not clinically meaningful because the PK of steady state tacrolimus (i.e., multiple doses) is substantially different from that of a single dose tacrolimus. In addition, the tacrolimus dose (0.5 mg) is not clinically relevant; the recommended dose is 0.1 to 0.15 mg/kg BID as an initial dose. Thus, the results of this study (i.e., the effect of a single dose of tacrolimus on the PK of ABT-450/r and ABT-333 and/or ABT-267) in this study are not informative to predict the effect of clinically relevant tacrolimus on the PK of ABT-450/r and ABT-333 and/or ABT-267 unless the PK of ABT-450/r and ABT-333 and/or ABT-267 were affected substantially due to the single dose of tacrolimus so that it is obvious to recommend a contraindication with tacrolimus and DAAs. A single dose of tacrolimus 0.5 mg decreased the  $C_{max}$  and  $AUC_{24}$  of ABT-450 by 50% and 40%, respectively in this study. Thus, the effect of a single dose of tacrolimus on the PK of ABT-450/r and ABT-333 and/or ABT-267 was not reviewed.*

**Methodology:**

This was a Phase 1, single center, open-label, sequential, multiple-dose. Adult male and female subjects in general good health were selected to participate in the study according to the selection criteria. Arms were enrolled sequentially; 12 subjects were enrolled per arm, each arm consisting of two periods. Subjects in each arm were to complete both Period 1 and Period 2.

Study drug was administered as follows:

- Regimen A** Tacrolimus 2 mg single dose followed by a washout interval of at least 14 days
- Regimen B** ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) from Days 1 to 28, tacrolimus 0.5 mg single dose on Day 15
- Regimen C** Tacrolimus 2 mg single dose followed by a washout interval of at least 14 days
- Regimen D** ABT-267 25 mg QD + ABT-450/r 150/100 mg QD from Study Days 1 to 28, tacrolimus 0.5 mg single dose on Day 15.
- Regimen E** Tacrolimus 2 mg single dose followed by a washout interval of at least 14 days



**Regimen F** ABT-333 400 mg BID + ABT-267 25 mg QD + ABT-450/r 150/100 mg QD from Days 1 to 28, tacrolimus 2 mg single dose on Day 15.

In Period 1, each dose of tacrolimus was taken orally with approximately 240 mL of water following a minimum 10-hour fast and approximately 4 hours before lunch. In Period 2, all doses of study drug were taken orally with approximately 240 mL of water approximately 30 minutes after the start of breakfast for all morning doses and approximately 30 minutes after the start of the evening snack for the evening doses of all study medications.

Blood samples for tacrolimus were collected by venipuncture prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 after dosing in Period 1, Study Day 1 and prior to dose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 hours in Period 2, Study 15. Trough samples were collected prior to morning tacrolimus doses on Days 2 to 7 in Period 1 and Days 16 to 28 in Period 2. Blood samples for ABT-267, ABT-450, ritonavir, and ABT-333, ABT-333 M1 metabolite (A1041392) (ABT-333 M1) were collected by venipuncture prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 15 and 18 hours after dosing on Study Day 14 and prior to dosing (0 hour) and at 1, 2, 3, 4, 6, 9, 12, 15, 18 and 24 hours after dosing on Study Day 15. Trough samples were collected prior to morning direct-acting antiviral agent (DAA) doses on 9, 12, 17, 19, 21, 23, 27 and a sample on Study Day 29, 24 hours after DAA dose on Study Day 28.

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were determined using a validated protein precipitation and on-line solid phase extraction method with liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). No metabolites for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were assayed for this study. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were established at 0.595 ng/mL, 4.91 ng/mL, 0.424 ng/mL, 4.53 ng/mL and 4.72 ng/mL, respectively, using a 100 µL plasma sample.

Blood concentrations of tacrolimus were determined using a validated protein precipitation followed by a liquid/liquid extraction and high performance liquid chromatography method with tandem mass spectrometric detection. The LLOQ for tacrolimus was established at 0.250 ng/mL using a 125 µL blood sample.

**Number of Subjects (Planned and Analyzed):**

Planned: 48; Entered: 36; Completed: 35; Evaluated for Safety: 36; Evaluated for Pharmacokinetics: 35.

For the 36 subjects who participated in the study, the mean age was 37.0 years (ranging from 24 to 55 years), the mean weight was 82.6 kg (ranging from 59 to 101 kg) and the mean height was 176 cm (ranging from 154 to 194 cm).

**Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram (ECG). Females were either postmenopausal for at least 2 years or surgically sterile and were not pregnant. Males were

either surgically sterile or practicing at least one of the acceptable methods of birth control. The subject's Body Mass Index (BMI) was  $\geq 18$  to  $< 30 \text{ kg/m}^2$ .

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

	ABT-267	ABT-450	Ritonavir	ABT-333	Tacrolimus	Tacrolimus
Dosage Form	(b) (4) Tablet	(b) (4) Tablet	SGC	Tablet	Capsule	Capsule
Strength (mg)	25 mg	50 mg	100 mg	400 mg	0.5 mg	1 mg
Bulk Product Lot Number	11-002033	11-000781	11-005635	11-000511	12-000662	12-000686
Potency (% of Label Claim)	(b) (4)				Unknown	Unknown
Manufacturing Site	AbbVie (b) (4)	AbbVie LC <sup>b</sup>	AbbVie LC <sup>b</sup>	AbbVie LC <sup>b</sup>	Manufactured for/by Astellas	Manufactured for/by Astellas
Manufacturing Date	(b) (4)				Unknown	Unknown
Finishing Lot Number:	12-000610 & 12-004817	12-000609 & 12-004816	12-000612 & 12-004821	12-000608	12-000688	12-000687 & 12-000662
Expiration/ Retest Date:	(b) (4)					

(b) (4) SGC = soft gelatin capsule

<sup>a</sup>. AbbVie (b) (4)

<sup>b</sup>. AbbVie, Lake County, USA.

**Duration of Treatment:**

Dosing for Arm 1 began on 14 March 2012 and ended on 24 April 2012. Dosing for Arm 2 began on 22 May 2012 and ended on 02 July 2012. Dosing for Arm 3 began on 23 August 2012 and ended on 03 October 2012.

**Criteria for Evaluation:**

Pharmacokinetic: Values for the pharmacokinetic parameters of ABT-267, ABT-450, ritonavir, ABT-333, ABT-333 M1 and tacrolimus were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{\max}$ ), the time to  $C_{\max}$  ( $T_{\max}$ ), and the pre-dose plasma concentration ( $C_{\text{trough}}$ ,  $C_{24}$ ,  $C_{12}$ ), the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ( $\text{AUC}_{24}$ ), the AUC from time 0 to 12 hours ( $\text{AUC}_{12}$ ), for ABT-333 and ABT-333 M1, the AUC from time 0 to the last measureable concentration ( $\text{AUC}_t$ ), and AUC from time 0 to infinity ( $\text{AUC}_{\text{inf}}$ ,  $\text{AUC}_{\infty}$ ) for tacrolimus, the dose-normalized  $C_{\max}$ ,  $C_{24}$ ,

$C_{12}$ ,  $AUC_t$ , and  $AUC_{inf}$ , and the apparent terminal phase elimination rate constant ( $\beta$ ), and the terminal phase elimination half-life ( $t_{1/2}$ ) for tacrolimus.

The effect of single dose of tacrolimus on the steady state exposures of 2 DAAs or 3 DAAs was evaluated by comparing the 2-DAA or 3-DAA exposures (Study Day 15) when the 2 DAAs or 3 DAAs in the presence of tacrolimus to the 2 DAAs or 3 DAAs steady state exposures (Study Day 14) where the 2 DAAs or 3 DAAs without tacrolimus. The effect of steady-state 2 DAAs or 3 DAAs on the single dose of tacrolimus was evaluated by comparing Study Day 15 (Period 2) dose-normalized tacrolimus exposures when tacrolimus was administered with 2 DAAs or 3 DAAs to Study Day 1 (Period 1) dose-normalized exposures when tacrolimus was administered alone.

**Safety Endpoints:** Safety was evaluated based on assessments of adverse events, physical examinations, vital signs, ECG and laboratory tests..

### **Statistical Methods:**

**Pharmacokinetic:** To assess the effect of ABT-450/r, ABT-333 and ABT-267 on tacrolimus, a repeated measure analysis was performed for the natural logarithms of tacrolimus  $C_{max}$ , AUC and  $C_{trough}$  utilizing data from Period 1 Study Day 1, and Period 2 Study Days 1 and 15 from Arms 1, 2, and 3. Arm 4 was not run. A separate analysis was performed for Arms 1, 2, and 3. The model had day as a fixed effect with three levels ('Period 1 study day 1', 'Period 2 study day 1' and 'Period 2 study day 15') and subject as a random effect.  $C_{max}$ , AUC and  $C_{trough}$  ratios were estimated by taking the ratio of 'Period 2 Study Day 1' and 'Period 1 Study Day 1' and the ratio of 'period 2 Study Day 15' and 'Period 1 Study Day 1' values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

To assess the effect of tacrolimus on ABT-450/r, ABT-333 and ABT-267, a repeated measure analysis was performed for the natural logarithms of ABT-450/r, ABT-333 and ABT-267  $C_{max}$ , AUC and  $C_{trough}$  utilizing data from Period 2 Study Days 14 and 15 from all arms. A separate analysis was performed for Arms 1, 2, and 3. The model had day as a fixed effect with two levels ('period 2 study day 14' and 'period 2 study day 15') and subject as a random effect. Additionally,  $C_{max}$ , AUC and  $C_{trough}$  ratios were estimated by taking the ratio of 'period 2 study day 15' and 'period 2 study day 14' values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term

using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

## Results:

### Pharmacokinetics:

The effects of the combination of ABT-450/r and ABT-333 and/or ABT-267 on the pharmacokinetics of tacrolimus administered as a single dose in healthy subjects are summarized in Tables 1-3. Repeated measures analyses were performed for the natural logarithm of dose-normalized tacrolimus  $C_{max}$ ,  $C_{24}$ , and AUC to assess the effect of DAAs on tacrolimus.

**Table 1.** The effect of ABT-333 400 mg twice daily (BID) + ABT-450/r 150/100 mg once daily (QD) on the PK of tacrolimus administered as a single dose in healthy subjects (Arm 1)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
$C_{max}/D$ (ng/mL/mg)	3.76	14.0	3.71	3.04 – 4.53
$AUC_t/D$ (ng•h/mL/mg)	30.6	1810	59.3	40.4 – 87.0
$AUC_{inf}/D$ (ng•h/mL/mg)	38.0	2990	78.6	55.3 – 112
$C_{24}/D$ (ng/mL/mg)	0.33	8.21	25.1	17.6 – 36.0

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Period 1, Day 1 (P1D1): Tacrolimus 2 mg single dose.

<sup>c</sup>. Period 2, Day 15 (P2D15): ABT-450/r 150/100 mg + ABT-333 400 mg BID + tacrolimus 0.5 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Table 2.** The effect of ABT-267 25 mg QD + ABT-450/r 150/100 mg QD on the PK of tacrolimus administered as a single dose in healthy subjects (Arm 2)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
$C_{max}/D$ (ng/mL/mg)	4.04	17.2	4.27	3.49 – 5.22
$AUC_t/D$ (ng•h/mL/mg)	32.6	2040	62.8	48.6 – 81.2
$AUC_{inf}/D$ (ng•h/mL/mg)	41.2	3540	85.8	67.9 – 108
$C_{24}/D$ (ng/mL/mg)	0.37	9.08	24.6	19.7 – 30.8

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. P1D1: Tacrolimus 2 mg single dose.

<sup>c</sup>. P2D15: ABT-450/r 150/100 mg + ABT-267 25 mg QD + tacrolimus 0.5 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Table 3.** The effect of ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + ABT-267 25 mg QD on the PK of tacrolimus administered as a single dose in healthy subjects (Arm 3)

PK parameters	Central Value <sup>a</sup>		Ratio of Central Values	
	P1D1 <sup>b</sup>	P2D15 <sup>c</sup>	Point Estimate <sup>d</sup>	90% CI
C <sub>max</sub> /D (ng/mL/mg)	5.28	21.1	3.99	3.21 – 4.97
AUC <sub>t</sub> /D (ng•h/mL/mg)	48.2	1930	40.1	31.1 – 51.7
AUC <sub>inf</sub> /D (ng•h/mL/mg)	55.9	3190	57.1	45.5 – 71.7
C <sub>24</sub> /D (ng/mL/mg)	0.50	8.24	16.6	13.0 – 21.2

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. P1D1: Tacrolimus 2 mg single dose.

<sup>c</sup>. P2D15: ABT-450/r 150/100 mg + ABT-267 25 mg QD + ABT-333 400 mg BID + tacrolimus 2 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

*Reviewer's comments: Regardless of combination of DAAs (two or three), the C<sub>24</sub> and AUC of tacrolimus was increased approximately 57- to 86-fold and 17- to 25-fold, respectively. It should be noted that the fold-changes in C<sub>24</sub> and AUC are not similar so that the recommended target range of C<sub>24</sub> for therapeutic monitoring of tacrolimus cannot be used when tacrolimus is co-administered with DAAs. The sponsor proposed* (b) (4)

*This does not appear to be reasonable* (b) (4)

*Accordingly, it is recommended that the co-administration of DAAs with tacrolimus be contraindicated. However, if unmet medical needs to use DAAs in organ transplant patients are justified, then we recommend* (b) (4)

### Safety Results:

The DAAs co-administered with tacrolimus in all the arms of this study were well tolerated by the subjects, with only an occasional moderate, self-limited treatment-emergent adverse event reported, none of which were assessed by the investigator as having a reasonable possibility of being related to the DAAs and one of which (vomiting) was assessed as having a reasonable possibility of being related to tacrolimus.

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

There were no clinically meaningful or significant trends noted among the potentially clinically significant laboratory values in this study. No new safety signals or unexpected toxicities were observed when the DAAs were co-administered with tacrolimus.

### **Conclusions:**

#### Two DAA Combination + tacrolimus

Dose-normalized tacrolimus  $AUC_t$ ,  $AUC_{inf}$ , and  $C_{24}$  in the presence of the 2-DAA combination (either ABT-450/r/ABT-333 or ABT-450/r/ABT-267) at steady state were 59- to 63-fold, 79- to 86-fold and 25-fold, respectively, of tacrolimus exposures when administered alone.

#### Three DAA Combination + tacrolimus

Dose-normalized tacrolimus  $AUC_t$ ,  $AUC_{inf}$ , and  $C_{24}$  in the presence of 3-DAA combination at steady state were 40-fold, 57-fold and 17-fold of the tacrolimus exposures when administered alone, respectively.

The DAAs co-administered with tacrolimus in all the arms of this study were well tolerated by the subjects. Adverse events were infrequent and mostly mild and self-limited: there was no pattern observed in the adverse events or the laboratory abnormalities reported. No deaths or other serious adverse events were reported in this study.

The sponsor made the following conclusion and labeling recommendation regarding co-administration of DAAs with tacrolimus.

[REDACTED] (b) (4)

Sponsor's labeling recommendation: [REDACTED] (b) (4)

[REDACTED]

#### *Reviewer's conclusion and labeling recommendation:*

*See the above comments. It is recommended that the co-administration of DAAs with tacrolimus be contraindicated. However, if unmet medical needs to use DAAs in organ transplant patients are justified, then we recommend* [REDACTED] (b) (4)

[REDACTED]

**Drug-Drug Interaction Trial with Omeprazole**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Coadministration of Omeprazole with Combination Therapy of ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) With and Without ABT-333 in Healthy Adult Subjects (M12-199)**

**Study period:** 04 April 2013 to 04 June 2013

**Objectives:** The objective of the study was to determine the effect of steady-state ABT-450/r/ABT-267 with and without ABT-333 on the pharmacokinetics, safety, and tolerability of a single dose of omeprazole in healthy subjects. In addition, the effect of a single and repeated once-daily dose of omeprazole on the pharmacokinetics, safety, and tolerability of steady state ABT-450/r/ABT-267 with and without ABT-333 was also examined.

**Methodology:**

This Phase 1, single center, randomized, multiple-dose, open-label study evaluated the pharmacokinetics, safety, and tolerability of two and three direct-acting antiviral agents (DAA) combinations (ABT 450/r/ABT-267 and ABT-450/r/ABT-267 + ABT-333) and omeprazole when given alone and in combination.

Adult male and female subjects (N = 24) in general good health were selected to participate in the study according to the selection criteria. After meeting the selection criteria, enrolled subjects were assigned in equal numbers to one of two treatment arms as follows:

Arm 1: A single dose of 40 mg of omeprazole was administered on Day 1 followed by a washout period for 5 days (Study Days 2 through 5). Starting on Study Day 6, ABT 450/r/ABT-267 150/100/25 mg was administered once daily (QD) and ABT-333 250 mg was administered twice daily (BID) for 19 days (Study Days 6 through 24). Starting on Study Day 20, 40 mg of omeprazole was administered QD for 5 days (Study Days 20 through 24).

Arm 2: A single dose of 40 mg of omeprazole was administered on Day 1 followed by a washout period for 5 days (Study Days 2 through 5). Starting on Study Day 6, ABT 450/r/ABT-267 150/100/25 mg was administered QD for 19 days (Study Days 6 through 24) and starting on Study Day 20, 40 mg of omeprazole was administered QD for 5 days (Study Days 20 through 24).

Each dose of DAAs was taken orally with water approximately 30 minutes after the start of breakfast for all morning doses and approximately 30 minutes after the start of the evening snack for the evening dose of ABT-333 (Arm 1). On Study Days 1, 20, and 21, omeprazole was administered approximately 30 minutes after the start of breakfast, and at the same time as the DAAs on Study Days 20 and 21. On Study Days 22 through 24, each dose of omeprazole was taken orally with water approximately 1 hour before the start of breakfast.

Blood samples for assay of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were collected by venipuncture on the following days:

- Prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, and 16 hours after morning dosing on Study Day 19.
- Prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24 (Study Day 21) hours after morning dosing on Study Day 20.
- Prior to DAA dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, 24 (Study Day 25), 48 (Study Day 26), and 72 (Study Day 27) hours after morning dosing on Study Day 24.

Additionally, trough concentration samples were drawn prior to the morning dose on Study Days 14 and 17.

Blood samples for assay of omeprazole were collected by venipuncture on the following days:

- Prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24 (Study Day 2) hours after morning dosing on Study Day 1.
- Prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24 (Study Day 21) hours after morning dosing on Study Day 20.

Plasma concentrations of ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The lower limits of quantitation (LLOQ) for ABT-450, ritonavir, ABT-267, ABT-333 and ABT-333 M1 metabolite were established at 0.6 ng/mL, 4.71 ng/mL, 0.417 ng/mL, 4.39 ng/mL and 4.58 ng/mL, respectively.

Plasma concentrations of omeprazole were determined using a validated liquid chromatography method with tandem mass spectrometric detection. The LLOQ for omeprazole was established at 1.02 ng/mL.

#### **Number of Subjects:**

Planned: 24, Entered: 24, Completed: 23, Evaluated for Safety: 24,  
Evaluated for Pharmacokinetics: 23

For the 24 subjects who participated in the study, the mean age was 35.3 years (ranging from 24 to 53 years), the mean weight was 77.5 kg (ranging from 55 to 105 kg) and the mean height was 171 cm (ranging from 154 to 188 cm).

#### **Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers whose ages were between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal for at least 2 years, surgically sterile, or practiced birth control and were not pregnant or breastfeeding. Males were surgically sterile, sexually inactive or practiced birth control.

#### **Test and Reference Product, Dose, Mode of Administration, Lot Nos:**

Investigational Products	ABT-450/Ritonavir/ABT-267	ABT-333	Omeprazole
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Dosage Form	Tablet	Tablet	Capsule
Strength (mg)	75/50/12.5 mg	250 mg	40 mg
Bulk Product Lot	12-008149	12-007842	13-001594
Potency (% of Label	(b) (4)	(b) (4)	NA
Manufacturer	AbbVie	AbbVie	Watson
Finishing lot	13-001688	13-001695	13-001697
Expiration/Retest Date	(b) (4)		
NA = Not available			

**Duration of Treatment:** Subjects received study drug on 25 April 2013 and from 30 April 2013 through 18 May 2013.

### Criteria for Evaluation:

**Pharmacokinetic:** The pharmacokinetic parameter values of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1, and omeprazole were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), time to  $C_{max}$  (peak time,  $T_{max}$ ), plasma trough concentration ( $C_{trough}$ :  $C_{12}$  or  $C_{24}$ ), apparent terminal phase elimination rate constant ( $\beta$ ), terminal phase elimination half-life ( $t_{1/2}$ ), the area under the plasma concentration-time curve during a dosing interval ( $AUC_{0-\tau}$ :  $AUC_{12}$  or  $AUC_{24}$ ) for ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 and AUC from time 0 to time of the last measurable concentration ( $AUC_t$ ) and AUC from time 0 to infinity ( $AUC_{\infty}$ ) for omeprazole. Dose-normalized  $C_{max}$ , AUC, and  $C_{trough}$  ( $C_{12}$  or  $C_{24}$ ) were also provided.

**Safety Endpoints:** Safety was evaluated based on assessments of adverse events, vital signs, physical examinations, ECGs and laboratory tests.

### Statistical Methods:

**Pharmacokinetic:** To assess the effect of single and repeated once-daily dose of omeprazole on ABT-450, ritonavir, ABT-267, and ABT-333 (ABT-333 for Arm 1), two sets of analysis were performed within each arm. In the first analysis, a repeated measure analysis was performed for the natural logarithms of ABT-450, ritonavir, ABT-267, and ABT-333 and ABT-333 M1 (ABT-333 and ABT-333 M1 for Arm 1)  $C_{max}$ ,  $C_{trough}$  and  $AUC_{0-\tau}$  values utilizing data from Study Days 19 and 20 to assess the effect of a single dose of omeprazole on the DAAs. In the second analysis, a repeated measure analysis was performed for the same variables analyzed above utilizing data from Study Days 19 and 24 to assess the effect of a QD dose of omeprazole on the DAAs. The model had day as a fixed effect and subject as a random effect. Additionally, the ratios of the ABT-450, ritonavir, ABT-267, and ABT-333 and ABT-333 M1 (ABT-333 and ABT-333 M1 for Arm 1)  $C_{max}$ ,  $C_{trough}$  and  $AUC_{0-\tau}$  when administered with omeprazole to that of administered without omeprazole was estimated by taking the ratio of Study Day 20 to Study Day 19, and Study Day 24 to Study Day 19 values, obtained from the repeated measures analysis of the mean of log-transformed data. Also, 90% confidence intervals for the ratios were provided. These confidence intervals were obtained by exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated measure analysis model.

To assess the effect of ABT-450, ritonavir, ABT-267, and ABT-333 (ABT-333 for Arm 1) on a single dose of omeprazole, a repeated measure analysis was performed for the natural logarithms  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  values of omeprazole obtained from Study Days 1 and 20. The model had day as a fixed effect and subject as a random effect. Additionally, the ratio of omeprazole  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  when administered with DAAs to that of administered without DAAs was estimated by taking the ratio of Study Day 20 to Study Day 1 values, obtained from the repeated measures analysis of the mean of log-transformed data. The 90% confidence intervals for the ratios were provided. These confidence intervals were obtained by exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated measure analysis model. A repeated measures analysis was used to assess the steady-state of each DAA analyte on the  $C_{trough}$  values (prior to the morning dose) utilizing corresponding data from Study Days 14, 17, 19, and 20. A separate analysis was performed for Arm 1 and Arm 2. The model had day as a fixed effect and subject as a random effect. Within the framework of the repeated measures analysis, tests were performed on contrasts in the study day effects to determine the earliest day after which there was not a statistically significant change. In addition, a trend analysis on  $C_{trough}$  versus time was performed by utilizing the orthogonal linear contrasts for the Study Days within the framework of the repeated measures analysis.

**Safety:** Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) was tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by the following study time segments within each arm:

- Arm 1: Three study time segments (Study Days 1 – 5 for omeprazole, Study Days 6 – 19 for ABT-450/r/ABT-267 + ABT-333, and Study Days 20 through study completion for ABT-450/r/ABT-267 + ABT-333 + omeprazole).
- Arm 2: Three study time segments (Study Days 1 – 5 for omeprazole, Study Days 6 – 19 for ABT-450/r/ABT-267, and Study Days 20 through study completion for ABT-450/r/ABT-267 + omeprazole).

The tabulation of the number of subjects with treatment-emergent adverse events were provided with further breakdown by severity rating and relationship to study drug. Within each study time segment, subjects reporting more than one adverse event for a given MedDRA Preferred Term were counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were identified.

## **Results:**

**Pharmacokinetics:** The effect of a single dose or multiple dosing of omeprazole on steady-state DAA pharmacokinetics were evaluated by comparing the DAA exposures on Study Day 20 to Study Day 19 and Study Day 24 to Study Day 19, respectively. The ratios of central values and 90% confidence intervals for the comparisons are presented in Tables 1 and 2.

**Table 1.** The effect of a single dose or multiple dosing of omeprazole on steady-state DAA pharmacokinetics (Arm 1: ABT-450/r/ABT-267 + ABT-333)

Analyte	Parameter (unit)	Central Value <sup>a</sup>			Ratio of Central Values			
		Day 19	Day 20	Day 24	Single Dose Omeprazole Day 20/Day 19		Multiple Dose Omeprazole Day 24/Day19	
					Point Estimate <sup>b</sup>	90% Confidence Interval	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	C <sub>max</sub> (ng/mL)	3040	3060	3623	1.007	0.882 – 1.149	1.192	1.044 – 1.360
	AUC <sub>24</sub> (ng•h/mL)	16515	17198	19536	1.041	0.902 – 1.202	1.183	1.025 – 1.366
	C <sub>24</sub> (ng/mL)	45.3	52.8	41.7	1.165	0.959 – 1.415	0.921	0.758 – 1.118
Ritonavir	C <sub>max</sub> (ng/mL)	2067	1993	2143	0.964	0.896 – 1.038	1.037	0.963 – 1.116
	AUC <sub>24</sub> (ng•h/mL)	12685	12341	12956	0.973	0.922 – 1.026	1.021	0.968 – 1.077
	C <sub>24</sub> (ng/mL)	34.7	36.0	33.5	1.038	0.953 – 1.130	0.966	0.887 – 1.052
ABT-267	C <sub>max</sub> (ng/mL)	130	126	132	0.968	0.903 – 1.038	1.016	0.948 – 1.090
	AUC <sub>24</sub> (ng•h/mL)	1332	1357	1394	1.019	0.956 – 1.086	1.046	0.981 – 1.115
	C <sub>24</sub> (ng/mL)	26.9	28.2	28.1	1.048	0.983 – 1.116	1.043	0.979 – 1.111
ABT-333	C <sub>max</sub> (ng/mL)	1063	1021	1205	0.960	0.872 – 1.056	1.133	1.029 – 1.246
	AUC <sub>12</sub> (ng•h/mL)	7287	6883	7894	0.945	0.850 – 1.050	1.083	0.975 – 1.204
	C <sub>12</sub> (ng/mL)	281	287	295	1.022	0.903 – 1.156	1.050	0.928 – 1.189
ABT-333 M1 Metabolite	C <sub>max</sub> (ng/mL)	702	711	738	1.012	0.913 – 1.123	1.051	0.948 – 1.166
	AUC <sub>12</sub> (ng•h/mL)	4678	4629	4871	0.989	0.875 – 1.119	1.041	0.921 – 1.178
	C <sub>12</sub> (ng/mL)	170	179	167	1.054	0.888 – 1.250	0.984	0.829 – 1.167

Day 19 = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID

Day 20 and 24 = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + omeprazole 40 mg

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference of the least squares means for logarithms.

**Table 2.** The effect of a single dose or multiple dosing of omeprazole on steady-state DAA pharmacokinetics (Arm 2: ABT-450/r/ABT-267)

Analyte	Parameter (unit)	Ratio of Central Values						
		Central Value <sup>a</sup>			Single Dose Omeprazole		Multiple Dose Omeprazole	
		Day 19	Day 20	Day 24	Day 20/Day 19	Day 24/Day 19	Day 20/Day 19	Day 24/Day 19
					Point Estimate <sup>b</sup>	90% Confidence Interval	Point Estimate <sup>b</sup>	90% Confidence Interval
ABT-450	C <sub>max</sub> (ng/mL)	2022	2395	2061	1.184	0.746 – 1.880	1.019	0.642 – 1.618
	AUC <sub>24</sub> (ng•h/mL)	11083	11956	10259	1.079	0.744 – 1.565	0.926	0.638 – 1.343
	C <sub>24</sub> (ng/mL)	29.6	30.2	24.7	1.020	0.818 – 1.273	0.834	0.669 – 1.041
Ritonavir	C <sub>max</sub> (ng/mL)	2140	2117	2259	0.989	0.889 – 1.101	1.056	0.949 – 1.175
	AUC <sub>24</sub> (ng•h/mL)	13650	13068	14638	0.957	0.852 – 1.075	1.072	0.955 – 1.205
	C <sub>24</sub> (ng/mL)	41.0	40.1	43.9	0.979	0.886 – 1.081	1.071	0.970 – 1.183
ABT-267	C <sub>max</sub> (ng/mL)	138	134	132	0.971	0.815 – 1.156	0.960	0.807 – 1.144
	AUC <sub>24</sub> (ng•h/mL)	1485	1492	1479	1.005	0.891 – 1.133	0.996	0.883 – 1.124
	C <sub>24</sub> (ng/mL)	31.5	31.8	30.7	1.008	0.919 – 1.107	0.973	0.887 – 1.068

Day 19 = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID  
Day 20 and 24 = ABT-450/r/ABT-267 150/100/25 mg QD + omeprazole 40 mg  
a. Antilogarithm of the least squares means for logarithms.  
b. Antilogarithm of the difference of the least squares means for logarithms.

The effect of steady-state DAAs on the single dose pharmacokinetics of omeprazole was evaluated by comparing the exposures of omeprazole on Study Day 20 to Study Day 1. The ratios of central values and 90% confidence intervals for the comparisons are presented in Table 3.

**Table 3.** Effect of steady-state DAAs on the single dose pharmacokinetics of omeprazole

Analyte	Arm	Parameter (Unit)	Central Value <sup>a</sup>		Ratio of Central Values	
			Day 1	Day 20	Point Estimate <sup>b</sup>	90% Confidence Interval
Omeprazole	1	C <sub>max</sub> (ng/mL)	466	288	0.618	0.478 – 0.797
		AUC <sub>t</sub> (ng•h/mL)	1219	751	0.616	0.505 – 0.751
		AUC <sub>inf</sub> (ng•h/mL)	1670	1024	0.613	0.411 – 0.915
	2	C <sub>max</sub> (ng/mL)	334	159	0.475	0.288 – 0.782
		AUC <sub>t</sub> (ng•h/mL)	1168	535	0.458	0.273 – 0.770

AUC <sub>inf</sub> (ng•h/mL)	1883	1753	0.931	0.530 – 1.635
Arm 1: Day 1 = Omeprazole 40 mg; Day 20 = ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + omeprazole 40 mg				
Arm 2: Day 1 = Omeprazole 40 mg; Day 20 = ABT-450/r/ABT-267 150/100/25 mg QD + omeprazole 40 mg				
a. Antilogarithm of the least squares means for logarithms.				
b. Antilogarithm of the difference of the least squares means for logarithms.				
Note: In Arm 1 N = 6 for AUC <sub>inf</sub> ; N = 11 for AUC <sub>t</sub> ; In Arm 2 N = 5 for AUC <sub>inf</sub> ; N = 12 for AUC <sub>t</sub> .				

**Safety:** The regimens tested were generally well tolerated by the subjects. No deaths, other serious adverse events or discontinuations due to adverse events occurred during the study. There was no pattern to the adverse events which were reported. Diarrhoea, abdominal discomfort and papule were the only adverse events reported by more than one subject. All treatment-emergent adverse events were assessed by the investigator as mild in severity and the majority of events were assessed as having a reasonable possibility of being related to the study drugs. No clinically significant values were observed during the study for any hematology, serum chemistry or urinalysis parameter. There were no clinically meaningful or significant trends noted among the potentially clinically significant vital signs values in this study.

### Conclusions:

This study evaluated the effect of steady-state ABT-450/r/ABT-267 with or without ABT-333 on the pharmacokinetics, safety, and tolerability of a single dose of omeprazole in healthy subjects. Additionally, the effect of a single or multiple doses of omeprazole on the pharmacokinetics, safety, and tolerability of steady-state ABT-450/r/ABT-267 with or without ABT-333 was also examined.

The co-administration of a single dose of omeprazole, a potent pH-elevating agent and an inhibitor of CYP2C19, had minimal effect on the steady-state pharmacokinetics of ABT-450/r/ABT-267 + ABT-333 or ABT-450/r/ABT-267. Following multiple dosing of omeprazole, the mean steady-state exposure (C<sub>max</sub> and AUC) of ABT-450/r/ABT-267 + ABT-333 or ABT-450/r/ABT-267 was comparable (< 20% change) to that observed when ABT-450/r/ABT-267 + ABT-333 or ABT-450/r/ABT-267 was administered alone. (b) (4)

Co-administration of omeprazole with the ABT-450/r/ABT-267 + ABT-333 regimen resulted in a ~ 40% decrease in omeprazole exposure and co-administration of omeprazole with the ABT-450/r/ABT-267 regimen resulted in a ~ 50% decrease in omeprazole exposure.

The regimens tested were generally well tolerated by the subjects. There was no pattern to the adverse events which were reported. No clinically significant values were observed during the study for any hematology, serum chemistry or urinalysis parameter.

*Reviewer's comments and labeling recommendation: The sponsor proposed* (b) (4)

(b) (4) Accordingly, we recommend that concomitant use of omeprazole with DAAs should be avoided unless benefits outweigh risks. We recommend the labeling should be revised as follows.

(b) (4)

**Drug-Drug Interaction Trial with Methadone**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs.***

**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 1 included a 3-DAA regimen of ABT-450/r with ABT-267 and ABT-333. Arm 2 included a 2-DAA regimen of ABT-450/r with ABT-267. Arm 3 included a 3-DAA regimen of co-formulated tablets of ABT-450, ABT-267 and ritonavir (ABT-450/r/ABT-267) and ABT-333, with methadone

administered approximately 4 hours after DAA administration. **An optional Arm 4 was not conducted.**

#### Methadone Dosing:

The dose of methadone did not differ throughout the study for a given subject. However, the timing of methadone doses in Arm 3 was determined based on available results of the preceding arms. For Arms 1 and 2, methadone dosing was approximately 30 minutes after the start of a standardized breakfast. For Arm 3, methadone dosing was approximately 30 minutes after start of a standardized lunch. At the investigator's discretion, in Arm 3, had a subject been enrolled in the study who was receiving chronic methadone maintenance therapy administered in the morning, the subject's time of methadone dose could have been gradually increased such that the subject was taking methadone approximately 30 minutes after the start of lunch by Study Day 6 for Arm 3. In these cases, subjects could have taken methadone without regard to meals from Study Days 1 to 5.

#### DAA Dosing:

For drugs dosed once daily and the morning dose of ABT-333, DAAs were administered approximately 30 minutes after the start of a standardized breakfast. For ABT-333, the evening dose was administered approximately 30 minutes after the start of an evening snack.

**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:

		Regimens	
		Study Days 1 through 8 and 23 through 25	Study Days 9 through 22
Arm	Subject Numbers		
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 and CYP2C8 is involved in ABT-333 metabolism. Ritonavir inhibits CYP3A4 and to a lesser extent, CYP2D6. The overlapping enzymes involved in the lead to the possibility of drug-drug interactions of methadone with ABT-450, ritonavir, ABT-333, and ABT-267.

## Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), ABT-267 (25 mg) and ABT-333 (400 mg twice daily) 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 (or doses that provided comparable systemic exposures) were also evaluated in the 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	(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)	(b) (4)				
Manufacturing Site	AbbVie, (b) (4)	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL
Manufacturing Date	(b) (4)				
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.

#### *Arms 3 Methadone Sampling*

The sampling schedule was identical to the Arm 2 sampling schedule with the exception that the 16 hour PK sample was not collected for Arm 3.

## 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, ABT-267, ABT-333, ABT-333 M1, R-methadone, and S-methadone 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 %
ABT-333	4.53-3090	4.53	11.7,195, 2430	5.6 % to 6.7 %	2.1 % to 9.9 %
ABT-333 M1	4.73-3220	4.73	12,199,2490	2.8 % to 4.2 %	-0.8 to -0.8 %
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 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 1 and Arm 3 are presented in this review.*

#### **Arm 1:**

#### **ABT-450**

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 1.

ABT-450 Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	Day 22 ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
C <sub>max</sub> (ng/mL)	124 ± 113	153 ± 97.1
T <sub>max</sub> (h)	5.3 ± 0.9	4.8 ± 0.8
AUC <sub>24</sub> (ng•h/mL)	711 ± 377	809 ± 352
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	8.74 ± 2.70
C <sub>24</sub> (ng/mL)	5.84 ± 2.13	6.13 ± 2.85

a. Harmonic mean ± pseudo-standard deviation.

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

#### **Ritonavir**

Table 7 shows the mean ± SD pharmacokinetic parameters of ritonavir in Arm 1.

Ritonavir Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
C <sub>max</sub> (ng/mL)	784 ± 451	1560 ± 763
T <sub>max</sub> (h)	5.3 ± 0.9	4.6 ± 0.7
AUC <sub>24</sub> (ng•h/mL)	5240 ± 2240	9560 ± 4080
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	6.73 ± 2.00
C <sub>24</sub> (ng/mL)	56.4 ± 21.8	83.3 ± 42.3

a. Harmonic mean ± pseudo-standard deviation.

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

## ABT-267

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 1.

ABT-267 Pharmacokinetic Parameter (Unit)	Day 9	Day 22
	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
C <sub>max</sub> (ng/mL)	78.2 ± 19.8	85.0 ± 26.0
T <sub>max</sub> (h)	5.3 ± 0.7	4.7 ± 0.9
AUC <sub>24</sub> (ng•h/mL)	713 ± 163	1030 ± 333
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	28.9 ± 8.42
C <sub>24</sub> (ng/mL)	11.6 ± 3.18	23.3 ± 8.30

a. Harmonic mean ± pseudo-standard deviation.

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

## ABT-333 and ABT-333 M1

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 and ABT-333 M1 in Arm 1.

Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	Day 22 ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
<b>ABT-333</b>		
C <sub>max</sub> (ng/mL)	654 ± 498	781 ± 303
T <sub>max</sub> (h)	3.6 ± 1.0	3.4 ± 1.2
AUC <sub>12</sub> (ng•h/mL)	3840 ± 2330	4490 ± 1710
C <sub>12</sub> (ng/mL)	121 ± 64.9	123 ± 50.5
C <sub>24</sub> (ng/mL)	165 ± 68.5	154 ± 51.1
<b>ABT-333 M1</b>		
C <sub>max</sub> (ng/mL)	355 ± 269	395 ± 156
T <sub>max</sub> (h)	5.0 ± 1.0	4.3 ± 0.9
AUC <sub>12</sub> (ng•h/mL)	1990 ± 1350	2240 ± 865
C <sub>12</sub> (ng/mL)	64.8 ± 33.2	56.5 ± 23.1
C <sub>24</sub> (ng/mL)	77.7 ± 24.4	70.0 ± 28.3

Note: t<sub>1/2</sub> could not be determined for ABT-333 and ABT-333 M1 because there were less than three measurable concentration-time points in the terminal phase.

## Methadone

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

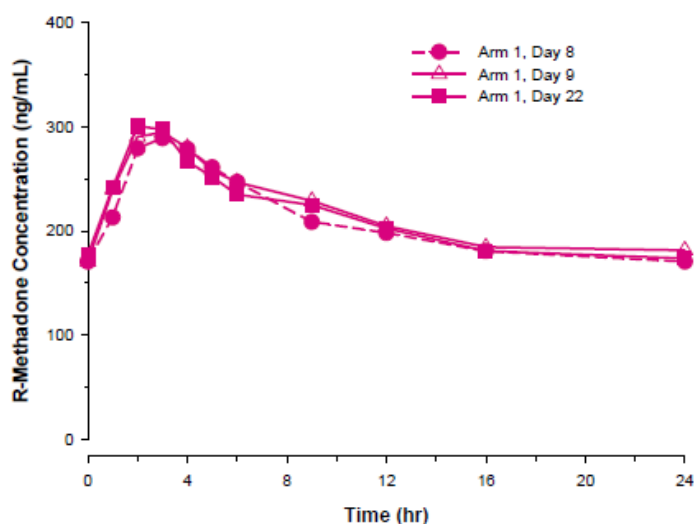


Fig 2 shows the mean S-methadone plasma concentration-time profiles.

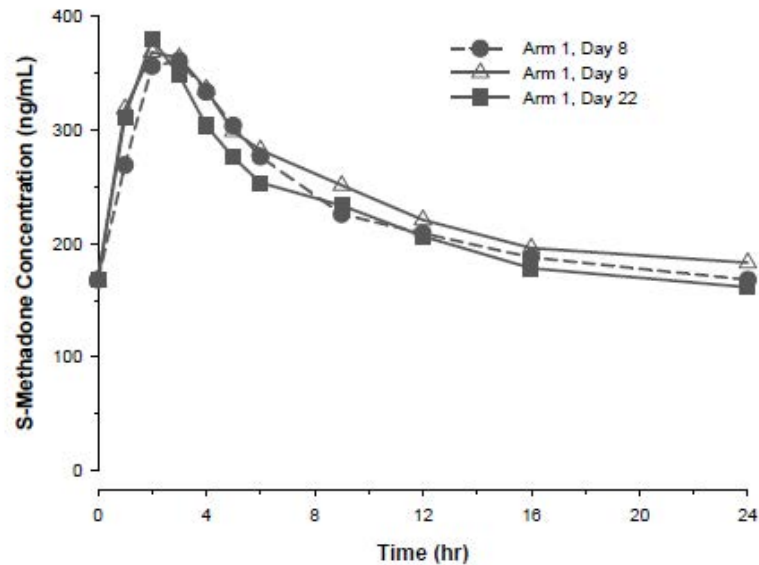


Table 10 shows the pharmacokinetic parameters (Mean  $\pm$ SD) of R-Methadone and S-Methadone.

Methadone Pharmacokinetic Parameter (Unit)	Day 8 Methadone QD (N = 12)	Day 9	Day 22
		ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)	ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + Methadone QD (N = 12)
R-Methadone			
C <sub>max</sub> (ng/mL)	297 ± 127	301 ± 130	306 ± 121
C <sub>max</sub> /Dose (ng/mL/mg)	3.26 ± 0.92	3.30 ± 0.90	3.35 ± 0.80
T <sub>max</sub> (h)	3.2 ± 0.9	3.2 ± 1.2	2.6 ± 1.0
AUC <sub>24</sub> (ng•h/mL)	4990 ± 2340	5070 ± 2290	5080 ± 2130
AUC <sub>24</sub> /Dose (ng•h/mL/mg)	54.1 ± 15.9	55.1 ± 15.5	55.5 ± 13.8
C <sub>24</sub> (ng/mL)	171 ± 91.8	182 ± 90.1	174 ± 78.6
S-Methadone			
C <sub>max</sub> (ng/mL)	372 ± 165	379 ± 166	385 ± 173
C <sub>max</sub> /Dose (ng/mL/mg)	4.09 ± 1.22	4.15 ± 1.22	4.20 ± 1.25
T <sub>max</sub> (h)	2.8 ± 0.8	2.3 ± 0.9	1.9 ± 0.5
AUC <sub>24</sub> (ng•h/mL)	5470 ± 2660	5650 ± 2680	5350 ± 2730
AUC <sub>24</sub> /Dose (ng•h/mL/mg)	59.2 ± 18.4	61.2 ± 18.2	58.0 ± 19.1
C <sub>24</sub> (ng/mL)	168 ± 94.9	183 ± 98.3	162 ± 98.9

Note: methadone dose (mg), mean  $\pm$  SD: 91.3  $\pm$  25.8.

### Arm 3:

#### ABT-450

Table 11 shows the mean pharmacokinetic parameters of ABT-450

ABT-450 Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>c</sup> )	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>c</sup> )
C <sub>max</sub> (ng/mL)	1100 ± 640	2060 ± 2300
T <sub>max</sub> (h)	3.7 ± 0.6	3.6 ± 0.7
AUC <sub>24</sub> (ng•h/mL)	5030 ± 3560	7820 ± 11000
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	7.04 ± 1.37
C <sub>24</sub> (ng/mL)	28.2 ± 22.5	19.6 ± 18.8

a. Harmonic mean ± pseudo-standard deviation.

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

c. One subject withdrew consent and was discontinued from the study on Study Day 10, and therefore was excluded from the pharmacokinetic analysis.

#### Ritonavir

Table 12 shows the mean pharmacokinetic parameters of ritonavir.

Ritonavir Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>c</sup> )	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>c</sup> )
C <sub>max</sub> (ng/mL)	1660 ± 574	2420 ± 953
T <sub>max</sub> (h)	3.7 ± 0.6	3.7 ± 0.5
AUC <sub>24</sub> (ng•h/mL)	10600 ± 5170	13500 ± 5630
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.47 ± 1.64
C <sub>24</sub> (ng/mL)	68.0 ± 52.1	66.1 ± 30.9

a. Harmonic mean ± pseudo-standard deviation.

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

c. One subject withdrew consent and was discontinued from the study on Study Day 10, and therefore was excluded from the pharmacokinetic analysis.

#### ABT-267

Table 13 shows the mean pharmacokinetic parameters of ABT-267.



ABT-267 Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>a</sup> )	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>b</sup> )
C <sub>max</sub> (ng/mL)	102 ± 31.1	116 ± 35.9
T <sub>max</sub> (h)	4.6 ± 0.7	4.4 ± 0.5
AUC <sub>24</sub> (ng•h/mL)	953 ± 151	1200 ± 261
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	23.5 ± 6.35
C <sub>24</sub> (ng/mL)	15.8 ± 2.45	23.7 ± 5.77

- a. Harmonic mean ± pseudo-standard deviation.  
b. t<sub>1/2</sub> calculated following the Study Day 22 dose only.  
c. One subject withdrew consent and was discontinued from the study on Study Day 10, and therefore was excluded from the pharmacokinetic analysis.

## ABT-333 and ABT-333 M1

Table 14 shows the mean pharmacokinetic parameters of ABT-333 and ABT-333 M1.

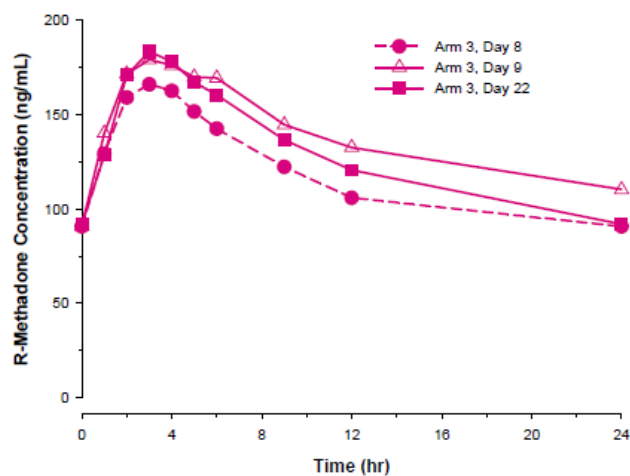
Pharmacokinetic Parameter (Unit)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>a</sup> )	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>a</sup> )
<b>ABT-333</b>		
C <sub>max</sub> (ng/mL)	1880 ± 751	1920 ± 737
T <sub>max</sub> (h)	3.3 ± 0.8	3.5 ± 0.7
AUC <sub>12</sub> (ng•h/mL)	10600 ± 4780	11100 ± 5410
C <sub>12</sub> (ng/mL)	344 ± 218	350 ± 239
C <sub>24</sub> (ng/mL)	387 ± 232	308 ± 198
<b>ABT-333 M1</b>		
C <sub>max</sub> (ng/mL)	1060 ± 242	1030 ± 339
T <sub>max</sub> (h)	4.0 ± 0.6	3.9 ± 0.5
AUC <sub>12</sub> (ng•h/mL)	5880 ± 1740	5430 ± 2190
C <sub>12</sub> (ng/mL)	218 ± 103	164 ± 110
C <sub>24</sub> (ng/mL)	174 ± 91.1	113 ± 68.9

- a. One subject withdrew consent and was discontinued from the study on Study Day 10, and therefore was excluded from the pharmacokinetic analysis.

Note: t<sub>1/2</sub> could not be determined for ABT-333 and ABT-333 M1 because there were less than three measurable concentration-time points in the terminal phase.

## Methadone

Fig 3 shows the mean R-methadone plasma concentration-time profiles



## Methadone

Fig 4 shows the mean S-methadone plasma concentration-time profiles

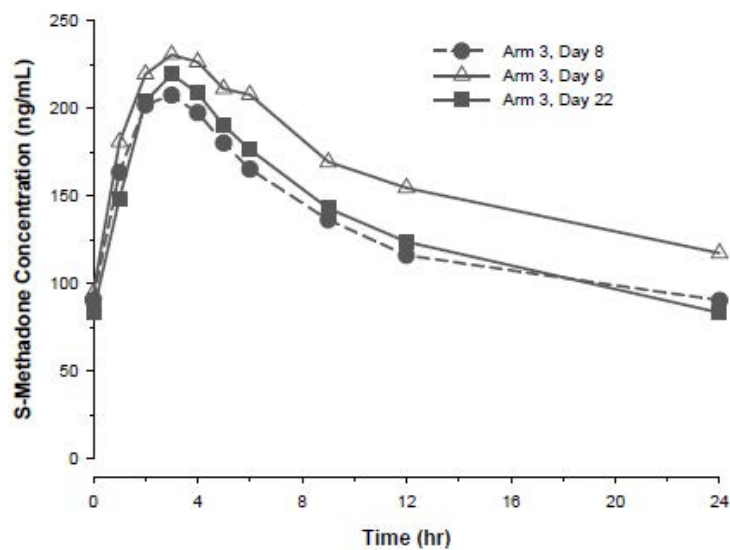


Table 15 shows the pharmacokinetic parameters (Mean  $\pm$ SD) of R-Methadone and S-Methadone.

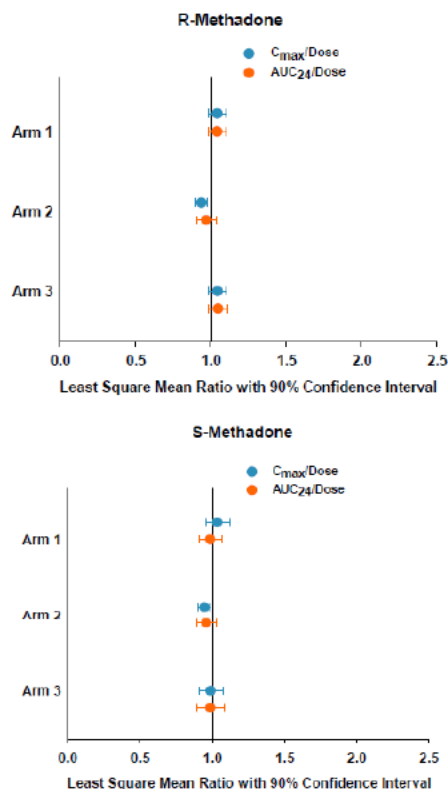
Methadone Pharmacokinetic Parameter (Unit)	Day 8 Methadone QD (N = 12)	Day 9 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>a</sup> )	Day 22 ABT-333 400 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD + Methadone QD (N = 11 <sup>a</sup> )
R-Methadone			
C <sub>max</sub> (ng/mL)	174 ± 90.4	191 ± 101	189 ± 108
C <sub>max</sub> /Dose (ng/mL/mg)	2.55 ± 0.71	2.80 ± 0.74	2.76 ± 0.70
T <sub>max</sub> (h)	2.8 ± 1.2	3.5 ± 1.5	3.3 ± 0.9
AUC <sub>24</sub> (ng•h/mL)	2810 ± 1510	3310 ± 1950	3060 ± 1810
AUC <sub>24</sub> /Dose (ng•h/mL/mg)	41.1 ± 12.3	48.2 ± 14.7	45.1 ± 12.2
C <sub>24</sub> (ng/mL)	90.8 ± 50.0	110 ± 74.1	92.0 ± 57.5
S-Methadone			
C <sub>max</sub> (ng/mL)	217 ± 110	246 ± 126	225 ± 123
C <sub>max</sub> /Dose (ng/mL/mg)	3.26 ± 1.05	3.71 ± 1.09	3.40 ± 0.93
T <sub>max</sub> (h)	2.6 ± 1.0	3.2 ± 1.4	3.1 ± 0.8
AUC <sub>24</sub> (ng•h/mL)	3150 ± 1720	3900 ± 2310	3220 ± 1720
AUC <sub>24</sub> /Dose (ng•h/mL/mg)	47.2 ± 17.2	58.0 ± 20.3	49.5 ± 14.1
C <sub>24</sub> (ng/mL)	90.4 ± 51.6	117 ± 81.4	83.4 ± 46.8

a. One subject withdrew consent and was discontinued from the study on Study Day 10, and therefore was excluded from the pharmacokinetic analysis.

Note: Methadone dose (mg), mean ± SD: 70.8 ± 32.9 (Day 8) and 69.5 ± 34.2 (Days 9 and 22)

### Statistical Evaluation of the Effect of 3-DAA on R-Methadone and S-Methadone (Arm 3)

Fig 5 shows the least squares mean ratio and 90 % confidence intervals for R-methadone and S-methadone dose normalized C<sub>max</sub> and AUC<sub>24</sub>.

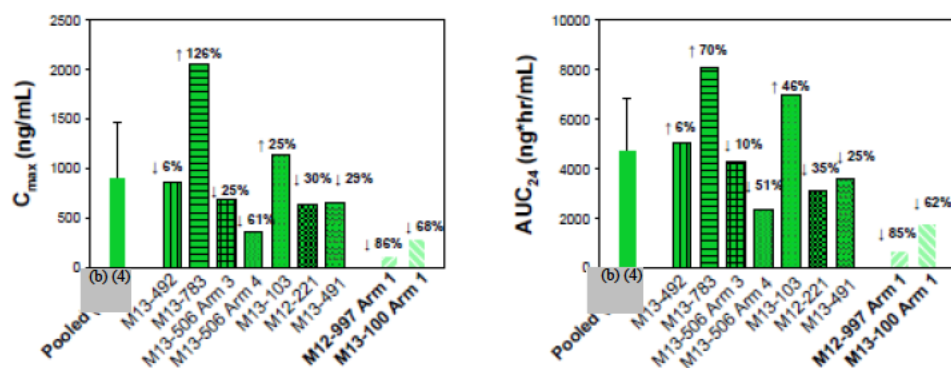


Arm 1: Coadministration of methadone with 3 DAAs (ABT-450 (b) (4) tablet).  
 Arm 2: Coadministration of methadone with 2 DAAs (ABT-450 (b) (4) tablet).  
 Arm 3: Methadone administered 4 hours after 3 DAAs (ABT-450/r/ABT-267 co-formulated tablet).

Co-administration of the 3-DAA regimen did not significantly alter the pharmacokinetics of either R-methadone or S-methadone. Further, the effect of the DAA regimen on the pharmacokinetics of R-methadone and R-methadone was similar irrespective of the formulation administered (ABT-450/r (b) (4) tablet-Arms 1 and 2; ABT-450/r/ABT-267 co-formulated tablet-Arm 3).

*Effect of Co-Administration of the DAA Regimen Using ABT-450 (b) (4) tablets with Methadone*

Fig 6 shows the effect of methadone and buprenorphine/naloxone on ABT-450 exposures from the ABT-450 (b) (4) tablet (source: White Paper submitted by the Applicant in March 2013).

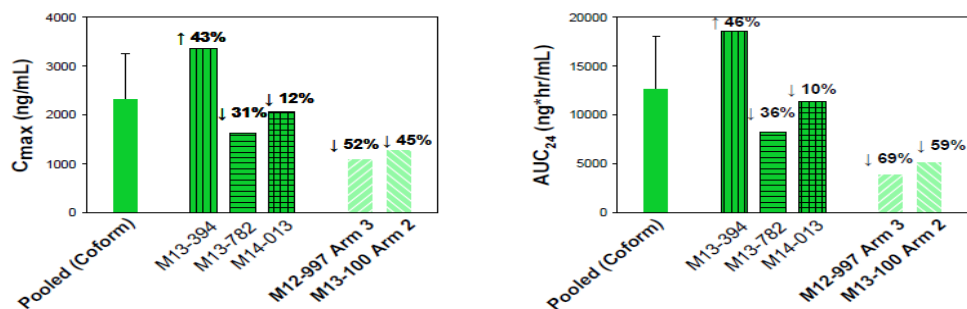


1. Study M12-997: 3 DAAs + methadone; Study M13-100: 3 DAAs + buprenorphine/naloxone.
2. Values of individual studies shown are geometric means.
3. Pooled studies represent mean + standard deviation (SD) data from six Phase 1 studies (total 7 arms) at steady state where the 3-DAA combination was administered with ABT-450 (b) (4) tablets.
4. Percentage represents the change of exposure of individual study relative to the mean of pooled studies.
5. (b) (4) ABT-450 (b) (4) tablet.

Based on a cross study comparison, co-administration of the 3-DAA regimen with methadone resulted in a 65 % to 95 % lower ABT-450 C<sub>max</sub> and 70-90 % lower AUC relative to ABT-450 exposures when the 3-DAA regimen was administered alone. Per the sponsor's hypothesis, a possible direct interaction due to simultaneous dosing of the DAAs with methadone could be a possible reason for the lower exposures of ABT-450 in the current trial as compared to the other trials. Hence, Arm 3 investigated the possibility of interaction due to simultaneous administration of the 3-DAAs and methadone by staggering the dosing (methadone was administered 4 hours after DAA dosing in Arm 3 of the trial) of the 3-DAA regimen and methadone.

*Effect of Co-Administration of the DAA Regimen Using ABT-450/r/ABT-267 coformulated tablets with Methadone*

Fig 7 shows the effect of methadone and buprenorphine/naloxone on ABT-450 exposures from the ABT-450/r/ABT-267 co-formulated tablets (source: White Paper submitted by the Applicant in March 2013).



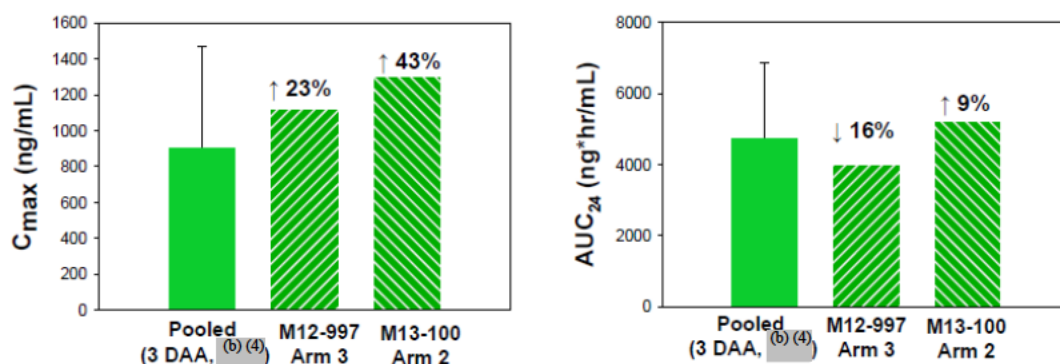
1. Study M12-997: 3 DAAs + methadone; Study M13-100: 3 DAAs + buprenorphine/naloxone.
2. Values of individual studies shown are geometric means.
3. Pooled studies represent mean + SD data from three Phase 1 studies at steady state where the 3-DAA combination was administered with ABT-450/r co-formulated tablet + ABT-267 + ABT-333.
4. Percentage represents the change of exposure of individual study relative to the mean of pooled studies.
5. Coform: ABT-450/r co-formulated tablet.

Based on a cross study comparison, co-administration of the 3-DAA regimen (using ABT-450/r/ABT-267 coformulated tablet+ ABT-333) with methadone resulted in a 30 % to 80 % lower ABT-450 C<sub>max</sub> and 70-90 % lower AUC relative to ABT-450 exposures when the 3-DAA regimen (using ABT-450/r/ABT-267 coformulated tablet+ABT-333) was administered alone. These results suggested that 1) simultaneous administration of the 3-DAA regimen with methadone cannot explain the decrease in ABT-450 exposures in Arm 1 and 2) changing the formulation from ABT-450 tablets to ABT-450/r/ABT-267 coformulated product and staggering the dosing of the 3-DAA regimen and methadone in Arm 3 did not affect the extent of the interaction.

*ABT-450 exposures with the ABT-450/r/ABT-267 coformulated tablets versus ABT-450 (b) (4) tablets*

Despite the decrease in ABT-450 exposure (dosed using ABT-450/r/ABT-67 co-formulated product) when co-dosed with methadone (based on cross study comparison), the ABT-450/r/ABT-267 co-formulated tablet provides ABT-450 exposures comparable to those from the ABT-450 (b) (4) formulation.

Fig 8 shows the ABT-450 exposures from the ABT-450/r/ABT-267 coformulated tablets in subjects receiving methadone or buprenorphine/naloxone versus ABT-450 exposures from ABT-450 (b) (4) tablets in subjects not receiving methadone or buprenorphine/naloxone (source: White Paper submitted by the Applicant in March 2013).



1. Study M12-997: 3 DAAs + methadone; Study M13-100: 3 DAAs + buprenorphine/naloxone.
2. Values of individual studies shown are geometric means.
3. Pooled studies represent mean + SD data from six Phase 1 studies (total 7 arms) at steady state where 3 DAAs were given in combination with ABT-450 (b) (4) tablet.
4. Percentage represents the change of exposure of individual study relative to the mean of pooled studies.
5. SDD: ABT-450 (b) (4) tablet.

SVR<sub>12</sub> rates in trial M11-652 exceeded 90 % in both treatment naïve and treatment experienced subjects who received the 3-DAA regimen with ribavirin. Of note, methadone had minimal impact on the pharmacokinetics of ritonavir, ABT-267, ABT-333, ABT-333 M1 exposures, irrespective of the formulations of the DAAs or combinations (3 DAAs or 2DAAs).

### Pharmacodynamic Assessments

Overall, addition of the 3-DAA regimen did not significantly change the pupil response, SOWS response, and DDQ response in patients who were stabilize on methadone maintenance therapy.

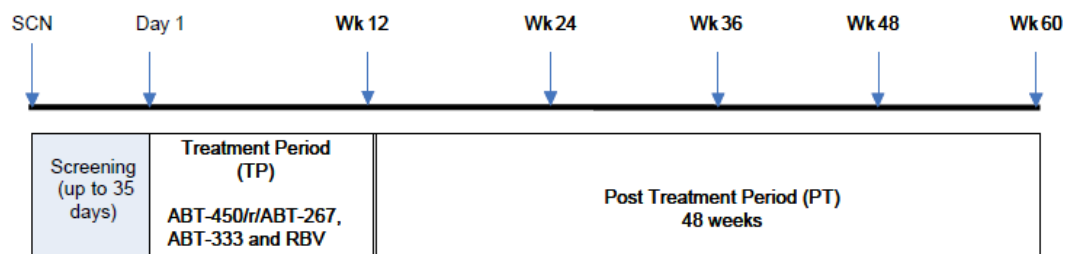
In order to further assess the clinical relevance of decrease in ABT-450 exposures in the presence of methadone (based on cross trial comparison), the sponsor assessed the efficacy and safety and the 3-DAA regimen in patients stabilized on methadone or buprenorphine/naloxone therapy in trial M14-103.

### 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  $\pm$  naloxone and 10 subjects on stable methadone therapy).

Table 16 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 17 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.

## Results

Co-administration of ABT-450/r/ABT-267 and ABT-333 with Methadone:

- Did not significantly alter the pharmacokinetic parameters of R-methadone and S-methadone.
- Decreased the mean C<sub>max</sub> of ABT-450 by 65-95 % and AUC of ABT-450 by 70-90 % (ABT-450 administered as (b) (4) tablets; cross study comparison).
- Decreased the mean C<sub>max</sub> of ABT-450 by 30-80 % and AUC of ABT-450 by 70-90 % (ABT-450 administered as ABT-450/r/ABT-267 co-formulated tablets; cross study comparison).
- No significant change in the pharmacokinetics of ABT-267, ABT-333, ABT-333 M1, and ritonavir (based on cross trial comparison).
- No significant change in any pharmacodynamic assessments.

## Conclusion

ABT-450/ritonavir/ABT-267 and ABT-333 can be co-administered with methadone without any dose adjustment based on the following:

- SVR<sub>12</sub> data (97.4 %) from trial M14-103 in which HCV infected subjects stabilized on methadone therapy were administered the 3-DAA regimen (+RBV) using the ABT-450/r/ABT-267 co-formulated tablets.
- Pharmacokinetic data from trial M14-103 which suggests that the pharmacokinetic parameters of ABT-450 using the ABT-450/r/ABT-267 coformulated tablets were in the range of the pharmacokinetic parameters of ABT-450 observed in other Phase 1 trials conducted using the ABT-450/r/ABT-267 coformulated tablets.
- Similarity between the ABT-450 exposures from the ABT-450/r/ABT-267 co-formulated tablet in subjects receiving methadone and the observed range of ABT-450 exposures from the ABT-450 (b) (4) tablet in subjects not receiving methadone. Of note, SVR12 rates in trial M11-652 (conducted using ABT-450 (b) (4) tablets) exceeded 90 % in both treatment naïve and treatment experienced subjects who received the 3-DAA regimen with ribavirin. Hence, the co-formulated tablet is expected to provide efficacious exposures in HCV-infected patients who are on a stable methadone or buprenorphine/naloxone maintenance therapy.

**Drug-Drug Interaction Trial with Raltegravir**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**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<sup>th</sup>, 2012  
Final report date: February 20, 2014

***Reviewer's Note: As the proposed labeling recommendations in NDA 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3DAAs (Arm 2 in trial M13-392)***

**Trial Objectives**

- To determine the pharmacokinetics, safety, and tolerability of the combination of ABT-450/r plus ABT-333, ABT-450/r plus ABT-333 plus ABT-267, and ABT-450/r 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-333 plus ABT-450/r, ABT-333 plus ABT-450/r plus ABT-267, and ABT-450/r 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 and approximately 30 minutes after the start of the evening snack for the evening doses of raltegravir and ABT-333. 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, ABT-333, and ABT-267), CYP2C8 (ABT-333 and to a lesser extent ABT-267) and CYP2D6 (ABT-333). 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), ABT-267 (25 mg) and ABT-333 (250 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	(b) (4)	(b) (4)	Soft Gelatin Capsule	Tablet	Film-Coated Tablet
	(b) (4) Tablet	(b) (4) 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)	(b) (4)				Unknown
Manufacturing Site	AbbVie, (b) (4)	AbbVie, Lake County, IL	AbbVie, Lake County, IL	AbbVie, Lake County, IL	Merck
Manufacturing Date	(b) (4)				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-333, ABT-333 M1, 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-333, ABT-333 M1, 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, ABT-333, ABT-333 M1 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 %
ABT-333	4.57-3290	4.57	13.5, 225, 2810	2 % to 4.3 %	-2.1 % to 2.7 %
ABT-333 M1	4.72-3400	4.72	13.8, 230, 2880	2.4 % to 4.1	0 to 1.7 %

				%	
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 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 2)

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

Parameter (Unit)	Day 4 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	Day 17 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	12	12
C <sub>max</sub> (ng/mL)	548 ± 285	1790 ± 1120
T <sub>max</sub> (h)	5.3 ± 1.5	4.8 ± 1.6
AUC <sub>24</sub> (ng•h/mL)	3470 ± 1480	8370 ± 3930
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	4.85 ± 0.62
C <sub>24</sub> (ng/mL)	23.0 ± 11.1	27.4 ± 17.1

a. Harmonic mean ± pseudo-standard deviation.

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

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 2)

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

Parameter (Unit)	Day 4	Day 17
	ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	12	12
C <sub>max</sub> (ng/mL)	1110 $\pm$ 291	1710 $\pm$ 550
T <sub>max</sub> (h)	5.3 $\pm$ 2.2	4.6 $\pm$ 0.79
AUC <sub>24</sub> (ng•h/mL)	7750 $\pm$ 2600	11800 $\pm$ 4480
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	4.40 $\pm$ 0.86
C <sub>24</sub> (ng/mL)	57.0 $\pm$ 48.0	51.5 $\pm$ 35.1

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

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

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 2)

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

Parameter (Unit)	Day 4	Day 17
	ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	12	12
C <sub>max</sub> (ng/mL)	149 $\pm$ 42.5	158 $\pm$ 49.0
T <sub>max</sub> (h)	5.2 $\pm$ 0.39	5.0 $\pm$ 0.85
AUC <sub>24</sub> (ng•h/mL)	1390 $\pm$ 389	1980 $\pm$ 690
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	35.2 $\pm$ 15.1
C <sub>24</sub> (ng/mL)	23.5 $\pm$ 8.16	47.0 $\pm$ 21.2

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

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

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

#### ABT-333 and ABT-333 M1 (Arm 2)

Table 8 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 in Arm 2.

Parameter (Unit)	Day 4 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	Day 17 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
<b>ABT-333</b>		
N	12	12
C <sub>max</sub> (ng/mL)	1430 ± 809	1300 ± 758
T <sub>max</sub> (h)	3.8 ± 1.0	3.4 ± 1.0
AUC <sub>24</sub> (ng•h/mL)	9560 ± 5580	9410 ± 6490
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.70 ± 0.85 <sup>c</sup>
C <sub>12</sub> (ng/mL)	436 ± 314	408 ± 370
C <sub>24</sub> (ng/mL)	461 ± 365	343 ± 361
<b>ABT-333 M1</b>		
N	12	12
C <sub>max</sub> (ng/mL)	769 ± 250	781 ± 296
T <sub>max</sub> (h)	4.7 ± 1.1	4.3 ± 1.1
AUC <sub>24</sub> (ng•h/mL)	4650 ± 1440	4930 ± 1750
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	5.89 ± 0.62 <sup>d</sup>
C <sub>12</sub> (ng/mL)	195 ± 62.2	172 ± 67.4
C <sub>24</sub> (ng/mL)	157 ± 51.0	96.6 ± 38.7

a. Harmonic mean ± pseudo-standard deviation.

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

c. N = 11.

d. N = 4.

## Raltegravir (Arm 2)

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

Parameter (Unit)	Day 3 Raltegravir 400 mg BID	Day 4 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID	Day 17 ABT-267 25 mg QD + ABT-333 400 mg BID + ABT-450/r 150/100 mg QD + Raltegravir 400 mg BID
N	12	12	12
C <sub>max</sub> (ng/mL)	937 ± 728	2280 ± 1270	2130 ± 1230
T <sub>max</sub> (h)	4.6 ± 3.3	6.8 ± 4.0	7.1 ± 3.1
AUC <sub>12</sub> (ng•h/mL)	4820 ± 2830	10700 ± 5110	10900 ± 5150
t <sub>1/2</sub> <sup>a,b</sup> (h)	--	--	8.56 ± 2.03 <sup>c</sup>
C <sub>12</sub> (ng/mL)	311 ± 340	918 ± 1230	644 ± 838
C <sub>24</sub> (ng/mL)	211 ± 191	198 ± 130	142 ± 134

a. Harmonic mean ± pseudo-standard deviation.

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

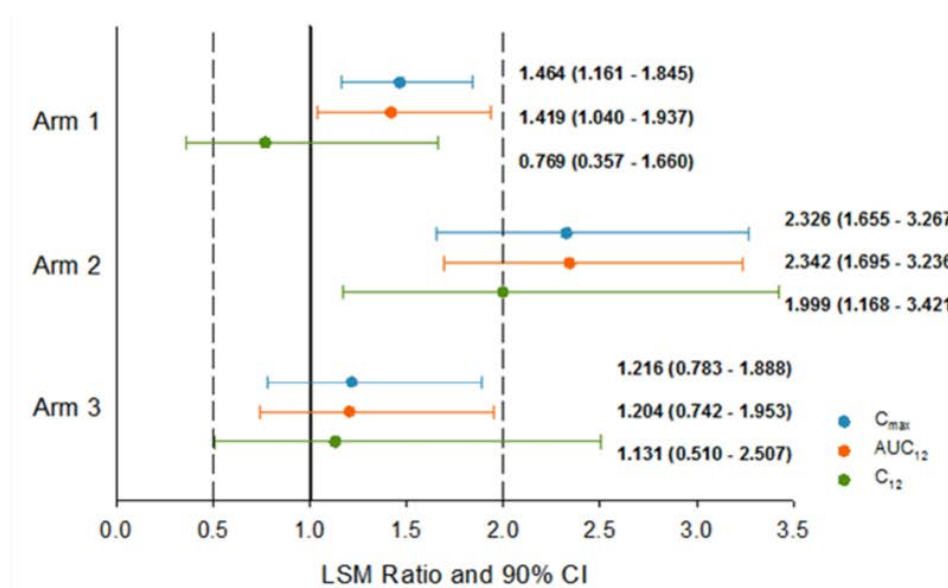
c. N = 4.



## Statistical Evaluation of the Pharmacokinetic Parameters

### Effect of DAAs on Raltegravir

Fig 1 shows the least squares mean ratios of  $C_{max}$ ,  $AUC_{12}$ , and  $C_{12}$ , and 90 % Confidence Intervals for Raltegravir (Study Day 17/Study Day 3)



Arm 1 DAAs: ABT-450/r + ABT-333

Arm 2 DAAs: ABT-450/r + ABT-333 + ABT-267

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

Co-administration of raltegravir with ABT-450/r + ABT-267 + ABT-333 (Arm 2) at steady state increased the mean RAL  $C_{max}$ ,  $AUC_{12}$ , and  $C_{12}$  by approximately 100 % to 130 % relative to the administration of raltegravir alone.

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

Co-administration of the 3-DAA regimen with Raltegravir (Arm 2) increased the mean raltegravir exposure  $C_{max}$  and  $AUC_{12}$  by approximately 132 % and 135 %, respectively, likely due to inhibition of UGT1A1 by the DAAs. The  $IC_{50}$  values for UGT1A1 inhibition for ABT-450, ABT-267, ABT-333 and ritonavir are 3.62, 2.12, 0.92 and 1.7  $\mu M$ , respectively. The M1 metabolite of ABT-333 is a weak UGT1A1 inhibitor in vitro with an  $IC_{50}$  of 6.53  $\mu M$ , while ritonavir is UGT inducer.

*The increase in RAL exposure observed in this trial when RAL was co-administered with DAAs does not warrant a dose adjustment based on the following:*

- 1) *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 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 10 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 and ABT-333 with Raltegravir:

- Increased the mean  $C_{\max}$  and  $AUC_{12}$  of RAL by 132 % and 135 %, 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 ABT-333 and Raltegravir can be co-administered without any dose adjustments.

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

**Reviewer: Vikram Arya, Ph.D., FCP**

### **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 206619 are based on 3 DAAs (ABT-450/ritonavir/ABT-267 and ABT-333), the results section in this review focuses only on the results observed with 3 DAAs.***

#### **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*</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*</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*</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 and approximately 30 minutes after starting the evening snack for the evening doses of ABT-333. 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 enable dose selection for the HIV/HCV Coinfection trial.

### Rationale for Dose Selection

The doses of ABT-450 (150 mg once daily), ritonavir (100 mg once daily), ABT-267 (25 mg) and ABT-333 (250 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	(b) (4)		
	ABT-333	Emtriva® (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	Gilead Sciences, Inc. Foster City, CA	Gilead Sciences, Inc. Foster City, CA
Finishing Lot Number	12-004028	12-004282	12-004165
Expiration Date	(b) (4)		

### 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, ABT-333, ABT-333 M1 metabolite, FTC, and TDF 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, TDF (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, ABT-333, ABT-333 M1 metabolite, FTC, and TDF were collected on the following days:

#### FTC and TDF (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.

#### DAAAs, FTC, TDF (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, ABT-333, ABT-333 M1 metabolite, FTC, and TDF 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 %
ABT-333	4.53-3090	4.53	12.3, 209, 2610	3.8 % to	-3.4 % to 0

				4.7 %	%
ABT-333 M1	4.73-3220	4.73	12.2,208,2590	2.5 % to 5.4 %	-1.6 % to -0.5 %
FTC	20-4000	20	40,100, 300, 800, and 3000	2.9 % to 3.59 %	-0.6 % to 2.8 %
TDF	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.

	<b>Mean ± SD (N = 36)</b>	<b>Min – Max</b>
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, TDF (Arm 1)

ABT-450

Table 6 shows the mean ± SD pharmacokinetic parameters of ABT-450 in Arm 1.



Pharmacokinetic Parameters		ABT-450 Arm 1/Cohort 1 (N = 9)		
	(Units)	Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	2380 ± 1710	2100 ± 1900	1860 ± 1400
T <sub>max</sub>	(h)	4.3 ± 1.0	4.4 ± 0.9	4.7 ± 0.7
AUC <sub>24</sub>	(ng•h/mL)	9920 ± 8570	9750 ± 10400	8810 ± 7390
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.1 ± 1.2
C <sub>24</sub>	(ng/mL)	27.0 ± 25.9	29.6 ± 24.1	26.3 ± 17.2
		Arm 1/Cohort 2 (N = 9)		
	(Units)	Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	468 ± 414	1420 ± 927
T <sub>max</sub>	(h)	--	5.1 ± 0.9	4.6 ± 0.5
AUC <sub>24</sub>	(ng•h/mL)	--	2690 ± 2040	6710 ± 4340
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.3 ± 0.8
C <sub>24</sub>	(ng/mL)	--	22.0 ± 14.9	22.2 ± 10.4

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen C: 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 1.

Pharmacokinetic Parameters		Ritonavir Arm 1/Cohort 1 (N = 9)		
	(Units)	Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	1660 ± 511	1320 ± 616	1420 ± 567
T <sub>max</sub>	(h)	4.7 ± 0.5	4.3 ± 1.0	4.8 ± 0.4
AUC <sub>24</sub>	(ng•h/mL)	9400 ± 2820	8720 ± 3170	9090 ± 2770
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.8 ± 1.4
C <sub>24</sub>	(ng/mL)	54.3 ± 23.6	68.3 ± 35.4	52.7 ± 23.3
		Arm 1/Cohort 2 (N = 9)		
	(Units)	Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	543 ± 286	1320 ± 573
T <sub>max</sub>	(h)	--	7.8 ± 5.5	4.4 ± 1.0
AUC <sub>24</sub>	(ng•h/mL)	--	4950 ± 2640	9360 ± 3860
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	4.2 ± 0.3
C <sub>24</sub>	(ng/mL)	--	64.6 ± 47.2	47.4 ± 24.6

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen C: 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.

## ABT-267 (Arm 1)

Table 8 shows the mean ± SD pharmacokinetic parameters of ABT-267 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-267 Arm 1/Cohort 1 (N = 9)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	132 ± 32.0	138 ± 33.9	117 ± 25.9
T <sub>max</sub>	(h)	4.9 ± 0.8	4.6 ± 1.0	4.9 ± 0.6
AUC <sub>24</sub>	(ng•h/mL)	1430 ± 378	1530 ± 407	1420 ± 397
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	33.5 ± 13.3
C <sub>24</sub>	(ng/mL)	30.2 ± 11.0	31.3 ± 11.2	29.3 ± 10.6

Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2 (N = 9)		
		Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	113 ± 21.3	99.4 ± 17.2
T <sub>max</sub>	(h)	--	5.0 ± 0.0	5.1 ± 0.3
AUC <sub>24</sub>	(ng•h/mL)	--	1060 ± 212	1230 ± 245
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	32.9 ± 7.8
C <sub>24</sub>	(ng/mL)	--	17.7 ± 3.4	25.9 ± 6.0

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen C: 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.

## ABT-333 and ABT-333 M1 metabolite (Arm 1)

Table 9 shows the mean ± SD pharmacokinetic parameters of ABT-333 in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 Arm 1/Cohort 1 (N = 9)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	1170 ± 476	1160 ± 484	1010 ± 408
T <sub>max</sub>	(h)	3.0 ± 1.5	3.2 ± 1.4	3.2 ± 0.8
AUC <sub>12</sub>	(ng•h/mL)	8460 ± 3670	7560 ± 3340	7290 ± 3230
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.4 ± 0.7 <sup>b</sup>
C <sub>12</sub>	(ng/mL)	324 ± 163	272 ± 144	279 ± 139
C <sub>24</sub>	(ng/mL)	216 ± 134	204 ± 132	168 ± 92.1

Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2 (N = 9)		
		Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	846 ± 242	767 ± 221
T <sub>max</sub>	(h)	--	2.8 ± 0.8	3.1 ± 0.9
AUC <sub>12</sub>	(ng•h/mL)	--	5780 ± 1880	5880 ± 1670
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	6.1 ± 0.7
C <sub>12</sub>	(ng/mL)	--	230 ± 76.2	221 ± 59.9
C <sub>24</sub>	(ng/mL)	--	238 ± 86.8	135 ± 34.1

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen C: 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.

b. N = 7.

Table 10 shows the mean ± SD pharmacokinetic parameters of ABT-333 M1 metabolite in Arm 1.

Pharmacokinetic Parameters	(Units)	ABT-333 M1 Metabolite Arm 1/Cohort 1 (N = 9)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	795 ± 210	759 ± 295	747 ± 274
T <sub>max</sub>	(h)	4.2 ± 1.0	3.8 ± 1.0	3.8 ± 0.7
AUC <sub>12</sub>	(ng•h/mL)	4940 ± 1880	4510 ± 2000	4600 ± 1790
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	ND
C <sub>12</sub>	(ng/mL)	158 ± 81.0	133 ± 60.0	150 ± 68.2
C <sub>24</sub>	(ng/mL)	82.0 ± 35.4	77.0 ± 33.4	66.6 ± 34.1
Arm 1/Cohort 2 (N = 9)				
Pharmacokinetic Parameters	(Units)	Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	693 ± 168	640 ± 183
T <sub>max</sub>	(h)	--	4.6 ± 0.9	4.4 ± 0.7
AUC <sub>12</sub>	(ng•h/mL)	--	4230 ± 1250	4240 ± 1450
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	5.8 <sup>b</sup>
C <sub>12</sub>	(ng/mL)	--	166 ± 58.7	142 ± 50.3
C <sub>24</sub>	(ng/mL)	--	132 ± 42.6	67.2 ± 28.7

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).  
Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).  
Regimen C: Emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 1 to 7 (Cohort 2).  
ND = Not determined  
a. Harmonic mean ± pseudo-standard deviation; evaluations of t<sub>1/2</sub> were based on statistical tests for β.  
b. N = 1.

Emtricitabine (Arm 1)

Table 11 shows the mean ± SD pharmacokinetic parameters of ABT-333 M1 metabolite in Arm 1.

Pharmacokinetic Parameters	(Units)	Emtricitabine Arm 1/Cohort 1 (N = 9)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	--	1530 ± 182	1600 ± 271
T <sub>max</sub>	(h)	--	2.8 ± 0.7	2.9 ± 0.8
AUC <sub>24</sub>	(ng•h/mL)	--	9430 ± 1120	11000 ± 1740
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	17.8 ± 7.3
C <sub>24</sub>	(ng/mL)	--	46.7 ± 9.7	86.7 ± 23.2
Arm 1/Cohort 2 (N = 9)				
Pharmacokinetic Parameters	(Units)	Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
C <sub>max</sub>	(ng/mL)	1490 ± 90.5	1530 ± 174	1580 ± 146
T <sub>max</sub>	(h)	2.7 ± 0.5	2.9 ± 0.6	2.3 ± 0.5
AUC <sub>24</sub>	(ng•h/mL)	10800 ± 1030	11100 ± 1450	11500 ± 1580
t <sub>1/2</sub> <sup>a</sup>	(h)	--	--	28.7 ± 14.3
C <sub>24</sub>	(ng/mL)	93.9 ± 20.9	95.0 ± 20.8	102 ± 22.1

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).  
Regimen B: 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 on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).  
Regimen C: 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.

Tenofovir (Arm 1)

Table 12 shows the mean  $\pm$  SD pharmacokinetic parameters of ABT-333 M1 metabolite in Arm 1.

Pharmacokinetic Parameters	(Units)	Tenofovir Arm 1/Cohort 1 (N = 9)		
		Regimen A: Day 14	Regimen B: Day 15	Regimen B: Day 21
$C_{max}$	(ng/mL)	--	271 $\pm$ 78.0	307 $\pm$ 67.5
$T_{max}$	(h)	--	1.7 $\pm$ 0.7	1.7 $\pm$ 1.1
$AUC_{24}$	(ng•h/mL)	--	2250 $\pm$ 418	3650 $\pm$ 641
$t_{1/2}^a$	(h)	--	--	19.2 $\pm$ 3.3
$C_{24}$	(ng/mL)	--	45.1 $\pm$ 7.4	80.5 $\pm$ 19.0

Pharmacokinetic Parameters	(Units)	Arm 1/Cohort 2 (N = 9)		
		Regimen C: Day 7	Regimen B: Day 8	Regimen B: Day 21
$C_{max}$	(ng/mL)	280 $\pm$ 20.2	279 $\pm$ 46.6	308 $\pm$ 83.7
$T_{max}$	(h)	2.0 $\pm$ 0.5	1.7 $\pm$ 0.5	1.6 $\pm$ 0.5
$AUC_{24}$	(ng•h/mL)	3210 $\pm$ 552	3140 $\pm$ 516	3620 $\pm$ 571
$t_{1/2}^a$	(h)	--	--	19.5 $\pm$ 4.2
$C_{24}$	(ng/mL)	67.1 $\pm$ 17.1	73.7 $\pm$ 15.9	81.4 $\pm$ 13.2

Regimen A: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID administered under non-fasting conditions on Study Days 1 to 14 (Cohort 1).

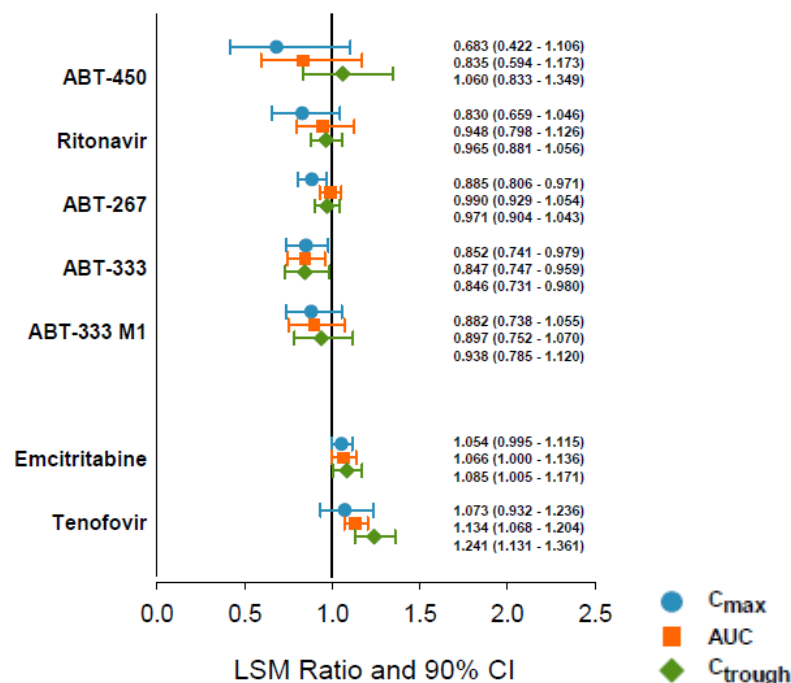
Regimen B: ABT-450/r 150/100 mg QD + ABT-267 25 mg QD + ABT-333 400 mg BID + emtricitabine 200 mg QD + tenofovir disoproxil fumarate 300 mg QD administered under non-fasting conditions on Study Days 15 to 21 (Cohort 1) and on Study Days 8 to 21 (Cohort 2).

Regimen C: 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  $t_{1/2}$  were based on statistical tests for  $\beta$ .

## Statistical Evaluation of the Pharmacokinetic Parameters

Fig 8 shows the statistical comparison of the pharmacokinetic parameters of ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite FTC, and TDF in Arm 1.



## Safety

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

## Results

Co-administration of ABT-450/r/ABT-267 and ABT-333 with FTC and TDF:

- Decreased the mean  $C_{\max}$  and  $AUC_{24}$  of ABT-450 by 32 % and 16 %, respectively, and increased the  $C_{24}$  by 6 %.
- Decreased the mean  $C_{\max}$ ,  $AUC_{24}$ , and  $C_{24}$  of ritonavir by 17 %, 5 %, and 3 %, respectively.
- Decreased the mean  $C_{\max}$ ,  $AUC_{24}$ , and  $C_{24}$  of ABT-267 by 11 %, 1 %, and 3 %, respectively.
- Decreased the mean  $C_{\max}$ ,  $AUC_{12}$ , and  $C_{12}$  of ABT-333 by 15 %, 15 %, and 15 %, respectively.
- Decreased the mean  $C_{\max}$ ,  $AUC_{12}$ , and  $C_{12}$  of ABT-333 M1 metabolite by 12 %, 10 %, and 6 %, respectively.
- Increase the mean  $C_{\max}$ ,  $AUC_{24}$ , and  $C_{24}$  of FTC by 5 %, 7 %, and 9 %, respectively.
- Increase the mean  $C_{\max}$ ,  $AUC_{24}$ , and  $C_{24}$  of TDF by 7 %, 13 %, and 24 %, respectively.

## Conclusion

ABT-450/ritonavir/ABT-267 and ABT-333 can be co-administered with emtricitabine/tenofovir without any dose adjustments.

**Drug-Drug Interaction Trial with Escitalopram or Duloxetine**  
**Reviewer: Seong Jang, Ph.D.**

**A Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability of the Co-administration of Escitalopram or Duloxetine with Combination Therapy of ABT-450, Ritonavir, ABT-267 (ABT-450/r/ABT-267) With and Without ABT-333 in Healthy Adult Volunteers (M12-204)**

**Study period:** 07 May 2013 to 30 September 2013

**Objectives:** The objectives of the study were to determine the effect of steady-state ABT-450/r/ABT-267 with and without ABT-333 on the pharmacokinetics, safety and tolerability of single dose escitalopram or duloxetine in healthy subjects. In addition, the effect of single dose escitalopram or duloxetine on the pharmacokinetics, safety and tolerability of steady-state ABT-450/r/ABT-267 with and without ABT-333 was also examined.

*Reviewer's comments: The effect of a single dose of escitalopram or duloxetine on the PK of ABT-450/r and ABT-333 and/or ABT-267 is not clinically meaningful because the PK of steady state escitalopram or duloxetine would not be similar to that of a single dose. The half-life of escitalopram is approximately 27-33 hours and the time to reach steady state is 7-10 days. The half-life of duloxetine is approximately 12 hours and the time to reach steady state is 2-3 days. Thus, the results of this study (i.e., the effect of a single dose of escitalopram or duloxetine on the PK of ABT-450/r and ABT-333 and/or ABT-267) are not informative to predict the clinically relevant effect of escitalopram or duloxetine on the PK of ABT-450/r and ABT-333 and/or ABT-267 unless the PK of ABT-450/r and ABT-333 and/or ABT-267 were affected substantially due to the single dose of escitalopram or duloxetine so that it is obvious to recommend a contraindication of DAAs with escitalopram or duloxetine (this is not the case based on the sponsor's study report). Thus, the effect of a single dose of escitalopram or duloxetine on the PK of ABT-450/r and ABT-333 and/or ABT-267 was not reviewed.*

**Methodology:**

This Phase 1, single center, multiple-dose, open-label study was designed to evaluate the pharmacokinetics, safety and tolerability of 2- and 3-DAA regimens (ABT-450/r/ABT-267 and ABT450/r/ABT-267 + ABT-333) and escitalopram or duloxetine when given alone and in combination. The study consisted of two independent parts, Part I and Part II. Each part consisted of two treatment arms, Arm 1 and Arm 2. Adult male and female subjects (N = 48) in general good health were selected to participate in the study according to the selection criteria.

Study drug was administered as follows:

- Regimen A** Escitalopram 10 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period for 6 days (Study Days 2 through 6).
- Regimen B** ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions for 20 days (Study Days 7 through 26) with the

- QD doses being administered in the morning. On Study Day 21, escitalopram 10 mg was administered under non-fasting conditions as a single dose.
- Regimen C** ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions for 20 days (Study Days 7 through 26). On Study Day 21, escitalopram 10 mg was administered under non-fasting conditions as a single dose.
- Regimen D** Duloxetine 60 mg administered under non-fasting conditions as a single dose on Study Day 1 followed by a washout period for 6 days (Study Days 2 through 6).
- Regimen E** ABT-333 250 mg BID + ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions for 16 days (Study Days 7 through 22) with the QD doses being administered in the morning. On Study Day 21, duloxetine 60 mg was administered under non-fasting conditions as a single dose.
- Regimen F** ABT-450/r/ABT-267 150/100/25 mg QD administered under non-fasting conditions for 16 days (Study Days 7 through 22). On Study Day 21, duloxetine 60 mg was administered under non-fasting conditions as a single dose.

Each dose of study drug was taken orally with approximately 240 mL of water approximately 30 minutes after starting breakfast for all morning doses and approximately 30 minutes after the start of the evening snack for the evening dose of ABT-333 (if appropriate to the arm). On Study Day 21, the dose of escitalopram or duloxetine was administered in the morning at the same time as the DAAs. Upon completion of the study, each subject had received two regimens as described above (Regimen A and Regimen B or C, or Regimen D and Regimens E or F). A washout interval of 6 days separated the dose of Regimen A or D on Study Day 1 from the first dose of Regimens B or C in Part I or Regimens E or F in Part II on Study Day 7.

#### Blood Samples for Escitalopram (Part I)

Blood samples for plasma concentration measurement of escitalopram and its metabolite S-desmethylescitalopram were collected by venipuncture on the following days: prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 24 (Study Day 2), 36 (Study Day 2), 48 (Study Day 3), 72 (Study Day 4), 96 (Study Day 5), 120 (Study Day 6), and 144 (Study Day 7) hours after morning dosing on Study Day 1, prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 24 (Study Day 22), 36 (Study Day 22), 48 (Study Day 23), 72 (Study Day 24), 96 (Study Day 25), 120 (Study Day 26), and 144 (Study Day 27) hours after morning dosing on Study Day 21.

#### Blood Samples for Duloxetine (Part II)

Blood samples for plasma concentration measurement of duloxetine were collected by venipuncture on the following days: prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 24 (Study Day 2), 36 (Study Day 2), and 48 (Study Day 3) hours after morning dosing on Study Day 1, prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 24 (Study Day 22), 36 (Study Day 22), and 48 (Study Day 23) hours after morning dosing on Study Day 21, or upon subject discontinuation due to an adverse event.

#### Analysis of Escitalopram and S-desmethylescitalopram Plasma Samples (Part I)

Plasma concentrations of escitalopram and S-desmethylescitalopram were determined using a validated high performance LC-MS/MS method and automated extraction. The LLOQs for

escitalopram and S-desmethylescitalopram were established at 200 pg/mL and 50 pg/mL using a 100 µL plasma sample. Samples quantified below the lowest standard were reported as zero.

#### Analysis of Duloxetine Plasma Samples (Part II)

Plasma concentrations of duloxetine were determined using a validated high performance LC-MS/MS method and automated extraction. The LLOQ for duloxetine was established at 0.51 ng/mL using a 100 µL plasma sample. Samples quantified below the lowest standard were reported as zero.

#### **Number of Subjects (Planned and Analyzed):**

Planned: 48; Entered: 48 (24 subjects each for Parts I and II); Completed: 46;

Evaluated for Safety & Pharmacokinetics: 47

For the 24 subjects who participated in Part I of the study, the mean age was 34.4 years (ranging from 21 to 55 years), the mean weight was 78.2 kg (ranging from 65 to 94 kg) and the mean height was 175 cm (ranging from 155 to 194 cm).

For the 24 subjects who participated in Part II of the study, the mean age was 38.5 years (ranging from 23 to 55 years), the mean weight was 75.6 kg (ranging from 58 to 104 kg) and the mean height was 171 cm (ranging from 154 to 194 cm).

#### **Diagnosis and Main Criteria for Inclusion:**

Subjects were male and female volunteers between 18 and 55 years, inclusive. Subjects in the study were judged to be in general good health based on the results of medical history, physical examination, vital signs, laboratory profile, and 12-lead electrocardiogram (ECG). Females were either postmenopausal for at least 2 years or surgically sterile and were not pregnant. Males were either surgically sterile or practicing at least one of the acceptable methods of birth control.

#### **Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

Investigational Products	ABT-450/Ritonavir/ ABT-267	ABT-333	Escitalopram	Cymbalta Duloxetine
Mode of Administration	Oral	Oral	Oral	Oral
Dosage Form	Tablet	Tablet	Tablet	Capsule
Strength (mg)	75/50/12.5 mg	250 mg	10 mg	60 mg
Manufacturer	AbbVie	AbbVie	Mylan	Eli Lilly
Bulk Product Lot Number	12-008149	12-007842	13-002269	12-003824
Potency	(b) (4)	(b) (4)	N/A	N/A
Finishing Lot Number	13-002231	13-002232	13-002233	13-002234
Expiration Date	(b) (4)	(b) (4)	(b) (4)	(b) (4)

N/A = Not available

#### **Duration of Treatment:**

Dosing for Part I, Arms 1 and 2, began on 29 May 2013 and ended on 23 June 2013. Dosing for Part II, Arms 1 and 2, began on 10 July 2013 and ended on 31 July 2013.

#### **Criteria for Evaluation:**



**Pharmacokinetic:** Values for the pharmacokinetic parameters of escitalopram, S-desmethylescitalopram and duloxetine were estimated using noncompartmental methods. These included: the maximum observed plasma concentration ( $C_{max}$ ), the time to  $C_{max}$  (peak time,  $T_{max}$ ), and the pre-dose trough plasma concentration [ $C_{trough}$  ( $C_{12}$  or  $C_{24}$ )], the area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable concentration ( $AUC_t$ ), the AUC from time 0 to infinite time ( $AUC_{\infty}$ ,  $AUC_{inf}$ ), the apparent terminal phase elimination rate constant ( $\beta$ ), the terminal phase elimination half-life ( $t_{1/2}$ ) and the AUC from time 0 to 12 hours or 24 hours ( $AUC_{12}$  or  $AUC_{24}$ ).

**Safety Endpoints:** The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, ECG and laboratory tests assessments.

### **Statistical Methods:**

**Pharmacokinetic:** To assess the effect of steady-state DAAs on a single dose of escitalopram or duloxetine, a repeated measures analysis was performed for the natural logarithms of the  $C_{max}$ , AUC and  $AUC_{\infty}$  values of escitalopram and its metabolite S-desmethylescitalopram (S-DCT), or duloxetine, utilizing data from Study Days 1 and 21. The model had day as a fixed effect and subject as a random effect. Additionally, the ratio of escitalopram and S-DCT or duloxetine  $C_{max}$ , AUC and  $AUC_{\infty}$  when administered with the DAAs to those when administered without the DAAs were estimated by taking the ratio of corresponding Study Day 21 versus Study Day 1 values, obtained from the repeated measures analysis of the difference of mean logarithms. The 90% confidence intervals were obtained for those ratio estimates by the exponentiation of the endpoints of confidence intervals for the difference of mean logarithms obtained within the framework of the repeated-analysis model.

**Safety:** Adverse events were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of randomized study drug) were tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by period within each arm. The tabulation of the number of subjects with treatment-emergent adverse events also was provided with further breakdowns by severity rating and relationship to study drug. Within each period, subjects reporting more than one adverse event for a given MedDRA Preferred Term was counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC were counted only once for that SOC.

Laboratory test values and vital signs measurements that are very high or very low, according to predefined criteria, were identified.

### **Results:**

#### **Pharmacokinetics:**

**Part 1:** The effects of the combination of ABT-450/r/ABT-267 and ABT-333 (3 DAAs) on the pharmacokinetics of escitalopram and S-desmethylescitalopram administered as a single dose in healthy subjects are summarized in Table 1. There are no clinically substantial changes in the PK of escitalopram and S-desmethylescitalopram due to the 3-DAA co-administration.

**Table 1.** The effect ABT-450/r/ABT-267 and ABT-333 (3 DAAs) on the pharmacokinetics of escitalopram and S-desmethylescitalopram administered as a single dose in healthy subjects

Escitalopram		Ratio of Central Values		
Pharmacokinetic Parameter	Central Values <sup>a</sup>		Point Estimate <sup>d</sup>	90% Confidence Interval
	D1 <sup>b</sup>	D21 <sup>c</sup>		
C <sub>max</sub> (ng/mL)	8.69	8.72	1.004	0.963 – 1.046
AUC <sub>t</sub> (ng•h/mL)	263	219	0.831	0.758 – 0.912
AUC <sub>inf</sub> (ng•h/mL)	282	246	0.873	0.799 – 0.954
<b>S-desmethylescitalopram</b>				
C <sub>max</sub> (ng/mL)	1.30	1.50	1.150	1.095 – 1.208
AUC <sub>t</sub> (ng•h/mL)	122	122	1.005	0.829 – 1.218
AUC <sub>inf</sub> (ng•h/mL)	153	208	1.364	1.033 – 1.801

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Day 1 (D1): Single dose of escitalopram 10 mg.

<sup>c</sup>. Day 21 (D21): ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + escitalopram 10 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The effects of the combination of ABT-450/r/ABT-267 (2 DAAs) on the pharmacokinetics of escitalopram and S-desmethylescitalopram administered as a single dose in healthy subjects are summarized in Table 2. There are no clinically substantial changes (<25%) in the PK of escitalopram and S-desmethylescitalopram due to the 2-DAA co-administration.

**Table 2.** The effect ABT-450/r/ABT-267 (2 DAAs) on the pharmacokinetics of escitalopram and S-desmethylescitalopram administered as a single dose in healthy subjects

Escitalopram		Ratio of Central Values		
Pharmacokinetic Parameter	Central Values <sup>a</sup>		Point Estimate <sup>d</sup>	90% Confidence Interval
	D1 <sup>b</sup>	D21 <sup>c</sup>		
C <sub>max</sub> (ng/mL)	9.68	8.86	0.915	0.849 – 0.987
AUC <sub>t</sub> (ng•h/mL)	267	200	0.748	0.666 – 0.840
AUC <sub>inf</sub> (ng•h/mL)	278	209	0.753	0.672 – 0.844
<b>S-desmethylescitalopram</b>				
C <sub>max</sub> (ng/mL)	1.51	1.77	1.167	1.084 – 1.257
AUC <sub>t</sub> (ng•h/mL)	133	146	1.099	1.048 – 1.152
AUC <sub>inf</sub> (ng•h/mL)	157	167	1.065	1.005 – 1.129

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Day 1 (D1): Single dose of escitalopram 10 mg.

<sup>c</sup>. Day 21 (D21): ABT-450/r/ABT-267 150/100/25 mg QD + escitalopram 10 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

**Part 2:** The effects of the combination of ABT-450/r/ABT-267 and ABT-333 (3 DAAs) on the pharmacokinetics of duloxetine administered as a single dose in healthy subjects are summarized in Table 3. There are no clinically substantial changes (<25%) in the PK of duloxetine due to the 3-DAA co-administration.

**Table 3.** The effect ABT-450/r/ABT-267 and ABT-333 (3 DAAs) on the pharmacokinetics of duloxetine administered as a single dose in healthy subjects

Duloxetine	Ratio of Central Values			
Pharmacokinetic Parameter	Central Values <sup>a</sup>		Point Estimate <sup>d</sup>	90% Confidence Interval
	D1 <sup>b</sup>	D21 <sup>c</sup>		
C <sub>max</sub> (ng/mL)	40	32	0.792	0.669 – 0.939
AUC <sub>t</sub> (ng•h/mL)	617	468	0.758	0.681 – 0.843
AUC <sub>inf</sub> (ng•h/mL)	659	491	0.745	0.670 – 0.829

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Day 1 (D1): Single dose of duloxetine 60 mg.

<sup>c</sup>. Day 21 (D21): ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + duloxetine 60 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

The effects of the combination of ABT-450/r/ABT-267 (2 DAAs) on the pharmacokinetics of duloxetine administered as a single dose in healthy subjects are summarized in Table 4. There are no clinically substantial changes (<25%) in the PK of duloxetine due to the 2-DAA co-administration.

**Table 4.** The effect ABT-450/r/ABT-267 (2 DAAs) on the pharmacokinetics of duloxetine administered as a single dose in healthy subjects

Duloxetine	Ratio of Central Values			
Pharmacokinetic Parameter	Central Values <sup>a</sup>		Point Estimate <sup>d</sup>	90% Confidence Interval
	D1 <sup>b</sup>	D21 <sup>c</sup>		
C <sub>max</sub> (ng/mL)	38	32	0.832	0.718 – 0.964
AUC <sub>t</sub> (ng•h/mL)	599	487	0.813	0.722 – 0.916
AUC <sub>inf</sub> (ng•h/mL)	648	519	0.800	0.711 – 0.901

<sup>a</sup>. Antilogarithm of the least squares means for logarithms.

<sup>b</sup>. Day 1 (D1): Single dose of duloxetine 60 mg.

<sup>c</sup>. Day 21 (D21): ABT-450/r/ABT-267 150/100/25 mg QD + duloxetine 60 mg single dose.

<sup>d</sup>. Antilogarithm of the difference of the least squares means for logarithms.

### Safety Results:

The DAAs co-administered with escitalopram in Part I of this study were generally well tolerated by the subjects. Overall, up to 41.7% of subjects experienced at least one adverse event. All adverse events were mild in severity without causing study treatment changes with the exceptions of the following three events. One subject (8.3%) in Part I Arm 1 discontinued from the study drugs due to increased AST which was assessed by the investigator as mild in severity and having a reasonable possibility of being related to the DAAs, but no reasonable possibility of being related to escitalopram. One subject (8.3%) in Part I Arm 2 discontinued from the study due to lobar pneumonia which was assessed by the investigator as mild in severity and having no reasonable possibility of being related to escitalopram or the DAAs. The same subject also experienced a serious adverse event of bacterial prostatitis which was assessed as moderate in severity and having no reasonable possibility of being related to the study drugs.

The DAAs co-administered with duloxetine in Part II of this study were generally well tolerated by the subjects. Overall, up to 66.7% of subjects experienced at least one adverse event. All adverse events were assessed as mild in severity.

No deaths were reported in this study. There were no clinically meaningful or significant trends noted among the potentially clinically significant laboratory values in either part of this study. No new safety signals or unexpected toxicities were observed when the DAAs were co-administered with escitalopram or duloxetine.

### **Conclusions:**

#### Part 1: Escitalopram

Escitalopram  $C_{max}$  and AUC values were not affected ( $< 20\%$  change) when co-administered with the 3-DAA regimen at steady state; however, the S-desmethylescitalopram (S-DCT)  $AUC_{inf}$  increased by 36% when co-administered with the 3-DAA regimen at steady state compared to that when escitalopram was administered alone.

When escitalopram was co-administered with the 2-DAA regimen, escitalopram AUC decreased by 25%, although escitalopram  $C_{max}$  and S-DCT exposures were not affected.

S-DCT has 7-fold less activity than escitalopram, and therefore, no dose adjustment is needed for escitalopram when co-administered with ABT-450/r + ABT-267 with and without ABT-333.

#### Part 1: Duloxetine

After a single dose of duloxetine was co-administered with the 2-DAA regimen at steady state, the exposures of ABT-450, ritonavir and ABT-267 were not affected ( $< 20\%$  difference) compared to that when the 2 DAAs were administered without duloxetine.

Duloxetine exposures were 21% to 25% lower when co-dosed with the 3-DAA regimen at steady state, but were not affected ( $\leq 20\%$  change) with the 2-DAA regimen at steady state. Decrease in duloxetine exposures by up to 30% does not require dose adjustment (based on decrease in duloxetine levels observed with CYP1A2 induction in smokers) and hence, no dose adjustment is needed for duloxetine when it is co-administered with either of the AbbVie DAA combination regimens.

#### Safety:

The DAA combinations co-administered with escitalopram or duloxetine in all the arms of this study were generally well tolerated by the subjects. No new safety signals or unexpected toxicities were observed when the DAAs were co-administered with escitalopram or duloxetine.

#### *Reviewer's conclusion and labeling recommendation:*

*Based on the results of this study, the sponsor proposed that no dose adjustments of duloxetine or escitalopram are required when co-administering with DAAs. We agreed that the sponsor's labeling recommendation. However, the results of this study do not support that no dose adjustments of DAAs are needed when DAAs are co-administered with duloxetine or escitalopram because this study was not designed to evaluate the effects of steady-state duloxetine and escitalopram on the PK of DAAs, which are not necessarily similar to the effects of a single dose of duloxetine and escitalopram on the PK of DAAs. For example, in this study, a single dose of escitalopram increased the  $C_{max}$  and  $AUC_{24}$  of ritonavir by 38% (15–66% of 90% CI) and 25% (7–46% of 90% CI), respectively, when it was co-administered with 2 DAAs. Similarly, a single dose of escitalopram increased the  $C_{max}$  and  $AUC_{24}$  of ritonavir*

*by 31% (-4–78% of 90% CI) and 18% (-2–41% of 90% CI), respectively, when it was co-administered with 3 DAAs. The increases in ritonavir  $C_{max}$  and  $AUC_{24}$  due to a single dose of escitalopram may not be quantitatively similar to those due to steady state escitalopram. Accordingly, we recommend that this should be noted in Section 7.4.*

**Extrapolations of Clinical Recommendations Due to Differences in ABT-450 Formulations Used in the Drug-Drug Interaction Trials**  
**Reviewer: Vikram Arya, Ph.D., FCP**

**Extrapolation of Clinical Recommendations Based on Drug-Drug Interaction Trials Conducted with ABT-450 (b) (4) Tablets to ABT-267/ABT-450/ritonavir Co-formulated Tablets**

Background

The Applicant used several different formulations of ABT-450 during development. In the Phase 3 trials, the applicant used the ABT-267/ABT-450/ritonavir co-formulated tablet formulation whereas in several Phase 1 drug-drug interaction trials, the applicant used the ABT-450 (b) (4) tablet formulation.

Table 1 shows the various ABT-450 formulations used in the DDI trials.

ABT-450 (b) (4) Tablet and Ritonavir Capsule (Used in Phase 1 and Phase 2 Studies)	ABT-450/r Co-Formulated Tablet (Used in Phase 1 Studies)	ABT-450/r/ABT-267 Co-Formulated Tablet (Used in Phase 1 and Phase 3 Studies)
M12-196 (Gemfibrozil) M13-104 (Atripla) M13-103 (Cyclosporine) M13-491 (Tacrolimus) M13-392 (Raltegravir) M13-783 (emtricitabine/tenofovir DF) M13-492 (Lopinavir/r BID) M13-506 (Darunavir QD and BID) M12-200 (Pravastatin and Rosuvastatin) M12-201 (Digoxin) M12-198 (Warfarin)	M13-394 (Atazanavir) M14-013 (Lopinavir/r QPM) M13-782 (Rilpivirine)	M12-997 (Methadone) <sup>a</sup> M13-100 (Buprenorphine/Naloxone) <sup>a</sup> M12-202 (Darunavir [QPM]) M14-027 (Carbamazepine) M12-189 (Ketoconazole) M12-199 (Omeprazole) M12-205 (Oral contraceptives) M12-204 (Escitalopram or Duloxetine) M14-324 (Alprazolam or Zolpidem Tartrate) M14-325 (Furosemide or Amlodipine Besylate)

QD = Once daily; BID = Twice daily; QPM = once daily in the evening; tenofovir DF = tenofovir disoproxil fumarate; Atripla = emtricitabine/tenofovir disoproxil fumarate/efavirenz; ABT-450/r co-formulated tablet = ABT-450 and ritonavir co-formulated tablet; ABT-450/r/ABT-267 co-formulated tablet = ABT-450, ritonavir and ABT-267 co-formulated tablet

- a. Methadone and buprenorphine/naloxone interactions were evaluated with both (b) (4) and co-formulated formulations.<sup>11,12</sup>

### Comparison of ABT-450 Exposures Across Various Formulations and Trials

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 is shown in table 2 below.

	ABT-450	RTV	ABT-267
	ABT-450/r/ABT-267 Co-formulated vs. (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<sub>max</sub> and AUC of ABT-450 administered as ABT-450/r/ABT-267 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.

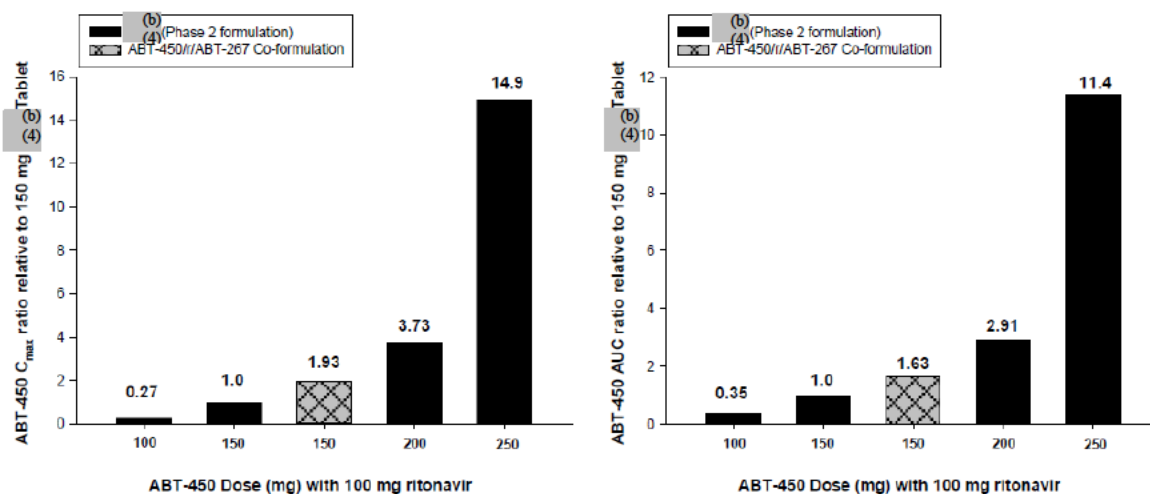
Table 3 shows the comparison of mean ABT-450 150 mg exposures across formulations at steady state (data pooled across various trials).

ABT-450 Formulation	Number of Study Arms	C <sub>max</sub>		AUC		
		Value <sup>a</sup> (ng/mL)	Ratio <sup>b</sup>	Value <sup>a</sup> (ng•hr/mL)	Ratio <sup>b</sup>	
3 DAAs						
ABT-450 (b) (4) Tablet	10	991	--	5270	--	
ABT-450/r Co-formulated Tablet	6	1660	1.67	9250	1.76	
ABT-450/r/ABT-267 Co-formulated Tablet	8	1470	1.48	6990	1.33	
2 DAAs (ABT-450, RTV and ABT-267)						
ABT-450 (b) (4) Tablet	8	557	--	3220	--	
ABT-450/r Co-formulated Tablet	2	1550	2.78	8230	2.56	
ABT-450/r/ABT-267 Co-formulated Tablet	3	807	1.45	4770	1.48	

a Overall geometric mean.

b Ratio of geometric: mean using (b) (4) tablet as reference.

Fig 1 shows the comparison of the ratios of the ABT-450 exposures ( $C_{max}$  and AUC) from the Phase 3 ABT-450 co-formulation (ABT-267/ABT-450/ritonavir) relative to the Phase 2 ABT-450 (b) (4) formulation versus ABT-450 dose.



Note: Ratios are based on exponentiated least squares mean  $C_{max}$  and AUC data from Studies M12-683 (ABT-450 (b) (4) doses: 100 mg, 150 mg), M13-391 (ABT-450 dose of 150 mg from the ABT-450/r/ABT-267 co-formulated tablet) and geometric mean  $C_{max}$  and AUCs from Study M12-221 (ABT-450 (b) (4) doses: 200 mg and 250 mg, Caucasian subjects).

The 150 mg dose of ABT-450 from the ABT-450/r/ABT-267 co-formulated tablet (Phase 3 formulation) provided 93% and 63% higher  $C_{max}$  and AUC, respectively, compared to that from the 150 mg dose of the (b) (4) Phase 2 tablet. However these exposures were lower than exposures from the 200 and 250 mg doses of the (b) (4) tablet formulation evaluated in Phase 2 studies. Overall, mean ABT-450 exposures after administration of ABT-267/ABT-450/ritonavir co-formulated tablet were approximately 30 % (after multiple doses) to 60 % (after single dose) higher as compared to ABT-450 exposures after single- and multiple dose administration, respectively, of ABT-450 (b) (4) tablets.

#### Comparison of Ritonavir and ABT-267 Pharmacokinetic Parameters Across Various Formulations and Trials

##### Ritonavir

Table 4 shows the comparison of ritonavir 100 mg steady state pharmacokinetic parameters across various formulations and trials.



ABT-450 Formulation	Number of Study Arms	C <sub>max</sub>		AUC	
		Value <sup>a</sup> (ng/mL)	Ratio <sup>b</sup>	Value <sup>a</sup> (ng•hr/mL)	Ratio <sup>b</sup>
3 DAAs					
ABT-450 (b) (4) tablet plus ritonavir SGC	10	1730	--	11100	--
ABT-450/r Co-formulated Tablet	6	1900	1.10	11400	1.03
ABT-450/r/ABT-267 Co-formulated Tablet	8	1600	0.92	9470	0.85
2 DAAs (ABT-450, RTV and ABT-267)					
ABT-450 (b) (4) tablet plus ritonavir SGC	8	1580	--	9740	--
ABT-450/r Co-formulated Tablet	2	1610	1.02	9440	0.97
ABT-450/r/ABT-267 Co-formulated Tablet	3	1330	0.84	8090	0.83

a Overall geometric mean.

b Ratio of geometric mean using the ritonavir exposures when co-dosed with ABT-450 (b) (4) tablet as reference.

Overall, ritonavir exposures were similar across formulations. The results from the single dose-assessment of trial M13-391 also showed that the mean C<sub>max</sub> and AUC of ritonavir was similar between the ABT-267/ABT-450/ritonavir co-formulated tablets and ritonavir SGC (co-administered with ABT-450 (b) (4) tablets and ABT-267 (b) (4) tablets).

ABT-267:

Table 5 shows the comparison of ABT-267 25 mg exposures following multiple dosing.

ABT-267 Formulation	Number of Study Arms	C <sub>max</sub>		AUC	
		Value <sup>a</sup> (ng/mL)	Ratio <sup>b</sup>	Value <sup>a</sup> (ng•hr/mL)	Ratio <sup>b</sup>
3 DAAs					
ABT-267 (b) (4) Tablet	16	117	--	1390	--
ABT-450/r/ABT-267 Co-formulated Tablet	8	127	1.09	1420	1.02
2 DAAs (ABT-450, RTV and ABT-267)					
ABT-267 (b) (4) Tablet	10	112	--	1250	--
ABT-450/r/ABT-267 Co-formulated Tablet	3	120	1.07	1370	1.10

a Overall geometric mean.

b Ratio of geometric mean using (b) (4) as reference.

ABT-267/ABT-450/ritonavir co-formulated tablets showed similar mean C<sub>max</sub> and AUC values to the (b) (4) tablet formulation used in Phase 2 studies, at the ABT-267 25 mg dose. The results from the single dose-assessment of trial M13-391 also showed that the mean C<sub>max</sub> and AUC of

ABT-267 was similar between the ABT-267/ABT-450/ritonavir co-formulated tablets and ABT-267 (b) (4) tablets (co-administered with ABT-450 (b) (4) tablets and ritonavir SGC).

#### Comparison of ABT-333 and ABT-333 M1 Pharmacokinetic Parameters Across Various Formulations and Trials

Table 6 shows the comparison of the mean steady state pharmacokinetic parameters of ABT-333 400 mg (Phase 2 formulation) and 250 mg (Phase 3 formulation) tablets following multiple dosing of the 3-DAA combination regimen.

ABT-333 Formulation	Number of Study Arms	C <sub>max</sub>		AUC	
		Value <sup>a</sup> (ng/mL)	Ratio <sup>b</sup>	Value <sup>a</sup> (ng•hr/mL)	Ratio <sup>b</sup>
3 DAAs					
400 mg Tablet	16	1120	--	7410	--
250 mg Tablet	8	1030	0.92	6840	0.92
2 DAAs (ABT-450, RTV and ABT-333)					
400 mg Tablet	6	887	--	5780	--

a Overall geometric mean.

b Ratio of geometric mean using 400 mg tablet as reference.

Table 7 shows the comparison of the mean steady state pharmacokinetic parameters of ABT-333-M1 for the ABT-333 400 mg and 250 mg tablet formulations following multiple dosing of the 3-DAA combination regimen

ABT-333 Formulation	Number of Study Arms	M1 C <sub>max</sub>		M1 AUC	
		Value <sup>a</sup> ng/mL)	Ratio <sup>b</sup>	Value <sup>a</sup> (ng•hr/mL)	Ratio <sup>b</sup>
3 DAAs					
400 mg ABT-333 Tablet	16	701	--	4260	--
250 mg ABT-333 Tablet	8	660	0.94	3890	0.91
2 DAAs (ABT-450, RTV and ABT-333)					
400 mg ABT-333 Tablet	6	668	--	3950	--

a Overall geometric mean.

b Ratio of geometric mean using 400 mg tablet as reference.

Overall, the mean steady state systemic exposures of ABT-333 and ABT-333 M1 were similar across various ABT-333 formulations and trials.

### Extrapolations of Clinical Recommendations:

As 11 trials were conducted using the (b) (4) tablets (table 1), the applicant conducted two analysis to determine if the clinical recommendations based on data collected in DDI trials using the ABT-450 (b) (4) tablets can be applied to the ABT-267/ABT-450/ritonavir coformulated tablets. Based on the results of the drug-drug interaction trials, the 3-DAA regimen will be contraindicated with gemfibrozil and atripla and the prescribing information will recommend against co-administration with lopinavir/ritonavir twice daily and darunavir (once daily and twice daily). Therefore, this review will focus on the applicant's proposed extrapolation approach for the remaining medications. The applicant proposed two different approaches to "bridge" the drug-drug interaction data: a "mechanism based/semi quantitative" approach and a "quantitative" approach.

#### *Mechanism Based/Semi Quantitative Approach*

The mechanism based approach to bridge the drug interaction data from the ABT-450 (b) (4) formulation to the Phase 3 co-formulated tablet is based on the evaluation of the mechanism of the drug-drug interaction between the DAA regimens and the co-administered drugs, based on the *in vitro* drug interaction data with drug transporters and drug metabolizing enzymes. Based on *in vitro* data, if ABT-450 is not likely to affect the disposition of the co-administered drug, the results from a drug-drug interaction study conducted with ABT-450 (b) (4) tablets can be applied to the Phase 3 co-formulated tablets. The tables below describe the rationale provided by the applicant.

## Cyclosporine:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M13-103 (Cyclosporine)	<p>Cyclosporine is primarily metabolized by CYP3A.<sup>18</sup> It is a substrate of P-gp transporter and an inhibitor of P-gp, BCRP and OATP1B1 transporters.<sup>20,21</sup> Ritonavir is a known CYP3A4 inhibitor. ABT-450 (IC<sub>50</sub>: 38.1 µM) and ABT-333 (IC<sub>50</sub>: 16.7 µM) are P-gp inhibitors in vitro.<sup>14</sup> In addition, ABT-450 is an OATP1B1 inhibitor (IC<sub>50</sub>: 0.031 µM).<sup>14</sup> This DDI study was designed to evaluate the effect of DAAs on cyclosporine and vice versa.</p>	<p>ABT-450 is not a CYP3A inhibitor (IC<sub>50</sub> &gt; 30 µM);<sup>19</sup> however, it is a P-gp inhibitor in vitro. The [I]/IC<sub>50</sub> ratio of ABT-450 based on molar dose (in 250 mL) is 20.6 for P-gp inhibition.<sup>14</sup> Hence, ABT-450 could possibly inhibit intestinal P-gp transporters. A minimal to moderate effect of the 3-DAA (ABT-450/r + ABT-267 + ABT-333) and 2-DAA (ABT-450/r + ABT-267) regimens on digoxin was observed in the DDI Study M12-201. Digoxin C<sub>max</sub> and AUC increased by about 15% during coadministration with the 3-DAA regimen and about 58% and 36% increase in digoxin C<sub>max</sub> and AUC, respectively, was observed during its coadministration with the 2-DAA regimen. These changes could be partly due to the inhibition of intestinal P-gp transporters by ABT-450.<sup>22</sup> However, the effect of ABT-450 on intestinal P-gp will be similar from the (b) (4) tablets and Phase 3 formulation as the same dose of ABT-450 150 mg was administered using the two formulations. The [I]/IC<sub>50</sub> ratio of ABT-450 for P-gp inhibition based on plasma total concentrations in humans (with Phase 3 formulation) is 0.05, indicating a very low likelihood of systemic interaction.<sup>14</sup> Hence, ABT-450 may have a very low likelihood of affecting cyclosporine exposures. The interaction of DAAs with cyclosporine appears to be mainly driven by ritonavir due to CYP3A inhibition as during coadministration with lopinavir/ritonavir (400/100 mg BID), cyclosporine dose reduction by 5- to 20-fold is needed to keep its exposure in therapeutic range.<sup>23</sup> Similarly, a 4-fold and 12-fold reduction in the cyclosporine dose is expected to be required during coadministration with telaprevir (CYP3A and P-gp inhibitors) and Amprenavir/ritonavir, respectively.<sup>24-26</sup></p>
M13-103 (Cyclosporine), Continued		<p>Based on the results from this DDI study, therapeutic drug monitoring for cyclosporine is recommended. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>



## Tacrolimus:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M13-491 (Tacrolimus)	<p>Tacrolimus is primarily metabolized by CYP3A.<sup>27</sup> It is a substrate of P-gp transporter and an inhibitor of OATP1B1 transporter.<sup>28</sup> Ritonavir is a known CYP3A4 inhibitor.</p> <p>ABT-450 (IC<sub>50</sub>: 38.1 μM) and ABT-333 (IC<sub>50</sub>: 16.7 μM) are P-gp inhibitors in vitro.<sup>14</sup> In addition, ABT-450 is an OATP1B1 inhibitor (IC<sub>50</sub>: 0.031 μM).<sup>14</sup></p> <p>This DDI study was designed to evaluate the effect of DAAs on tacrolimus and vice versa.</p>	<p>ABT-450 is not a CYP3A inhibitor (IC<sub>50</sub> &gt; 30 μM); however, it is a P-gp inhibitor in vitro.</p> <p>The [I]/IC<sub>50</sub> ratio of ABT-450 based on molar dose (in 250 mL) is 20.6 for P-gp inhibition.<sup>14</sup> Hence, ABT-450 could possibly inhibit intestinal P-gp transporters. As previously mentioned, a minimal to moderate effect of the 3-DAA (ABT-450/r + ABT-267 + ABT-333) and 2-DAA (ABT-450/r + ABT-267) regimens on digoxin was observed in the DDI Study M12-201. Digoxin C<sub>max</sub> and AUC increased by about 15% during coadministration with the 3-DAA regimen and about 58% and 36% increase in digoxin C<sub>max</sub> and AUC, respectively, was observed during its coadministration with the 2-DAA regimen. These changes could be partly due to the inhibition of intestinal P-gp transporters by ABT-450.<sup>22</sup> However, the effect of ABT-450 on intestinal P-gp will be similar from the (b) (4) tablets and Phase 3 formulation as the same dose of ABT-450 150 mg was administered using the two formulations.</p> <p>The [I]/IC<sub>50</sub> ratio of ABT-450 for P-gp inhibition based on plasma total concentrations in humans (with Phase 3 formulation) is 0.05, indicating a very low likelihood of systemic interaction.<sup>14</sup></p>
M13-491 (Tacrolimus). Continued		<p>Hence, ABT-450 may have a very low likelihood of affecting tacrolimus exposures. Both ABT-450 and tacrolimus are OATP1B1 inhibitors; hence, their interaction at OATP1B1 will be difficult to predict based on the available information.</p> <p>The interaction of DAAs with tacrolimus appears to be mainly driven by ritonavir due to CYP3A inhibition as during coadministration with lopinavir/ritonavir (400/100 mg BID), tacrolimus dose reduction by 28-fold to 140-fold is needed to keep its exposure in the therapeutic range.<sup>29,30</sup></p> <p>Similarly, a 70-fold reduction in tacrolimus dose is expected to be required during coadministration with telaprevir (CYP3A and P-gp inhibitor).<sup>24</sup></p> <p>Based on the results from this DDI study, therapeutic drug monitoring for tacrolimus is recommended. (b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>

## Raltegravir:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M13-392 (Raltegravir)	<p>Raltegravir is eliminated mainly by metabolism via a UGT1A1 mediated glucuronidation pathway. ABT-450 (IC<sub>50</sub>: 3.6 µM), ABT-267 (IC<sub>50</sub>: 2.1 µM) and ABT-333 (IC<sub>50</sub>: 0.92 µM) are UGT1A inhibitors.<sup>14</sup></p> <p>This DDI study was designed to evaluate the effect of DAAs on raltegravir.</p>	<p>The maximum steady-state plasma total concentration of ABT-450, ABT-267 and ABT-333 are approximately 1.92 (1470 ng/mL), 0.14 (127 ng/mL) and 2.00 µM (1030 ng/mL), respectively.<sup>32</sup> Since these concentrations are comparable to the IC<sub>50</sub> values of these DAAs for UGT1A1 inhibition, the higher exposures of ABT-450 from the Phase 3 formulation could potentially have greater impact on the exposures of raltegravir. This impact is further evaluated quantitatively in the next section.</p>

## Emtricitabine/Tenofovir:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M13-783 (emtricitabine/tenofovir DF)	<p>Emtricitabine and tenofovir DF are primarily renally eliminated with a combination of glomerular filtration and active tubular secretion. Emtricitabine is actively secreted through OCT1, while tenofovir DF is secreted through OAT1 and OAT3.<sup>15-17</sup></p> <p>The elimination of DAAs is primarily through the hepatic route with negligible contribution from the renal route (&lt; 1%).</p> <p>ABT-450 is an inhibitor of OAT1 (half maximal inhibitory concentration (IC<sub>50</sub>): 14 µM) and OAT3 (IC<sub>50</sub>: 95 µM).<sup>14</sup></p> <p>However, it is not an inhibitor of OCT1 (&lt; 20% inhibition at 30 µM) and OCT2 (no inhibition at 30 µM).<sup>14</sup> ABT-267 and ABT-333 are weak inhibitors of these transporters (≤ 30% inhibition at 30 µM or an IC<sub>50</sub> of &gt; 100 µM).<sup>14</sup></p> <p>This DDI study evaluated the effect of DAAs on emtricitabine + tenofovir DF and vice versa.</p>	<p>The unbound C<sub>max</sub>/IC<sub>50</sub> ratio of ABT-450 for OAT1 and OAT3 inhibition based on plasma concentrations in humans (using Phase 3 formulation) is 0.004 and 0.0005, respectively.<sup>14</sup> Also, ABT-450 showed minimal or no inhibition of OCT1 and OCT2. This suggests that ABT-450 is unlikely to inhibit these OAT and OCT transporters at clinically relevant doses.</p> <p>Additionally, no clinically relevant effect of the 3-DAA (ABT-450/r + ABT-267 + ABT-333) and 2-DAA (ABT-450/r + ABT-267) regimens on emtricitabine (± 7% change in C<sub>max</sub> and AUC) and tenofovir emtricitabine (± 20% change in C<sub>max</sub> and AUC) was observed in the DDI study.</p> <p>Hence, a 90% increase in C<sub>max</sub> and 60% increase in AUC of ABT-450 with Phase 3 formulation are unlikely to change the magnitude of the interaction. Results from this DDI study can be applied to the Phase 3 formulation.</p>

## Statins (Pravastatin and Rosuvastatin):

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M12-200 (Statins: Pravastatin and Rosuvastatin)	<p>Pravastatin and rosuvastatin are substrates of OATP1B1, OATP2B1 and OATP1B3. In addition, rosuvastatin is a substrate for BCRP and pravastatin is a substrate for MRP2 transporters.</p> <p>ABT-450 is an inhibitor of OATP1B1 (<math>IC_{50}</math>: 0.031 <math>\mu</math>M), BCRP (<math>IC_{50}</math>: 14.4 <math>\mu</math>M) and MRP2 (<math>IC_{50}</math>: 12 <math>\mu</math>M) transporters, in vitro.<sup>14</sup> ABT-333 is an inhibitor of BCRP (<math>IC_{50}</math>: 15.6 <math>\mu</math>M) in vitro.<sup>14</sup></p> <p>Additionally, ritonavir is also an inhibitor of OATP1B1 (<math>IC_{50}</math>: 0.5 <math>\mu</math>M), OATP1B3 (<math>IC_{50}</math>: 0.6 <math>\mu</math>M) and BCRP (<math>IC_{50}</math>: 24 <math>\mu</math>M) in vitro.<sup>14</sup></p> <p>This DDI study primarily evaluated the effect of DAAs on statins.</p>	<p>The R-value of ABT-450 150 mg dose for OATP1B1 and OATP1B3 inhibition (using the pharmacokinetic model based <math>k_a</math> value) was estimated to be 3.07 and 4.77, respectively.<sup>14</sup> These data suggest that ABT-450 could potentially be OATP1B1 and OATP1B3 inhibitors in vivo.</p> <p>The [I]/<math>IC_{50}</math> ratio of ABT-450 based on molar dose (in 250 mL) is 1328 and 65 for BCRP and MRP2 inhibition.<sup>14</sup> Hence, ABT-450 could possibly inhibit intestinal BCRP and MRP2 transporters. However, the effect of ABT-450 on intestinal BCRP and MRP2 transporters will be similar from the (b)(4) tablets and Phase 3 formulation as the same dose of ABT-450 150 mg was administered using the two formulations.</p> <p>The [I]/<math>IC_{50}</math> ratio of ABT-450 for BCRP and MRP2 inhibition based on plasma total <math>C_{max}</math> in humans (with Phase 3 formulation) is 3.25 and 0.16, respectively, indicating that ABT-450 could be an inhibitor of hepatic BCRP and MRP2 transporters.<sup>14</sup></p> <p>Hence, the higher exposures of ABT-450 from the Phase 3 formulation could potentially have greater impact on the exposures of statins. This impact is further evaluated quantitatively in the next section.</p>

## Digoxin:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M12-201 (Digoxin)	<p>Digoxin is a model P-gp substrate.</p> <p>Ritonavir (<math>IC_{50}</math>: 0.35 <math>\mu</math>M), ABT-450 (<math>IC_{50}</math>: 38.1 <math>\mu</math>M) and ABT-333 (<math>IC_{50}</math>: 16.7 <math>\mu</math>M) are P-gp inhibitors in vitro.</p> <p>This DDI study primarily evaluated the effect of DAAs on digoxin.</p>	<p>The [I]/<math>IC_{50}</math> ratio of ABT-450 based on molar dose (in 250 mL) is 20.6 for P-gp inhibition.<sup>14</sup> Hence, ABT-450 could possibly inhibit intestinal P-gp transporters. A minimal to moderate effect of the 3-DAA (ABT-450/r + ABT-267 + ABT-333) and 2-DAA (ABT-450/r + ABT-267) regimens on digoxin was observed in the DDI Study M12-201. Digoxin <math>C_{max}</math> and AUC increased by about 15% during coadministration with the 3-DAA regimen and about 58% and 36% increase in digoxin <math>C_{max}</math> and AUC, respectively, was observed during its coadministration with the 2-DAA regimen.<sup>23</sup> These changes could be partly due to the inhibition of intestinal P-gp transporters by ABT-450. However, the effect of ABT-450 on intestinal P-gp will be similar from the (b)(4) tablets and Phase 3 formulation as the same dose of ABT-450 150 mg was administered using the two formulations.</p> <p>The [I]/<math>IC_{50}</math> ratio of ABT-450 for P-gp inhibition based on plasma total concentrations in humans (with Phase 3 formulation) is 0.05, indicating a very low likelihood of systemic interaction.<sup>14</sup></p> <p>Hence, the results from this DDI study can be applied to the Phase 3 formulation.</p>

Warfarin:

Study (Coadministered Drugs)	Mechanism of Interaction and Objective of the DDI Study	Effect of ABT-450 on Coadministered Drugs
M12-198 (Warfarin)	<p>Warfarin is a model CYP2C9 substrate.</p> <p>Among the DAAs, only ABT-333 is a weak CYP2C9 inhibitor (IC<sub>50</sub>: 8.6 µM).<sup>14</sup></p> <p>This DDI study evaluated the effect of ABT-333 and ritonavir (administered as part of the DAA regimen) on warfarin.</p>	<p>ABT-450 is not a CYP2C9 inhibitor (IC<sub>50</sub> &gt; 30 µM).<sup>19</sup></p> <p>Additionally, no clinically relevant effect of the 3-DAA (ABT-450/r + ABT-267 + ABT-333) and 2-DAA (ABT-450/r + ABT-267) regimens on warfarin (up to ± 15% change in C<sub>max</sub>, AUC and C<sub>24</sub> values) was observed in the DDI study of DAAs with warfarin.<sup>31</sup></p> <p>Hence, the results from this DDI study can be applied to the Phase 3 formulation.</p>

Overall, the mechanism based/semi quantitative approach suggested that raltegravir, pravastatin, rosuvastatin, and darunavir (not discussed in the review) may need further quantitative assessment.

### Quantitative Approach

Data from all the drug-drug interaction studies (except gemfibrozil and Atripla because both drugs will be contraindicated with the 3-DAA regimen) were used in the quantitative analysis. The table below shows the list of DDI studies along with the different arms dosed to evaluate the DDIs between different 2-DAAs (ABT-450/r + ABT-267 or ABT-450/r + ABT-333) and 3-DAA (ABT-450/r + ABT-267 + ABT-333).

Study (Coadministered Drug)	3-DAA Arm (ABT-450/r + ABT-267 + ABT-333)	2-DAA Arm (ABT-450/r + ABT-267)	2-DAA Arm (ABT-450/r + ABT-333)
M13-103 (Cyclosporine)	X	X	X
M13-491 (Tacrolimus)	X	X	X
M13-392 (Raltegravir)	X	X	X
M13-783 (emtricitabine/tenofovir DF)	X	X	NA
M13-492 (Lopinavir/r BID)	X	X	X
M13-506 (Darunavir QD and BID)	X	X	X
M12-200 (Pravastatin and Rosuvastatin)	X	X	NA
M12-201 (Digoxin)	X	X	NA
M12-198 (Warfarin)	X	X	NA

X = study arm was dosed and the available data were used in the analyses; NA = study arm was not dosed in the DDI study



Two different analyses were used to bridge the DDI data using the Phase 2 (b) (4) tablet of ABT-450 with the Phase 3 co-formulated tablet. The response variable for these analyses was the magnitude of interaction, calculated as the ratio of the AUC of the co-administered drug with and without co-administration of the DAA regimens. This ratio was calculated for each individual subject. The AUC of the co-administered drugs used in the analyses were either AUC<sub>τ</sub>, the AUC in a dosing interval at steady state for trials which evaluated the effect of steady-state dosing of DAAs on steady-state exposures of co-administered drugs, or AUC<sub>∞</sub>, for trials evaluating the effect of steady-state dosing of DAAs on a single dose of co-administered drugs. The predictor variable for these analyses was ABT-450 AUC<sub>τ</sub>, the AUC in a dosing interval at steady state.

#### Analysis # 1:

A regression analysis was conducted using the extent of interaction, the ratio of AUC of the co-administered drug with and without DAAs as the response variable and ABT-450 AUC as the predictor. The regression analysis was conducted separately for each study and within each study, two separate analyses were conducted, one analysis using the data only from the 3-DAA regimen of ABT-450/r + ABT-267 + ABT-333 and a second analysis using the combined data from both the 3-DAA regimen and the 2-DAA regimens (ABT-450/r + ABT-267 or ABT-450/r + ABT-333). For each of these analyses, the regression coefficients were used to estimate the response variable (the ratio of the co-administered drug AUC with and without DAAs) at the geometric mean of ABT-450 AUC as well as at the ABT-450 AUC 60% higher than the geometric mean values. The response variable represents the expected ratio of the co-administered drug AUC at ABT-450 exposures similar to the exposures expected with the Phase 3 formulation.

The table below shows the estimated effect on co-administered drug AUC at the geometric mean ABT-450 AUC and ABT-450 AUC 60 % higher than Geometric Mean Values.

Study	Dataset	Estimated Effect on Coadministered Drug AUC at Geometric Mean ABT-450 AUC (A)	Estimated Effect on Coadministered Drug AUC at ABT-450 AUC 60% Higher Than Geometric Mean (B)	Relative Effect of 60% Higher ABT-450 AUC (Ratio of [B] to [A])
M13-392 (Raltegravir DDI)	3-DAA Arm	2.46	3.31	1.35
	3-DAA + 2-DAA Arms	2.02	2.08	1.03
M12-200 (Pravastatin DDI)	3-DAA Arm	1.83	1.91	1.04
	3-DAA + 2-DAA Arms	1.82	1.87	1.03
M12-200 (Rosuvastatin DDI)	3-DAA Arm	2.63	2.97	1.13
	3-DAA + 2-DAA Arms	1.85	2.19	1.18
M13-492 (LPV/r BID DDI)	3-DAA Arm	0.92	0.96	1.04
	3-DAA + 2-DAA Arms	1.07	1.07	1.0
M13-783 (Emtricitabine + Tenofovir DF DDI)	3-DAA Arm (Emtricitabine)	1.07	1.07	1.0
	3-DAA + 2-DAA Arms (Emtricitabine)	1.06	1.08	1.02
	3-DAA Arm (Tenofovir DF)	1.14	1.14	1.0
	3-DAA + 2-DAA Arms (Tenofovir DF)	1.07	1.09	1.02

Study	Dataset	Estimated Effect on Coadministered Drug AUC at Geometric Mean ABT-450 AUC (A)	Estimated Effect on Coadministered Drug AUC at ABT-450 AUC 60% Higher Than Geometric Mean (B)	Relative Effect of 60% Higher ABT-450 AUC (Ratio of [B] to [A])
M13-506 (DRV + r DDI)	3-DAA Arm + DRV QD	0.76	0.76	1.0
	3-DAA Arm + DRV BID	0.80	0.79	0.99
	3-DAA + 2-DAA Arms	0.82	0.82	1.0
M12-201 (Digoxin DDI)	3-DAA Arm	1.16	1.17	1.0
	3-DAA + 2-DAA Arms	1.29	1.27	0.98
M12-198 (Warfarin DDI)	3-DAA Arm	0.87 <sup>R</sup> , 0.90 <sup>S</sup>	0.90 <sup>R</sup> , 0.88 <sup>S</sup>	1.03 <sup>R</sup> , 0.98 <sup>S</sup>
	3-DAA + 2-DAA Arms	0.86 <sup>R</sup> , 0.88 <sup>S</sup>	0.89 <sup>R</sup> , 0.88 <sup>S</sup>	1.03 <sup>R</sup> , 1.0 <sup>S</sup>
M13-103 (Cyclosporine DDI)	3-DAA Arm	5.74	6.13	1.07
	3-DAA + 2-DAA Arms	4.73	5.17	1.09
M13-491 (Tacrolimus DDI)	3-DAA Arm	58.92	66.1	1.12
	3-DAA + 2-DAA Arms	78.87	86.81	1.10

R = values for R-warfarin; S = values for S-Warfarin; DRV + r = darunavir + ritonavir

As shown in the table above, a 60 % increase in ABT-450 AUC relative to the (b) (4) formulation predicted up to 20 % increase in the effect of the 2-DAA and 3-DAA regimens for all studies except for raltegravir for which a 35 % higher AUC was predicted.

#### Analysis # 2:

Subjects with steady state ABT-450 AUC values higher than the expected ABT-450 AUC for the Phase 3 formulation were identified. The magnitude of interaction (ratio of the co-administered drug AUC with and without DAAs) for these subjects was determined and compared to the mean observed magnitude of interaction across all subjects in the study.

The table below shows the estimated effect on co-administered drug AUC among subjects with ABT-450 AUC greater than the expected ABT-450 AUC for the Phase 3 formulation.

Study	Dataset	Mean Predicted Effect on Coadministered Drug Across All Subjects (A)	Mean Predicted Effect on Coadministered Drug Among Subjects with ABT-450 AUC Greater Than the AUC 60% Higher Than the Mean (B)	Relative Effect of 60% Higher ABT-450 AUC (Ratio of [B] to [A])
M13-392 (Raltegravir DDI)	3-DAA Arm	2.79 (N = 12)	3.12 (N = 5)	1.12
	3-DAA + 2-DAA Arms	2.06 (N = 35)	2.55 (N = 12)	1.24
M12-200 (Pravastatin DDI)	3-DAA Arm	1.87 (N = 12)	2.17 (N = 3)	1.16
	3-DAA + 2-DAA Arms	1.86 (N = 22)	2.06 (N = 7)	1.11
M12-200 (Rosuvastatin DDI)	3-DAA Arm	2.76 (N = 11)	3.78 (N = 2)	1.37
	3-DAA + 2-DAA Arms	2.05 (N = 23)	2.82 (N = 7)	1.38
M13-492 (LPV/r BID DDI)	3-DAA Arm	0.96 (N = 6)	1.07 (N = 2)	1.11
	3-DAA + 2-DAA Arms	1.07 (N = 30)	1.09 (N = 11)	1.02
M13-783 (Emtricitabine +Tenofovir DF DDI)	3-DAA Arm (Emtricitabine)	1.07 (N = 9)	1.07 (N = 4)	1.00
	3-DAA + 2-DAA Arms (Emtricitabine)	1.07 (N = 17)	1.10 (N = 6)	1.03
	3-DAA Arm (Tenofovir DF)	1.14 (N = 9)	1.15 (N = 4)	1.01
	3-DAA + 2-DAA Arms (Tenofovir DF)	1.08 (N = 17)	1.11 (N = 6)	1.03
M13-506 (DRV + r DDI)	3-DAA Arm + DRV QD	0.77 (N = 8)	0.87 (N = 2)	1.13
	3-DAA Arm + DRV BID	0.80 (N = 7)	0.77 (N = 1)	0.96
	3-DAA + 2-DAA Arms	0.82 (N = 30)	0.85 (N = 7)	1.04
M12-201 (Digoxin DDI)	3-DAA Arm	1.17 (N = 12)	1.19 (N = 3)	1.02
	3-DAA + 2-DAA Arms	1.28 (N = 23)	1.27 (N = 8)	0.99

Study	Dataset	Mean Predicted Effect on Coadministered Drug Across All Subjects (A)	Mean Predicted Effect on Coadministered Drug Among Subjects with ABT-450 AUC Greater Than the AUC 60% Higher Than the Mean (B)	Relative Effect of 60% Higher ABT-450 AUC (Ratio of [B] to [A])
M12-198 (Warfarin DDI)	3-DAA Arm	0.89 (N = 12) <sup>R</sup> 0.89 (N = 12) <sup>S</sup>	1.00 (N = 3) <sup>R</sup> 0.77 (N = 3) <sup>S</sup>	1.12 <sup>R</sup> , 0.87 <sup>S</sup>
	3-DAA + 2-DAA Arms	0.88 (N = 23) <sup>R</sup> 0.88 (N = 23) <sup>S</sup>	0.92 (N = 8) <sup>R</sup> 0.86 (N = 8) <sup>S</sup>	1.05 <sup>R</sup> , 0.98 <sup>S</sup>
M13-103 (Cyclosporine DDI)	3-DAA Arm	5.93 (N = 10)	6.89 (N = 2)	1.16
	3-DAA + 2-DAA Arms	4.99 (N = 34)	5.77 (N = 11)	1.16
M13-491 (Tacrolimus DDI)	3-DAA Arm	62.53 (N = 12)	89.56 (N = 3)	1.43
	3-DAA + 2-DAA Arms	84.62 (N = 35)	132.60 (N = 7)	1.57

R = values for R-warfarin; S = values for S-Warfarin; DRV + r = darunavir + ritonavir

Subjects who have ABT-450 AUC higher than the expected ABT-450 AUC for the Phase 3 formulation in both the 2-DAA and 3-DAA regimens, showed only up to about 20% increase in

the DDI effect (evaluated by the ratio of co-administered drugs AUC with and without DAA regimens) except for the DDI studies of raltegravir), tacrolimus and rosuvastatin.

#### Summary:

Overall, based the mechanism based semi quantitative approach and the quantitative approach, four medications (raltegravir, tacrolimus, pravastatin, rosuvastatin) were identified where 60 % higher ABT-450 AUC may lead to further increase in the systemic exposure of the co-administered drug.

Raltegravir: The results of the DDI trial (M13-392; conducted with the (b) (4) tablets) showed that the mean  $C_{max}$  and AUC of raltegravir increased by 132 % and 135 %, respectively when raltegravir was co-administered with the 3-DAA regimen. The approved prescribing information of raltegravir indicates that the mean  $C_{max}$  and AUC<sub>12</sub> of raltegravir 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 does not recommend any dose adjustments when raltegravir is co-administered with omeprazole. Therefore, the predicted increase in raltegravir exposures is not expected to alter the proposed clinical recommendation based on the results of the DDI trial conducted using ABT-450 (b) (4) tablets.

Tacrolimus: The final clinical recommendation for tacrolimus will be based on the results of the drug-drug interaction trial and the results of the clinical study M12-199 (conducted using the Phase 3 co-formulated tablet formulation in adult liver transplant recipients). Hence, any implications of anticipated increase in tacrolimus exposures observed after co-administration with the 3-DAA regimen (using the co-formulated tablets) will be addressed by the findings of trial M12-199. Further, tacrolimus trough levels are routinely monitored through therapeutic drug monitoring, hence dose adjustments of tacrolimus is expected to take into account the anticipated increase in tacrolimus exposures when tacrolimus is combined with the 3-DAA regimen.

Pravastatin and Rosuvastatin: The effect of predicted increase in pravastatin and rosuvastatin exposures based on the quantitative analysis is expected to be addressed by the proposed clinical recommendation (when co-administered with the 3-DAA regimen, the dose of pravastatin and rosuvastatin should not exceed 40 mg per day and 10 mg per day, respectively).

#### Conclusion:

Overall, the applicant's proposal of extrapolating the clinical recommendations based on drug-drug interaction trials conducted with ABT-450 (b) (4) tablets to ABT-267/ABT-450/ritonavir co-formulated tablets is acceptable. The final clinical recommendation for each "3-DAA regimen-co-administered drug" combination will be based on the results of the drug-drug interaction trial and the exposure-response information of individual components of the DAA regimen and the co-administered drug.

## Prediction of Enzymes and Transporter Based Drug-Drug Interactions

Reviewer: Vikram Arya, Ph.D., FCP

### Prediction of Enzymes- and Transporter Based Drug-Drug Interactions Based on In Vitro Data and Mechanistic Analysis

#### Summary:

Based on *in vitro* assessments:

- All compounds in the 3-DAA regimen are substrates of CYP3A; however, the extent of CYP3A contribution to the elimination of the 3-DAA varies.
- CYP2C8 plays a major role in the metabolism of ABT-333.
- ABT-450, ABT-267, ABT-333, and ABT-333 M1 have low potential for inhibiting CYP enzymes. Of note, ritonavir is always co-administered as part of the 3-DAA regimen and hence, is expected to mediate majority of the CYP/UGT mediated DDIs
- All compounds in the 3-DAA regimen and ritonavir are inhibitors of UGT1A1.
- ABT-450, ABT-333, ABT-333 M1 and ABT-267 are substrates for the efflux transporters P-gp and BCRP. Ritonavir is a substrate of P-gp but not BCRP.
- ABT-450, ABT-333, and ritonavir are inhibitors of P-gp and BCRP.
- ABT-450, ABT-333, and ABT-333 M1 are inhibitors of MRP2. ABT-267 and ritonavir are weak inhibitors of MRP2.
- ABT-450 and ritonavir are inhibitors of BSEP. Weak inhibition of BSEP was observed for ABT-267, ABT-333, and ABT-333 M1.
- ABT-450 and ABT-333 M1 are substrates for the hepatic uptake transporters OATP1B1 and OATP1B3. No OATP-mediated uptake was observed for ABT-333, ABT-267 or ritonavir.
- Only ABT-450 is anticipated to inhibit OATP1B1 and OATP1B3.
- None of the compounds in the DAA regimen is anticipated to inhibit renal transporters OAT1, OAT3, OCT2, MATE1 and MATE2K.

## ABT-450, ABT-267, and ABT-333 as Substrates of Various CYP Enzymes

### *CYP3A*

Based on the in vitro studies with recombinant CYPs, all compounds in the 3-DAA regimen are substrates of CYP3A, however, the extent of CYP3A contribution to the elimination of the 3-DAA varies. For example, CYP3A plays a major role in the metabolism of ABT-450, whereas the contribution of CYP3A in the metabolism of ABT-267 and ABT-333 is minor.

The contribution of CYP3A to the elimination of ABT-450 was confirmed in a clinical trial (M10-749) which showed that the mean C<sub>max</sub> and AUC of ABT-450 at the 300/100 mg ABT-450/ritonavir dose increased by 28- and 48-fold, respectively as compared to administration of 300 mg ABT-450 alone. The minor contribution of CYP enzymes in the elimination of ABT-333 was confirmed in a drug-drug interaction trial with ketoconazole (M12-189) which showed ~40 % increase in the systemic exposure of ABT-333 when the 3-DAA regimen was administered with ketoconazole, a potent CYP3A inhibitor. The results of the drug-drug interaction trial with carbamazepine showed a decrease in the systemic exposures of ABT-450, ABT-267, and ABT-333 by 70 %, 31 %, and 70 %, respectively, suggesting that CYP3A plays a role (albeit to a different extent) in the metabolism of ABT-450, ABT-267, and ABT-333.

### *CYP2C8*

CYP2C8 plays a major role in the metabolism of ABT-333 and a minor role in the metabolism of ABT-450 and ABT-267. The contribution of CYP2C8 to the metabolism of ABT-333 was confirmed in a drug-drug interaction trial with gemfibrozil (M12-196); the results of the trial showed that the mean C<sub>max</sub> and AUC of ABT-333 increased by 101 % and 1025 %, respectively, when the ABT-450/r and ABT-333 was co-administered with gemfibrozil.

## ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 as Substrates of Various Transporters

### *P-glycoprotein transporters*

Transporter mediated bi-directional efflux was evaluated in an MDCK cell line overexpressing P-gp or BCRP. Efflux in the overexpressed cells was normalized to by efflux observed in the wild-type cells.

Table 1 shows the summary of the in vitro substrate interactions and the efflux ratios (ER).

Transporter	ABT-450	Ritonavir	ABT-267	ABT-333	M1 (A-1041392)
P-gp/MDR1	Net ER: 13.1 <sup>43</sup>	Net ER: 26.1 <sup>44</sup>	Not a substrate <sup>45</sup>	Net ER: 6.4 <sup>46</sup>	Net ER: 32.5 <sup>47</sup>
BCRP	Net ER: 5.0 <sup>43</sup>	Not a substrate <sup>44</sup>		Net ER: 1.9 <sup>46</sup>	Net ER: 2.0 <sup>47</sup>

ABT-450, ABT-333 and ABT-333 M1 are substrates for P-gp and BCRP; ritonavir is a substrate for P-gp only. No in vitro efflux by P-gp or BCRP was observed for ABT-267, however, in the

more sensitive triple knockout mouse model, ABT-267 was shown to be a substrate for P-gp and BCRP.

*Reviewer's Note:*

*The superscripts used in the table above and other tables in this summary indicate the references provided by the applicant in the original reports.*

*OATP transporters*

Table 2 shows the kinetic parameters of *in vitro* OATP substrate interactions

Transporter	ABT-450	Ritonavir	ABT-267	ABT-333	M1 (A-1041392)
OATP1B1	$K_m$ 0.18 $\mu M$ <sup>70</sup>	Not a substrate <sup>73</sup>	Not a substrate <sup>74</sup>	Not a substrate <sup>75</sup>	$K_m$ 1.30 $\mu M$ <sup>72</sup>
OATP1B3	$K_m$ 0.089 $\mu M$ <sup>71</sup>				$K_m$ 1.71 $\mu M$ <sup>72</sup>

ABT-450 and M1 are substrates of OATP1B1 and OATP1B3. The data from drug-drug interaction trials with OATP inhibitors such as cyclosporine and atazanavir suggested that ABT-450 is more sensitive to OATP inhibition as compared with ABT-333 M1. The results of the drug-drug interaction trial with atazanavir (M13-394; Arm 1) showed that the mean systemic exposure of ABT-450 increased by 93 % whereas; there was an 11 % decrease in the mean systemic exposure of ABT-333 M1.

*Renal Transporters*

The primary route of elimination of ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 is biliary excretion and the available data from clinical trials suggest minor renal elimination. Hence, the applicant did not conduct any specific renal transporter substrate studies.

ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 as Inhibitors of Various Enzymes

The potential for drug-drug interactions of the 3-DAA regimens mediated *via* CYP enzymes was predicted using the following mechanistic static model for reversible inhibition:

$$AUCR = \left( \frac{1}{[A_g] \times (1 - F_g) + F_g} \right) \times \left( \frac{1}{[A_h] \times f_m + (1 - f_m)} \right)$$

$$A_g = \frac{1}{1 + \frac{[I]_g}{K_i}} \quad [I]_g = F_a \times K_a \times Dose / Q_{en}$$

$$A_h = \frac{1}{1 + \frac{[I]_h}{K_i}} \quad [I]_h = f_{u,b} \times ([I]_{max,b} + F_a \times K_a \times Dose / Q_h)$$

The following assumptions were made for the predictions:

The fraction metabolized ( $f_m$ ) of CYP probe substrates was assumed to be 0.99 for all CYPs probe substrates in order to generate conservative estimates. In the case where the measured free fraction in plasma ( $f_{u,p}$ ) is  $<0.01$  due to high plasma protein binding, it is assumed that  $f_{u,p}$  is equal to 0.01 in order generate conservative estimates.  $Q_{en}$  and  $Q_h$  are blood flow through enterocytes (18 L/hr/70 kg) and hepatic blood flow (97 L/hr/70 kg), respectively. For ritonavir, only reversible inhibition of CYP3A was considered, and the impact of inhibition on intestinal CYP3A and the intestinal  $A_g$  component was not considered.

Table 3 shows the parameters used in calculations of CYP and transporter inhibition R-value predictions.

Compound	Molecular Weight	Dose (mg)	$f_{u,p}$	$f_{u,b}^{\dagger}$	$C_{max,ss}$ (ng/mL) <sup>11</sup>	$F_a$	$K_a$ (hr <sup>-1</sup> ) <sup>11</sup>
ABT-450	765.89	150	0.026*	0.038	1470	1	0.25
Ritonavir	720.96	100	0.01	0.01	1600	1	0.17
ABT-267	894.12	25	0.01	0.02	127	1	0.21
ABT-333	493.58	250	0.01	0.02	1030	1	0.58
M1 (A-1041392)	509.58	--	0.066*	0.094	660	--	--

$\dagger f_{u,b}$  is calculated from  $f_{u,p}$  and the blood to plasma ratio; if the measured  $f_{u,p}$  is  $<0.01$ , it is then assumed to be equal to 0.01 to err on the conservative side in the calculations.<sup>12-19</sup>

\*  $f_{u,p}$  for ABT-450 and M1 from *in vitro* studies where tested concentration is near  $C_{max}$ .<sup>12,18</sup>

Based on the parameters shown in the table above and *in vitro* assessments,  $I/IC_{50}$  and  $I/K_i$  estimates were generated as shown in table 4 below.

	ABT-450 <sup>2,20</sup>		Ritonavir <sup>8</sup>		ABT-267 <sup>3,21</sup>		ABT-333 <sup>4,22</sup>		M1 (A-1041392) <sup>5,22</sup>	
CYP	$IC_{50}$ (μM)	$K_i^{\dagger}$ (ng/mL)	$IC_{50}$ (μM)	$K_i^{\dagger}$ (ng/mL)	$IC_{50}$ (μM)	$K_i^{\dagger}$ (ng/mL)	$IC_{50}$ (μM)	$K_i^{\dagger}$ (ng/mL)	$IC_{50}$ (μM)	$K_i^{\dagger}$ (ng/mL)
CYP2B6	-	-	1.00	361	-	-	29	7157	-	-
CYP2C8	13	4978	1.52	548	7.4	3308	16.5	4072	-	-
CYP2C9	-	-	0.57	206	-	-	8.6	2122	-	-
CYP2C19	-	-	4.28	1543	-	-	17.5	4319	-	-
CYP2D6	-	-	1.04	375	-	-	42.5	10489	-	-
CYP3A4	-	-	0.0055	2.0	-	-	-	-	-	-
UGT1A1	3.6	1386	1.7 <sup>23</sup>	613	2.1	948	0.92	227	6.5	1664

$\dagger K_i = IC_{50}/2$

“-”: No significant inhibition observed ( $IC_{50} > 30 \mu M$ ) in the *in vitro* studies.

Table 5 shows the  $I/K_i$  ratio computed based on the anticipated  $C_{max}$  (as shown in table 4) and the  $K_i$  estimates (as shown in table 5).

	ABT-450	Ritonavir	ABT-267	ABT-333	ABT-333 M1
CYP Enzyme	$I/K_i$ values				
CYP2B6	-	4.43	-	0.14	-
CYP2C8	0.29	2.91	0.038	0.25	-
CYP2C9	-	7.76	-	0.48	-
CYP2C19	-	1.03	-	0.23	-



CYP2D6	-	4.26	-	0.09	-
CYP3A4	-	800	-	-	-
UGT1A1	1.06	2.61	0.13	4.53	0.39

The model parameters and the R-values based on the mechanistic static model are shown in table 6 below.

CYP	ABT-450			Ritonavir			ABT-267			ABT-333		
	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R	[I] <sub>h</sub> (ng/mL)	A <sub>h</sub>	R
CYP2B6	-	-	-	30	0.92	1.08	-	-	-	36	0.99	1.00
CYP2C8	71	0.99	1.01	30	0.95	1.05	3.7	1	1.00	36	0.99	1.01
CYP2C9	-	-	-	30	0.87	1.14	-	-	-	36	0.98	1.02
CYP2C19	-	-	-	30	0.98	1.02	-	-	-	36	0.99	1.01
CYP2D6	-	-	-	30	0.93	1.08	-	-	-	36	1.00	1.00
CYP3A4	-	-	-	30	0.06	13.9	-	-	-	-	-	-
UGT1A1	71	0.95	1.05	30	0.95	1.05	3.7	1	1.00	36	0.86	1.16

For all the compounds evaluated (except ritonavir), the R values suggested a low potential for CYP inhibition. Based on *in vitro* assessments, ritonavir is an inhibitor of CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The highest R value of 13.9 is for CYP3A4, which is consistent with the potent inhibition of CYP3A4 by ritonavir. All compounds in the DAA regimen, including ABT-333 M1 metabolite, inhibited UGT1A1 with different potencies. Based on rank ordering of the R values, ABT-333 has a relatively higher potential (R= 1.16) to show interaction with UGT1A1 substrates as compared with other DAAs and ritonavir. It should be noted that ritonavir is always co-administered as part of the 3-DAA regimen and hence, is expected to be mechanistically responsible for the majority of the CYP/UGT mediated DDIs.

ABT-450 shows minor CYP3A induction *in vitro* (31 % of the response of positive control rifampin in human hepatocytes from three donors); however, due to presence of ritonavir, the 3-DAA regimen is anticipated to show a net inhibitory effect on CYP enzymes. ABT-450 is not an inducer of CYP1A2 and CYP2B6 mRNA expression when tested up to 10 µM in cultured human hepatocytes from multiple donors. ABT-267 and ABT-333 do not induce CYP1A2, CYP2B6, and CYP3A4 *in vitro* and are not expected to alter the systemic exposures of CYP3A substrates *via* CYP induction.

#### ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 as Inhibitors of Various Transporters

##### *Efflux Transporters (P-gp and BCRP)*

The compounds in the 3-DAA regimen were characterized for their interactions with the major drug efflux transporters, P-gp (P-glycoprotein) and BCRP (Breast Cancer Resistance Protein). In addition, inhibition of BSEP (Bile Salt Export Pump) and MRP2 (Multi-drug Resistance Protein 2) was also explored.

Table 7 shows the summary of the inhibition parameters.

Transporter	IC <sub>50</sub> (μM)				
	ABT-450	Ritonavir	ABT-267	ABT-333	M1 (A-1041392)
P-gp/MDR1	38.1 <sup>50</sup>	0.35*, >50 <sup>52,53</sup>	>100 <sup>56</sup>	16.7 <sup>54</sup>	80.6 <sup>55</sup>
BCRP	14.4, 0.59* <sup>50,51</sup>	24*, 66 <sup>52,53</sup>	>100 <sup>56</sup>	15.6 <sup>54</sup>	54.7 <sup>55</sup>
MRP2*	12 <sup>57</sup>	>100 <sup>60</sup>	<30% inhibition at 100 μM <sup>61</sup>	52 <sup>58</sup>	22 <sup>59</sup>
BSEP*	1.5 <sup>62</sup>	0.1 <sup>63</sup>	95 <sup>66</sup>	34 <sup>64</sup>	63 <sup>65</sup>

\*data from membrane vesicle study

Based on the anticipated clinical C<sub>max</sub> and the inhibition parameters, the potential for drug interactions due to inhibition of P-gp and BCRP was predicted. Table 8 shows the P-gp and BCRP inhibition predictions.

Compound	Dose	C <sub>max, ss</sub> (ng/mL)	P-gp/MDR1			BCRP		
			IC <sub>50</sub> (μg/mL)	[I <sub>2</sub> ]/IC <sub>50</sub>	[I <sub>1</sub> ]/IC <sub>50</sub>	IC <sub>50</sub> (μg/mL)	[I <sub>2</sub> ]/IC <sub>50</sub>	[I <sub>1</sub> ]/IC <sub>50</sub>
ABT-450	150	1470	29.2	20.6	0.05	0.45*	1328	3.25
Ritonavir	100	1600	0.25*	1585	6.34	17.3*	23.1	0.09
ABT-267	25	127	>89.4	<10	<0.1	>89.4	<10	<0.1
ABT-333	250	1030	8.24	121	0.12	7.70	130	0.13
M1 (A-1041392)	-	660	41.1	N/A	0.02	27.9	N/A	0.02

[I<sub>2</sub>] = Dose/250 mL, [I<sub>1</sub>] = C<sub>max, ss</sub> \*Most potent measured IC<sub>50</sub> values (from Table 6) used in the calculations.

Inhibition of intestinal efflux may be possible based on the theoretical concentrations (Dose/250 mL) of ABT-450, ritonavir and ABT-333 in the GI tract; [I<sub>2</sub>]/IC<sub>50</sub> values >10 or IC<sub>50</sub> values ≤0.1\*dose/250 mL (substituting IC<sub>50</sub> for K<sub>i</sub>). Inhibition of P-gp/MDR1 by ABT-333 or ritonavir, or BCRP by ABT-450 or ABT-333 at other tissue sites may be possible; [I<sub>1</sub>]/IC<sub>50</sub> values >0.1. ABT-450, ABT-333, and ABT-333 M1 are inhibitors of MRP2. ABT-267 and ritonavir are weak inhibitors of MRP2 (less than 30 % inhibition at 100 μM and IC<sub>50</sub> > 100 μM, respectively). ABT-450 and ritonavir are also inhibitors of BSEP with IC<sub>50</sub> values of 1.5 μM and 0.1 μM, respectively. Weak inhibition of BSEP (IC<sub>50</sub> > 30 μM) was observed for ABT-267, ABT-333, and ABT-333 M1.

### Hepatic Uptake Transporters (OATP and OCT1)

The hepatic uptake transporter inhibition was explored by evaluating the effect of each DAA on the transport of known probe substrates in HEK cells over expressing the uptake transporters of interest.

Table 9 shows the summary of the *in vitro* hepatic inhibition predictions.

Transporter	IC <sub>50</sub> (μM)				
	ABT-450	Ritonavir	ABT-267	ABT-333	M1 (A-1041392)
OATP1B1	0.031 <sup>70</sup>	0.5 <sup>78</sup>	<25% inhibition at 100 μM <sup>81</sup>	0.9 <sup>79</sup>	2.6 <sup>80</sup>
OATP1B3	0.017 <sup>77</sup>	0.6 <sup>78</sup>	<15% inhibition at 100 μM <sup>81</sup>	6.6 <sup>79</sup>	9.7 <sup>80</sup>
OATP2B1	0.2 <sup>82</sup>	0.55 <sup>83</sup>	-	-	-
OCT1	<20% inhibition at 30μM <sup>77</sup>	2.5 <sup>78</sup>	<20% inhibition at 30 μM <sup>81</sup>	≤30% inhibition at 30 μM <sup>79,80</sup>	

-, not tested

Table 10 shows the summary of the OATP inhibition predictions.

Compound	Dose	C <sub>max, ss</sub> (ng/ml)	f <sub>u,p</sub>	k <sub>a</sub> (h <sup>-1</sup> )	fa*fg	OATP1B1		OATP1B3	
						IC <sub>50</sub> (μg/mL)	R-Value	IC <sub>50</sub> (μg/mL)	R-Value
ABT-450	150	1470	0.026	0.25	1	0.024	3.07	0.013	4.77
Ritonavir	100	1600	0.01	0.17	1	0.36	1.05	0.43	1.04
ABT-267	25	127	0.01	0.21	1	>89.4	<1.25	>89.4	<1.25
ABT-333	250	1030	0.01	0.58	1	0.44	1.06	3.26	1.01
M1 (A-1041392)	-	660	0.066	-	1	1.32	1.03	4.94	1.01

Predictions are consistent with the clinical finding of increased plasma exposure of the OATP substrates, rosuvastatin and pravastatin when co-dosed with the 3-DAA regimen and may also explain the clinical observations of elevations in indirect bilirubin due to ABT-450 mediated inhibition of OATP transporters.

### *Inhibition of Renal Transporters*

The interactions of the compounds in the DAA regimen was evaluated with renal transporters, Organic Anion Transporter (OAT) 1 and 3, Organic Cation Transporter (OCT2), Multi Drug and Toxin Extrusion Transporter (MATE) 1 and 2K.

Table 11 shows the summary of the in vitro renal inhibition parameters.

	IC <sub>50</sub> (μM)				
Transporter	ABT-450	Ritonavir	ABT-267	ABT-333	M1 (A-1041392)
OAT1	14 <sup>77</sup>	14 <sup>78</sup>	<20% inhibition at 30 μM <sup>81</sup>	≤30% inhibition at 30 μM <sup>79</sup>	≤30% inhibition at 30 μM <sup>80</sup>
OAT3	95 <sup>77</sup>	8.1 <sup>78</sup>		>100 <sup>79</sup>	
OCT2	No inhibition at 30 μM <sup>77</sup>	>30 <sup>78</sup>		≤30% inhibition at 30 μM <sup>79</sup>	
MATE1	<20% inhibition at 30 μM <sup>77</sup>	3.3 <sup>78</sup>		28 <sup>80</sup>	
MATE2K	170 <sup>77</sup>	90 <sup>78</sup>		72 <sup>80</sup>	

Table 12 shows the summary of the inhibition predictions for the various renal transporters.

Compound	Dose	C <sub>max, ss</sub> (ng/ml)	f <sub>u,p</sub>	OAT1		OAT3		OCT2	
				IC <sub>50</sub> (µg/mL)	C <sub>max,ss,u</sub> / IC <sub>50</sub>	IC <sub>50</sub> (µg/mL)	C <sub>max,ss,u</sub> / IC <sub>50</sub>	IC <sub>50</sub> (µg/mL)	C <sub>max,ss,u</sub> / IC <sub>50</sub>
ABT-450	150	1470	0.026	10.7	0.004	72.8	0.0005	>22.9	<0.1
Ritonavir	100	1600	0.01	10.1	0.002	5.84	0.003	>21.6	<0.1
ABT-267	25	127	0.01	>26.8	<0.1	>26.8	<0.1	>26.8	<0.1
ABT-333	250	1030	0.01	>14.8	<0.1	>49.3	<0.1	>14.8	<0.1
M1 (A-1041392)	-	660	0.066	>15.2	<0.1	>15.2	<0.1	>15.2	<0.1

Based on the predictions, none of the compounds in the DAA regimen is anticipated to inhibit the renal transporters OAT1, OAT3, and OCT2. Further, none of the compounds in the DAA regimen are predicted to inhibit MATE 1 and MATE2K; (C<sub>max,u</sub>/IC<sub>50</sub> values<0.1).

Table 13 shows the summary of drug-drug interaction trials which evaluated DAAs as substrates of various enzymes and/or transporters

Enzyme/Transporter	Substrate	Inhibitor/Inducer	Clinical Study
CYP2C8	ABT-333	Gemfibrozil	M12-196 (gemfibrozil)
CYP2C9	Warfarin	ABT-333	M12-198 (warfarin)
CYP3A	ABT-450	Ritonavir	M10-749 (ritonavir)
CYP3A	Tacrolimus	Ritonavir	M13-491 (tacrolimus)
CYP3A	ABT-450/r ABT-267 ABT-333	Ketoconazole	M12-189 (ketoconazole)
UGT1A1	Raltegravir	Ritonavir ABT-267 ABT-333 M1 (A-1041392)	M13-392 (raltegravir)
P-gp/MDR1	ABT-450 Ritonavir ABT-333 M1 (A-1041392)	ABT-450, Ritonavir ABT-333, M1 (A-1041392)	M12-201 (digoxin) M12-189 (ketoconazole) M14-103 (cyclosporine)
BCRP	ABT-450 ABT-333 M1 (A-1041392)	ABT-450, Ritonavir ABT-333, M1 (A-1041392)	M12-200 (rosuvastatin) M14-103 (cyclosporine)
OATP1B1, OATP1B3	ABT-450 M1 (A-1041392)	ABT-450	M13-394 (atazanavir) M14-103 (cyclosporine) M12-200 (rosuvastatin) M12-200 (pravastatin)
OAT1	Tenofovir	No inhibition predicted	M13-783 (tenofovir)

In addition to the information shown in the table above, the effect of CYP1A2 using duloxetine as a substrate and CYP2B6 inhibition using methadone as a substrate was also evaluated.

# OFFICE OF CLINICAL PHARMACOLOGY:

## PHARMACOMETRIC REVIEW

<b>Application Number</b>	NDA 206619
<b>Compound</b>	VIEKIRA PAK™ (Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ Ritonavir and Dasabuvir (ABT-333)); 12.5 mg/75 mg/50 mg ABT-267/ABT-450/ritonavir coformulated tablets; 250 mg ABT-333 tablets
<b>Indication</b>	Treatment of HCV Genotype 1 Infection
<b>Submission Date</b>	April 22, 2014
<b>Sponsor</b>	Abbvie Inc.
<b>Pharmacometrics Reviewer</b>	Dhananjay D. Marathe, PhD
<b>Pharmacometrics Team Leader</b>	Jeffrey Florian, PhD
<b>Related IND</b>	103526

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## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions:

### **1.1.1 What are the characteristics of the exposure-response (E-R) relationships for efficacy and safety for Viekira Pak (± RBV)?**

Please refer to the section 2.2.4.1 for E-R relationship for efficacy and section 2.2.4.2 for E-R relationship for safety in the Clinical Pharmacology Question Based Review (QBR).

### **1.1.2 What is the appropriate dose and dosing regimen for HCV genotype 1?**

Please refer to the section 2.2.4.4 of Clinical Pharmacology QBR for appropriate dosing regimen for non-cirrhotic and cirrhotic patients infected with HCV genotype 1a or 1b (treatment naïve and treatment experienced).

### **1.1.3 Is a dose adjustment required based on intrinsic factors of age, body weight, gender, and race?**

There is no dose adjustment warranted based on any of the intrinsic factors including age, body weight, gender, race. Please refer to the sections 2.3.2.1 through 2.3.2.4 of Clinical Pharmacology QBR for the details about differences in exposures of each of the Viekira Pak components (ABT-450, ABT-267, ABT-333) and ribavirin (RBV) with these factors. Table 13 in section 2.2.5.2 of Clinical Pharmacology QBR shows differences in exposures between cirrhotic and non-cirrhotic patients. Based on the benefit/risk assessment, a longer duration regimen of 24-weeks is recommended in GT1a-infected cirrhotic patients, with no dose adjustment recommended in this population.

## **1.2 Recommendations**

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed NDA 206619 and has the following recommendations:

- The following proposed dosing regimens are reasonable:
  - 3-DAA (direct acting antiviral) regimen (without RBV) for 12 weeks in GT1b-infected non-cirrhotic patients
  - 3-DAA+RBV regimen for 12 weeks in GT1b-infected cirrhotic patients
- Regarding the GT1a-infected non-cirrhotic population, the sponsor proposed a 12 week regimen of 3-DAA+RBV (b) (4). Upon review, the 3-DAA+RBV regimen for 12 weeks is recommended for GT1a-infected non-cirrhotic patients.
- Regarding the GT1a-infected cirrhotic patient population, the sponsor initially proposed (b) (4). Upon review, the (b) (4) treatment duration (24 weeks) with 3-DAA+RBV is recommended for GT1a-infected cirrhotic patients.
- No dose modifications are required based on age, weight, race, and gender.

## **1.3 Label Statements**

Please refer to labeling recommendations in Clinical Pharmacology QBR.



## 2 PERTINENT REGULATORY BACKGROUND

VIEKIRA PAK™, a combination of Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ritonavir co-formulated tablets and Dasabuvir (ABT-333) tablets (3-DAA regimen), is currently being developed by Abbvie Inc. for the treatment of HCV genotype 1 infections. ABT-267 is a non-structural protein 5A [NS5A] inhibitor, ABT-450 is a NS3/4A protease inhibitor, and ABT-333 is a NS5B polymerase inhibitor. The previously FDA approved therapies for this indication are pegylated interferon (pegIFN) and ribavirin (RBV) co-administered with one of the direct-acting antivirals (DAAs)- telaprevir, boceprevir, sofosbuvir or simeprevir. **Table 1** shows the comparative performance of these previously approved therapies.

**Table 1: Efficacy (Sustained virologic response rates 24 Weeks after stopping Treatment) in subjects with HCV GT1 in Pivotal Studies of Approved Therapies**

Regimen	Treatment Duration (weeks)	Treatment Naïve	Partial Responder to pegIFN/RBV	Null Responder to pegIFN/RBV
Boceprevir + pegIFN/RBV	28 – 48	63%	52% <sup>a</sup>	38% <sup>b</sup>
Cirrhotic (F4) subset	48	42% <sup>c</sup>	not available	not available
Telaprevir + pegIFN/RBV	24 – 48	75% <sup>d</sup>	61% <sup>e</sup>	31% <sup>e</sup>
Cirrhotic (F4) subset	24 – 48	54% <sup>d</sup>	33% <sup>e</sup>	19% <sup>e</sup>
Simeprevir + pegIFN/RBV	24 – 48	80% <sup>f</sup>	65% <sup>g</sup>	53% <sup>g</sup>
F3/F4 subset	24 – 48	68% <sup>f</sup>	not available	not available
Sofosbuvir + pegIFN/RBV	12	89% <sup>h</sup>	not available <sup>i</sup>	not available <sup>i</sup>
Cirrhotic (F4) subset	12	80% <sup>h</sup>		

RGT = response guided therapy; SVR<sub>12</sub> = sustained virologic response 12 weeks postdosing; SVR<sub>24</sub> = sustained virologic response 24 weeks postdosing

- Victrelis Summary of Product Characteristics (SmPC) – SVR<sub>24</sub> 48 weeks from RESPOND-2.
- Victrelis United States Package Insert (USPI) – SVR<sub>24</sub> from PROVIDE.
- Victrelis USPI – SVR<sub>24</sub> 48 weeks from SPRINT-2.
- Incivo SmPC – SVR<sub>24</sub> RGT composite from studies C211, 108 (ADVANCE), and 111 (ILLUMINATE).
- Incivo SmPC – SVR<sub>24</sub> 48 weeks from C216 (REALIZE).
- Olysio USPI – SVR<sub>12</sub> RGT composite from QUEST 1 and QUEST 2.
- Olysio USPI – SVR<sub>24</sub> 48 weeks from ASPIRE.
- Sovaldi SmPC – SVR<sub>12</sub> 12 weeks from NEUTRINO.
- Sovaldi USPI estimates a 71% response rates in prior pegIFN/RBV nonresponders based on rates in patients with multiple negative predictors of response.

*Source: Sponsor's Clinical Overview Report, Table 1, Page 5*

The clinical development program for the 3-DAA regimen submitted data from 6 pivotal Phase 3 studies and 2 key Phase 2 studies in HCV GT1-infected adult subjects (**Table 2**). This regimen was administered with or without ribavirin (RBV) at the proposed doses or higher—ABT-450 150 mg once daily (QD), ritonavir 100 mg QD, ABT-267 25 mg QD, and ABT-333 250 mg twice daily (BID).

**Table 2: Overview of pivotal and key phase 2/3 studies**

Study	Population	Regimen	Number Treated with DAAs ± RBV
<b>Phase 3</b>			
<a href="#">M11-646</a>	HCV GT1-infected (1a and non-1a), treatment-naïve, noncirrhotic, adult subjects	3-DAA <sup>a</sup> + RBV versus placebo for 12 weeks	630
<a href="#">M13-098</a>	HCV GT1-infected (1a and non-1a), pegIFN and RBV treatment-experienced, noncirrhotic, adult subjects	3-DAA + RBV versus placebo for 12 weeks	393
<a href="#">M13-389</a>	HCV GT1b-infected, pegIFN and RBV treatment-experienced, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	186
<a href="#">M13-961</a>	HCV GT1b-infected, treatment-naïve, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	419
<a href="#">M14-002</a>	HCV GT1a-infected, treatment-naïve, noncirrhotic, adult subjects	3-DAA + RBV versus 3-DAA for 12 weeks	305
<a href="#">M13-099</a>	HCV GT1-infected (1a and non-1a), treatment-naïve and previous pegIFN and RBV treatment-experienced adult subjects with compensated cirrhosis (Child-Pugh A)	3-DAA + RBV for 12 weeks versus 24 weeks	380
<b>Phase 2</b>			
<a href="#">M11-652</a>	HCV GT1-infected, treatment-naïve subjects and previous null responders to pegIFN and RBV treatment	ABT-450/r, and ABT-267 and/or ABT-333 ± RBV 8, 12, or 24 weeks	571
<a href="#">M14-103</a>	HCV GT1-infected (1a and non-1a), noncirrhotic, treatment-naïve or pegIFN and RBV treatment-experienced, adult noncirrhotic subjects on a stable opioid replacement therapy of methadone or buprenorphine ± naloxone for ≥ 6 months prior to screening	3-DAA <sup>a</sup> + RBV for 12 weeks	38

a. 3-DAA is ABT-450/r/ABT-267 (150/100/25 mg QD) + ABT-333 (250 mg BID).

Source: Sponsor's Clinical Overview Report, Table 2, Page 9

Adverse events (AEs) of clinical interest for Viekira PAK included drug-induced rash, ALT elevations, Bilirubin elevation and decreases in Hemoglobin levels (anemia).

All phase 2/3 clinical studies mentioned in **Table 2** for the Viekira PAK program are included in the PK/PD assessments. The sponsor provided pharmacometric reports for population PK models and exposure-response analyses results for efficacy and safety parameters in early phase and pivotal trials.



### 3 RESULTS OF SPONSOR'S ANALYSIS AND REVIEWER'S COMMENTS

#### 3.1 Dose Selection

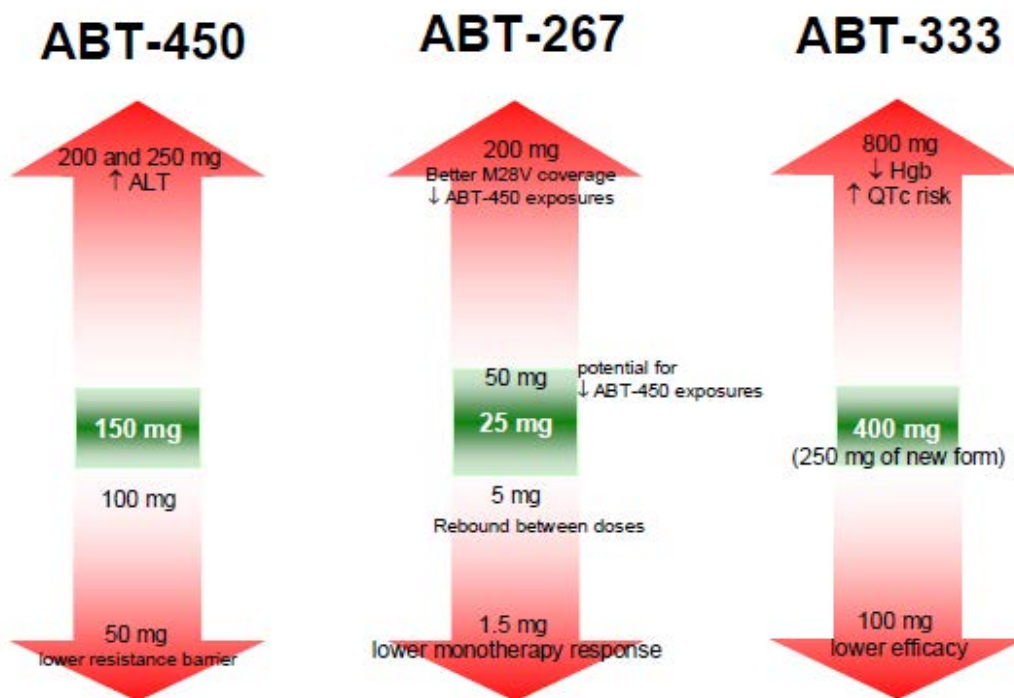
The sponsor conducted dose-ranging studies with each DAA as monotherapy and in combination with pegIFN + RBV. But, dose-ranging evaluation for pegIFN-free regimens involving different DAA combinations were conducted only with ABT-450 doses, with constant dose of ABT-333 (250 mg BID) and ABT-267 (25 mg QD). This strategy was based on the greater potency of ABT -450 in decreasing the viral load following monotherapy in treatment-naïve HCV-infected subjects as shown in **Table 3** (Studies M11-602, M12-116 and M13-386). The rationale for the final dose selection for pivotal trials is based on efficacy-safety balance as shown in **Figure 1**.

**Table 3: Anti-Viral Efficacy of DAAs as Monotherapy and with Peg-IFN+RBV**

DAA	Doses	Viral Load Change from Baseline Following 2 to 3 Days of Monotherapy	SVR <sub>24</sub> (%) in Combination with Peg-IFN and RBV
ABT-450/r	50/100 to 200/100 mg QD	~4 log <sub>10</sub>	62.5 to 100
ABT-267	1.5 to 200 mg QD	~3 log <sub>10</sub>	44.4 to 66.7 <sup>a</sup>
ABT-333	300 to 800 mg BID	~1 log <sub>10</sub>	62.5 <sup>b</sup>

- a. SVR<sub>24</sub> for ABT-267 in combination with peg-IFN and RBV was evaluated at ABT-267 doses of 5, 50 and 200 mg QD.
- b. SVR<sub>24</sub> for ABT-333 in combination with peg-IFN and RBV was evaluated at ABT-333 doses of 400 and 800 mg BID.

Source: Sponsor's Dose and Duration Report R&D/14/0150, Table 3, Page 12



**Figure 1: DAA dose selection rationale**

Source: Sponsor's Clinical Overview Report, Figure 1, Page 34

The sponsor's rationale for selected dose for each individual components of the 3-DAA (Viekira Pak) ± RBV dosing regimen is provided below.

**ABT-450/r dose:**

The selection of ABT-450/r 150/100 mg was based on efficacy, resistance, safety and exposure-response analyses:

- In treatment-naïve GT1-infected subjects, ABT-450 doses  $\geq 100$  mg (b) (4) combined with pegIFN and RBV showed lower virologic failure rates compared to the lower dose of 50 mg.
- In treatment-experienced GT1a-infected subjects, on-treatment virologic breakthroughs were lower at the ABT-450 150 mg dose ( (b) (4) tablet) compared to 100 mg when combined with ABT-333, ABT-267, and RBV for 12 or 24 weeks.
- Higher ABT-450 doses were associated with reduced emergence of R155K variant during treatment with ABT-450/r monotherapy and in IFN-free DAA combination regimens.
- ABT-450 doses  $\geq 200$  mg ( (b) (4) tablet) were associated with increased risk of grade 3+ ALT elevations.
- Modeling and simulation predicted optimal SVR at ABT-450 exposures corresponding to ABT-450 dose  $\geq 150$  mg from the Phase 3 coformulated ABT-450/r/ABT-267 tablets.
- ABT-450 exposures from the ABT-450/r/ABT-267 150/100/25 mg coformulated tablets (Phase 3 formulation) were greater than those from ABT-450 150 mg (b) (4) tablets (Phase 2 formulation) but less than those from the 200 mg (b) (4) tablets, thus providing the optimal balance between safety and maximal efficacy for the 3-DAA combinations.

*Source: Sponsor's Clinical Overview Report, Page 34-35*

**Ritonavir dose:**

The ritonavir dose selected for coadministration with ABT-450 is 100 mg. The ritonavir 100 mg dose is being used to enhance ABT-450 pharmacokinetics as it provides optimal boosting and this dose is also frequently used to boost HIV protease inhibitors, thus providing historical safety information for using ritonavir 100 mg.

The effect of ritonavir on ABT-450 100 mg was evaluated at 3 ritonavir doses: 50, 100, and 200 mg. ABT-450 exposure increased by 3-fold when the ritonavir dose was doubled from 50 mg to 100 mg. Doubling the ritonavir dose from 100 mg to 200 mg, however, increased the ABT-450 AUC by less than 2-fold despite a 6.5-fold increase in ritonavir AUC. Alternately, doubling the ABT-450 dose from 100 mg to 200 mg (with ritonavir 100 mg) increased ABT-450 AUC by 5- to 9-fold. Thus, increasing ABT-450 dose at a constant ritonavir dose provided a greater increase in ABT-450 exposure compared to keeping the ABT-450 dose constant and increasing the ritonavir dose to  $> 100$  mg. Hence, the ritonavir 100 mg dose is optimal for enhancing ABT-450 exposures and has a well-established safety profile in HIV-infected patients.

*Source: Sponsor's Clinical Overview Report, Page 35*

**ABT-333 dose:**

The selection of the ABT-333 250 mg dose was based on efficacy, resistance, and safety data:

- Exposures obtained with the ABT-333 400 mg dose (Phase 2 formulation) showed maximal response following monotherapy for 2 to 3 days, with no improvement in antiviral activity seen at higher doses.
- Exposures associated with the ABT-333 250 mg dose (Phase 3 formulation, bioequivalent exposures to the 400 mg Phase 2 formulation) when combined with the other DAAs gave very high SVR rates in Phase 2 and Phase 3 studies.
- Doses higher than 400 mg BID (800 to 1600 mg BID, Phase 2 formulation) are not expected to improve the resistance profile to polymerase variants.
- ABT-333 doses greater than 400 mg (Phase 2 formulation) were associated with greater mean hemoglobin decrease over 12 weeks of treatment with pegIFN and RBV and have a greater potential to prolong QTc.

*Source: Sponsor's Clinical Overview Report, Page 35-36*

### **ABT-267 dose:**

The selection of ABT-267 25 mg dose for Phase 3 studies was based on efficacy, resistance, and drug-interaction data:

- The ABT-267 25 mg dose showed maximal viral load decline following monotherapy for 2 to 3 days. When doses lower than 25 mg were administered as monotherapy, rebound between dose administrations was observed. Doses greater than 25 mg did not demonstrate a greater reduction in viral load.
- The ABT-267 25 mg dose when combined with the other DAAs gave very high SVR rates in Phase 2 and Phase 3 studies.
- ABT-267 doses significantly greater than 25 mg would be needed to improve the resistance profile.
- The ABT-267 200 mg dose decreased ABT-450 exposures by ~80%. As ABT-450 is the most potent DAA in the combination regimens, the increase in ABT-267 exposure at the expense of ABT-450 exposures is undesirable.

*Source: Sponsor's Clinical Overview Report, Page 36*

### **Ribavirin dose:**

The daily dose of RBV is 1,000 mg or 1,200 mg, divided BID, based on subject weight. This dose is approved for treatment of adult patients with chronic HCV infection in combination with pegIFN by itself and pegIFN with DAAs. The same dose is selected for use with the 3-DAA regimen because its safety profile has been well characterized when administered with pegIFN, including the incidence of hemolytic anemia, and there are well-defined dose modification criteria in the event of RBV-induced anemia. In addition, this dose was studied in the absence of pegIFN in Phase 2 and Phase 3 studies in the combination DAA regimen and was found to be generally safe and well tolerated and resulted in high SVR rates.

*Source: Sponsor's Clinical Overview Report, Page 36-37*

*Reviewer's comments: The dose selection for pivotal trials seems reasonable.*

- *In the pivotal phase 3 trials in GT1b infected patients, the % SVR<sub>12</sub> were high both in presence or absence of RBV with the 3-DAA regimen and the virological failures were too low to judge whether RBV provided any additional value. Thus 3-DAA regimen without RBV was proposed to be suitable for this population.*

- In GT1a infected patients, absence of either RBV or any DAA component (ABT-233 or ABT-267) resulted in incrementally higher virological failure. Removal of either ABT-333 or ABT-267 from the 3-DAA + RBV regimen was associated with a substantially higher virologic failure rate in HCV GT1a-infected treatment-experienced subjects (19.2% to 50%, compared to 4% for 3-DAA+RBV regimen). Thus, RBV containing 3-DAA regimen was found to be suitable for the majority of these patients. For the GT1a-infected non-cirrhotic population, the sponsor had initially proposed a 12 week regimen of 3-DAA+RBV (b) (4). But, the pooled data from pivotal phase 3 studies with GT1a infected treatment naïve non-cirrhotic patients showed that 3-DAA+RBV 12 week regimen had fewer on treatment virological failures as well as relapses as compared to just the 3-DAA 12 week regimen as shown in **Table 4**. Also there were no substantial safety issues with including RBV in the regimen in this population considering that treatment failure with 3-DAA may result in resistant substitutions that limit retreatment options and the other treatment options currently available would also involve RBV in their regimens for equal or even longer durations. Thus, upon review, the 3-DAA+RBV regimen for 12 weeks is recommended for the entire cohort of GT1a-infected non-cirrhotic population.

**Table 4: SVR<sub>12</sub> And Virological Failures in GT1a-infected Treatment Naïve Patients with No Cirrhosis**

Treatment	3-DAA + Placebo (Study M14-002)	3-DAA + RBV (Study M14-002 & M11-646)	Difference (95% CI)
SVR <sub>12</sub> (ITT*)	182/202 (90.1%)	401/419 (95.7%)	5.6% (1.2, 11.1)
On-Treatment VF (virological breakthrough)	6/202 (3.0%)	2/419 (0.5%)	2.5% (0.2, 6.2)
Relapse	11/202 (5.4%)	7/419 (1.7%)	3.8% (0.6, 8.2)

\*5 cirrhotic patients who were in ITT set were removed from the above study populations to reflect the analysis for just the non-cirrhotic patients.

- In cirrhotic subjects, only RBV containing regimens were evaluated since such patients are known to have lower response rates compared to patients without cirrhosis, necessitating the addition of longer treatment durations or additional drugs to further improve response. In addition, there is a focus on reducing treatment failure when possible as treatment failure is associated with the development of resistant viral mutations (see Dr. Harrington's review), meaning retreatment options may be unavailable or limited. Different durations of treatment (12 week vs 24-weeks) were tested (Study M13-099) in these cirrhotic patients to come up with final dosing proposal. Specifically for GT1a-infected cirrhotic patients, the sponsor initially proposed a longer duration (24 weeks) regimen with 3-DAA+RBV (b) (4).

(b) (4) (b) (4) the data from this phase 3 study (M13-099) showed that 3-DAA+RBV 24 week regimen had fewer relapses as compared to 3-DAA+RBV 12 week regimen in treatment naïve as well as treatment experienced GT1a infected population as shown in **Table 5**. Longer treatment durations are generally associated with reduction in treatment failures caused by relapse. Thus, upon review, the longer duration regimen of 3-DAA+RBV for 24 weeks is recommended for the entire cohort of GT1a-infected cirrhotic population.

**Table 5: SVR<sub>12</sub> And Virological Failure due to Relapse in GT1a-infected Patients with Cirrhosis**

Study M13-099	3-DAA + RBV x 12 weeks		3-DAA + RBV x 24 weeks		Difference in relapse (95% CI)
	SVR <sub>12</sub>	Relapse	SVR <sub>12</sub>	Relapse	
GT 1a naïve	59/64 (92.2%)	5/64 (7.8%)	52/56 (92.9%)	2/56 (3.6%)	4.2% (-6.7, 14.9)
GT 1a experienced	65/76 (85.5%)	9/76 (11.8%)	62/65 (95.4%)	0/65 (0%)	11.8% (2.7, 21.8)
-prior null	40/50 (80%)	8/50 (16%)	39/42 (92.9%)	0/42 (0%)	16.0% (2.6, 29.7)
-prior partial	11/11 (100%)	1/11 (9.1%) <sup>§</sup>	10/10 (100%)	0/10 (0%)	
-prior relapse	14/15 (93.3%)	0/15 (0%)	13/13 (100%)	0/13 (0%)	

<sup>§</sup>Reflects 1 patient with post-SVR12 relapse



### 3.2 Population Pharmacokinetic Analysis

A brief synopsis of sponsor's population pharmacokinetic (PPK) analyses for all constituents of the 3-DAA (ABT-450/ritonavir, ABT-267, ABT-333) ± RBV regimen is given below (*source: excerpted from Sponsor's Population Pharmacokinetics Report R&D/14/0047*):

<b>Name of Study Drugs:</b> ABT-450/ritonavir, ABT-267, ABT-333 and ribavirin
<b>Title of Study:</b> Population pharmacokinetics of ABT-450, ABT-267, ABT-333, ritonavir and ribavirin in hepatitis C genotype 1 virus-infected subjects
<b>Objective:</b> The objective of this report is to describe the population pharmacokinetics of ABT-450, ritonavir, ABT-267, ABT-333 and ribavirin following administration of the combination of ABT-450 with ritonavir (ABT-450/r), ABT-267 and ABT-333 with or without ribavirin, in six Phase 3 and one Phase 2 clinical trials in hepatitis C virus (HCV) genotype 1-infected subjects.
<b>Subjects:</b> All subjects who received the to-be-marketed formulation (ABT-450/r/ABT-267 co-formulated tablet + ABT-333 tablet) as part of a 3- direct-acting antiviral agent (DAA) regimen with or without ribavirin were included. A total of 2348 subjects from six Phase 3 studies (M11-646, M13-098, M13-099, M13-389, M13-961, and M14-002) and one Phase 2 study (M14-103) representing ABT-450, ABT-267, ABT-333 and ritonavir concentration-time data were included for the population pharmacokinetic analyses of the 3-DAAs and ritonavir. Ribavirin concentration-time data available from 1841 subjects were included in the population pharmacokinetic analysis. Study M14-103 was included in the analyses as it used the same doses and formulations as the Phase 3 studies.
<b>Methodology:</b> Population pharmacokinetic models were built using nonlinear mixed-effects modeling based on NONMEM 7.3 compiled with the GNU Fortran compiler (Version 4.5.1). The infrastructure for model development and evaluation of final models was a cluster featuring 24 Hewlett-Packard ProLiant servers under the OpenSUSE operating system with MOSIX Cluster and Grid Management (Version 2.32.0.2). The first-order conditional estimation method with $\eta$ - $\epsilon$ interaction (FOCE-INT) was employed for all model runs within NONMEM. A common parameter was estimated to account for the interindividual variability (IIV) of multiple volume parameters, if any, in the models. A $\Omega$ -block matrix for IIV parameters was implemented in order to account for the correlation between apparent clearance (CL/F) and volume parameters. First, a base model was developed that defined the structural model, as well as the models for the interindividual and residual variabilities. The development of the structural model involved a comparison of all potential model representations based on available data and parameter identifiability. IIV was modeled using an exponential error model across all population pharmacokinetic models. Residual unexplained variability (RUV) was explored using a proportional error model (constant coefficient of variation) and a combination of additive and proportional error model. In the population pharmacokinetic analyses, the following covariates were tested: body weight, body mass index, body surface area, sex, age, creatinine clearance, non-responders/naïve, genotype 1 a/b, black race, ethnicity, asian race, cirrhosis, methadone/buprenorphine use, ribavirin use and comedications on CL/F, and age, sex, body weight, body mass index and body surface area on apparent volume parameters (apparent volume of central compartment $[V_c/F]$ and apparent volume of peripheral compartment $[V_p/F]$ ).

**Methodology (Continued):**

An exhaustive list of comedication drug classes and categories (inhibitor or inducer) was considered to evaluate the effect on ABT-450, ABT-267, ABT-333, ritonavir and ribavirin CL/F. The selection of the comedications groups was based on the comparison of the base model *post hoc* steady-state exposures (area under the plasma concentration-time curve from time 0 to 24 hours at steady state [ $AUC_{24,ss}$ ]) between test and control groups. Only the comedication drug classes or categories (inhibitors or inducers) that met the following selection criteria were included in step-wise covariate model building in the population pharmacokinetic analysis:

- Number of subjects representing a comedication drug class or category:  $\geq 15$
- $AUC_{24,ss}$  ratio:  $\leq 0.5$  or  $\geq 2.0$  for all drug classes
- $AUC_{24,ss}$  ratio:  $\leq 0.5$  for inducer categories
- $AUC_{24,ss}$  ratio:  $\geq 2.0$  for inhibitor categories

Relevant covariate-parameter relationships were investigated using forward inclusion and backward elimination procedures. Continuous covariates were normalized to a reference value (approximate median value of the covariate) and included in the model with a power function. Categorical covariates were tested with a multiplicative model in order to obtain the fractional difference of pharmacokinetic parameters between the tested categorical groups. Covariate effects were added to the model in a multiplicative fashion. Inferences about the clinical importance of covariate effects were made based on the magnitude and precision of covariate parameter estimates.

**Statistical Methods:**

Two competing nested models were compared based on objective function value (OFV) at a significance level of  $p < 0.01$  ( $\chi^2$  distribution). Non-nested models were compared based on Akaike Information Criterion (AIC).

For the step-wise covariate selection, a significance of  $p < 0.01$  and  $p < 0.001$  ( $\chi^2$  distribution) was implemented in forward inclusion and backward elimination procedures, respectively.

**Summary/Conclusions:**

This report detailed the population pharmacokinetic analyses conducted to characterize the pharmacokinetics of ABT-450, ABT-267, ABT-333, ritonavir and ribavirin following administration of the DAAs (ABT-450, ABT-267 and ABT-333), ritonavir, with or without ribavirin, in six Phase 3 and one Phase 2 clinical trials in subjects infected with HCV genotype 1. Furthermore, the effect of various covariates, including body weight, body mass index, body surface area, type of subjects (treatment-experienced or naive), liver cirrhosis, ethnicity, sex, age, HCV genotype, creatinine clearance, black race, asian race and concomitant medications (methadone/buprenorphine, opioids, ribavirin, anti-diabetics, hormonal replacement therapy, anti-psychotics, anti-epileptics), on the pharmacokinetics of DAAs, ritonavir and ribavirin was evaluated.

All individual ABT-450, ABT-267, ABT-333, ritonavir and ribavirin population pharmacokinetic models described their respective plasma concentration-time data with reasonable accuracy and the estimation of parameter values was robust. These model-predicted individual plasma concentration-time profiles were used to conduct exposure-efficacy and exposure-safety analyses.



**Summary/Conclusions (Continued):**

**ABT-450:** A one-compartment model with first-order absorption and elimination and a lag time in absorption adequately described ABT-450 plasma concentration-time data. Age, sex, liver cirrhosis and concomitant opioid/anti-diabetic medication use had statistically significant effect on CL/F, while age and body weight had statistically significant effect on  $V_c/F$ . Based on the final model predictions:

- 10 year change in age or 10 kg change in weight led to approximately 20% change in exposures ( $AUC_{24,ss}$ , maximum observed plasma concentration at steady state [ $C_{max,ss}$ ] and pre-dose trough plasma concentration [ $C_{trough}$ ]).
- Female subjects had approximately 100% higher exposures than male subjects.
- Cirrhotic subjects had approximately 120 - 140% higher exposures than Non Cirrhotic subjects.
- Subjects on concomitant anti-diabetics or on concomitant opioids had  $\leq 55\%$  higher exposures than those not on concomitant medications.

**ABT-267:** A one-compartment model with first-order absorption and elimination adequately described ABT-267 plasma concentration-time data. Age, sex, body weight and liver cirrhosis had statistically significant effect on CL/F, and age and body weight had statistically significant effect on  $V_c/F$ . Based on the final model predictions:

- Female subjects had approximately 55% higher exposures ( $AUC_{24,ss}$ ,  $C_{max,ss}$  and  $C_{trough}$ ) than male subjects.
- Presence of cirrhosis, 10 year change in age or a 10 kg change in body weight had a minimal impact ( $\leq 10\%$  change) on ABT-267 exposures.

**ABT-333:** A two-compartment model with first-order absorption and elimination adequately described ABT-333 plasma concentration-time data. Sex, liver cirrhosis, body weight and creatinine clearance had statistically significant effect on CL/F, and age and body weight had statistically significant effect on  $V_c/F$  and  $V_p/F$ . Based on the final model predictions:

- Cirrhotic subjects had approximately 30 - 40% higher exposures ( $AUC_{24,ss}$ ,  $C_{max,ss}$ ) than Non-Cirrhotic subjects.
- Effect of other covariates on exposures was minimal,  $\leq 30\%$  change for female subjects and  $\leq 10\%$  change with 10 kg change in weight, 10 year change in age or mild renal impairment.

**Ritonavir:** A one-compartment model with first-order absorption and elimination adequately described ritonavir plasma concentration-time data. Sex, creatinine clearance and genotype had statistically significant effect on CL/F. Based on the final model predictions:

- Subjects with genotype 1a had approximately 35% higher ritonavir exposures ( $AUC_{24,ss}$ ,  $C_{max,ss}$  and  $C_{trough}$ ) than those with genotype 1b. However, this effect likely represents random variability and is of limited clinical significance.
- Female subjects and subjects with mild renal impairment had approximately 15% higher exposures compared to male subjects and subjects with normal renal function.



**Summary/Conclusions (Continued):**

**Ribavirin:** A two-compartment model with first-order absorption and elimination adequately described ribavirin plasma concentration-time data. Sex, liver cirrhosis and creatinine clearance had statistically significant effect on CL/F, and sex had statistically significant effect on  $V_c/F$  and  $V_p/F$ . Based on the final model predictions:

- Female subjects had approximately 30% higher exposures ( $AUC_{24,ss}$ ,  $C_{max,ss}$  and  $C_{trough}$ ) than male subjects.
- Cirrhosis and mild renal impairment though significant covariates had minimal effect on exposures (< 10%).

Furthermore, these analyses suggested:

- Absence of a clinically relevant pharmacokinetic interaction between ribavirin and the DAAs (ABT-450, ABT-267, ABT-333) and ritonavir following coadministration in the HCV genotype 1-infected subject population.
- Lack of a significant impact of Asian race on the pharmacokinetics of ABT-450, ABT-267, ABT-333 and ritonavir.
- The steady-state DAA exposures achieved in the HCV genotype 1-infected subject (Non-Cirrhotic) population during the Phase 2/3 studies did not exceed those observed in healthy volunteers during Phase 1. Therefore, the Phase 1 studies (drug-drug interaction, renal/hepatic impairment, QT, Asians) conducted to characterize the pharmacokinetics of DAAs provided adequate coverage of the range of exposures that can be anticipated during post-marketing use.

Overall, the regimen of ABT-450/ritonavir, ABT-267 and ABT-333 with or without ribavirin was safe and well tolerated in Phase 3 studies. The results of the population pharmacokinetic analyses suggest that some covariates were significant predictors of higher exposures compared to the average population. However, given the safety profiles of the proposed regimens, no dose adjustment is recommended for the DAAs and ritonavir in the subpopulations. Ribavirin dose should be adjusted per the ribavirin label for reductions in renal function and for anemia.

Final parameter estimates from the final population PK models for ABT-450, ABT-267, ABT-33, ritonavir and RBV are summarized in **Table 6**.

**Table 6: Pharmacokinetic Parameter Estimates and Variability Estimates of the Final POP-PK Models**

<b><u>ABT-450</u></b>
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Parameter	Population Estimate (SEE <sup>a</sup> )	%RSE <sup>b</sup>	95% CI <sup>c</sup>
CL/F (L/day)	1580 (64.5)	4.08	1450 - 1710
$\theta_{CL/F\_AGE}$ (54)	-0.93 (0.10)	10.5	-1.12 - -0.74
$\theta_{CL/F\_CRHS}$ (Cirrhosis)	0.42 (0.03)	7.04	0.36 - 0.48
$\theta_{CL/F\_SEX}$ (Male)	1.94 (0.10)	4.94	1.75 - 2.13
$\theta_{CL/F\_OPIOID}$ (Concomitant Use)	0.65 (0.05)	8.13	0.54 - 0.75
$\theta_{CL/F\_Anti-Diabetic}$ (Concomitant Use)	0.69 (0.08)	10.9	0.54 - 0.84
V <sub>c</sub> /F (L)	16.7 (2.87)	17.2	11.1 - 22.3
$\theta_{Vc/F\_WTKG}$ (76)	1.00 (fixed)	-	-
$\theta_{Vc/F\_AGE}$ (54)	-1.90 (0.42)	22.3	-2.73 - -1.07
k <sub>a</sub> (1/day)	1.74 (fixed)	-	-
ALAG (day)	0.04 (fixed)	-	-
IIV of CL/F	1.18 (150)	3.47	1.10 - 1.26
RUV (exponential)	1.14 (0.027)	2.40	1.09 - 1.19

a. SEE = Standard Error of Estimate.  
b. %RSE was estimated as the SEE divided by the population estimate multiplied by 100.  
c. 95% CI was approximated as the point estimate  $\pm 1.96 * SEE$ .  
- Not applicable

<b><u>ABT-267</u></b>			
Parameter	Population Estimate (SEE <sup>a</sup> )	%RSE <sup>b</sup>	95% CI <sup>c</sup>
CL/F (L/day)	453 (6.68)	1.47	440 - 466
$\theta_{CL/F\_WTKG}$ (76)	0.59 (0.05)	8.17	0.50 - 0.69
$\theta_{CL/F\_SEX}$ (Male)	1.54 (0.03)	1.89	1.48 - 1.60
$\theta_{CL/F\_AGE}$ (54)	-0.48 (0.04)	7.46	-0.55 - -0.41
$\theta_{CL/F\_CRHS}$ (Cirrhosis)	1.11 (0.03)	2.48	1.06 - 1.16
V <sub>c</sub> /F (L)	50.1 (2.61)	5.21	45.0 - 55.2
$\theta_{Vc/F\_WTKG}$ (76)	0.48 (0.20)	41.8	0.09 - 0.87
$\theta_{Vc/F\_AGE}$ (54)	-0.96 (0.21)	22.4	-1.37 - -0.54
k <sub>a</sub> (1/day)	1.08 (0.03)	2.98	1.02 - 1.14
IIV of CL/F	0.14 (39.2)	4.20	0.13 - 0.15
RUV (proportional)	0.11 (0.006)	5.86	0.095 - 0.119
RUV (additive)	0.000024 (0.000009)	38.4	0.00001 - 0.00004

a. SEE = Standard Error of Estimate.  
b. %RSE was estimated as the SEE divided by the population estimate multiplied by 100.  
c. 95% CI was approximated as the point estimate  $\pm 1.96 * SEE$ .

<b><u>ABT-333</u></b>
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Parameter	Population Estimate (SEE <sup>a</sup> )	%RSE <sup>b</sup>	95% CI <sup>c</sup>
CL/F (L/day)	1150 (26.3)	2.29	1100 – 1200
$\theta_{CL/F\_SEX}$ (Male)	1.20 (0.03)	2.61	1.14 – 1.26
$\theta_{CL/F\_CrCL}$ (104)	0.23 (0.06)	25.8	0.11 – 0.35
$\theta_{CL/F\_WTKG}$ (76)	0.31 (0.09)	28.0	0.14 – 0.47
$\theta_{CL/F\_CRHS}$ (Cirrhotic)	0.72 (0.02)	3.46	0.67 – 0.77
Q/F (L/day)	182 (32.8)	18.0	118 – 246
V <sub>c</sub> /F (L)	110 (9.42)	8.56	91.5 – 128
V <sub>p</sub> /F (L)	286 (47.8)	16.7	192 – 380
$\theta_{Vc/F, Vp/F\_AGE}$ (54)	-0.78 (0.20)	25.2	-1.16 – -0.39
$\theta_{Vc/F, Vp/F\_WTKG}$ (76)	0.59 (0.19)	32.8	0.21 – 0.97
k <sub>a</sub> (1/day)	4.61 (0.32)	6.94	3.98 – 5.24
IIV of CL/F	0.26 (54.9)	7.07	0.23 – 0.30
RUV (proportional)	0.26 (0.007)	2.80	0.246 – 0.274
RUV (additive)	0.004 (0.001)	28.1	0.002 – 0.006

a. SEE = Standard Error of Estimate.

b. %RSE was estimated as the SEE divided by the population estimate multiplied by 100.

c. 95% CI was approximated as the point estimate  $\pm 1.96 * SEE$ .

<b><u>Ritonavir</u></b>			
Parameter	Population Estimate (SEE <sup>a</sup> )	%RSE <sup>b</sup>	95% CI <sup>c</sup>
CL/F (L/day)	439 (48.1)	11.0	345 – 533
$\theta_{CL/F\_CrCL}$ (104)	0.36 (0.08)	21.5	0.21 – 0.51
$\theta_{CL/F\_SEX}$ (Male)	1.15 (0.05)	4.26	1.05 – 1.25
$\theta_{CL/F\_GTP}$ (1b, 1B, B)	1.34 (0.08)	5.78	1.19 – 1.49
V <sub>c</sub> /F (L)	21.5 (8.07)	37.5	5.68 – 37.3
k <sub>a</sub> (1/day)	2.32 (0.33)	14.0	1.68 – 2.96
IIV of CL/F	0.81 (112)	12.1	0.62 – 1.00
RUV (proportional)	0.53 (0.023)	4.26	0.489 – 0.577
RUV (additive)	0.000004 (0.000002)	50.4	0.00000 – 0.00001

a. SEE = Standard Error of Estimate.

b. %SE was estimated as the SEE divided by the population estimate multiplied by 100.

c. 95% CI was approximated as the point estimate  $\pm 1.96 * SEE$ .

<b><u>RBV</u></b>
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Parameter	Population Estimate (SEE <sup>a</sup> )	%RSE <sup>b</sup>	95% CI <sup>c</sup>
CL/F (L/day)	427 (4.21)	0.99	419 – 435
$\theta_{CL/F\_CrCL}$ (105)	0.40 (0.03)	6.82	0.34 – 0.45
$\theta_{CL/F\_SEX}$ (Male)	1.09 (0.01)	1.32	1.06 – 1.12
$\theta_{CL/F\_CRHS}$ (Cirrhotic)	1.10 (0.02)	1.57	1.07 – 1.13
Q/F (L/day)	877 (48.5)	5.53	782 – 972
V <sub>c</sub> /F (L)	1100 (62.4)	5.67	978 – 1220
V <sub>p</sub> /F (L)	3230 (84.6)	2.62	3060 – 3400
$\theta_{Vc/F, Vp/F\_SEX}$ (Male)	1.66 (0.04)	2.64	1.57 – 1.75
k <sub>a</sub> (1/day)	21.3 (1.33)	6.24	18.7 – 23.9
IIV of CL/F	0.06 (25.2)	4.18	0.06 – 0.07
IIV of V <sub>c</sub> /F, V <sub>p</sub> /F	0.20 (46.7)	6.50	0.17 – 0.22
RUV (proportional)	0.02 (0.001)	7.65	0.014 – 0.019
RUV (additive)	0.039 (0.005)	12.4	0.029 – 0.048

a. SEE = Standard Error of Estimate.

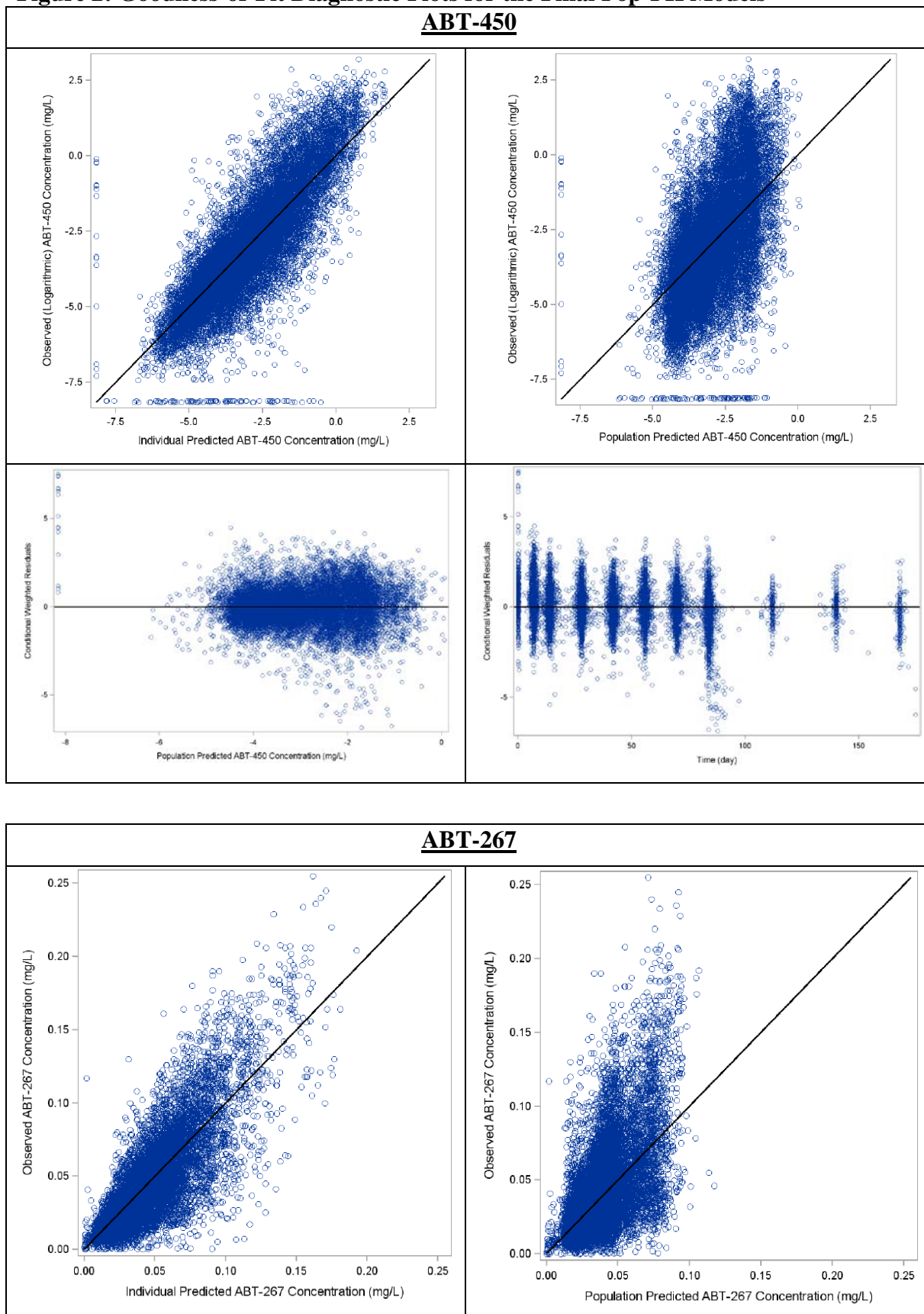
b. %RSE was estimated as the SEE divided by the population estimate multiplied by 100.

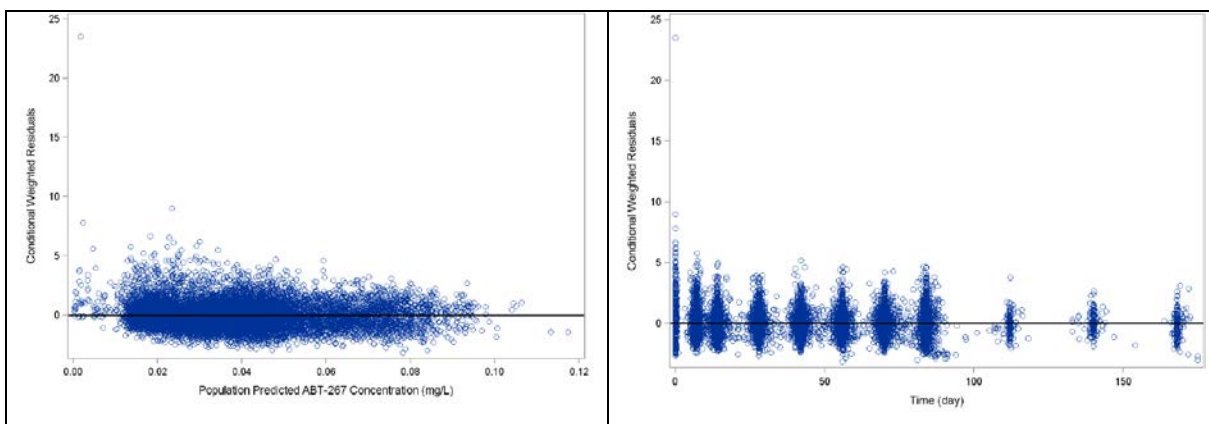
c. 95% CI was approximated as the point estimate  $\pm 1.96 * SEE$ .

Source: Sponsor's Population PK Study Report, Table 10, Table 13, Table 16, Table 19, and Table 22

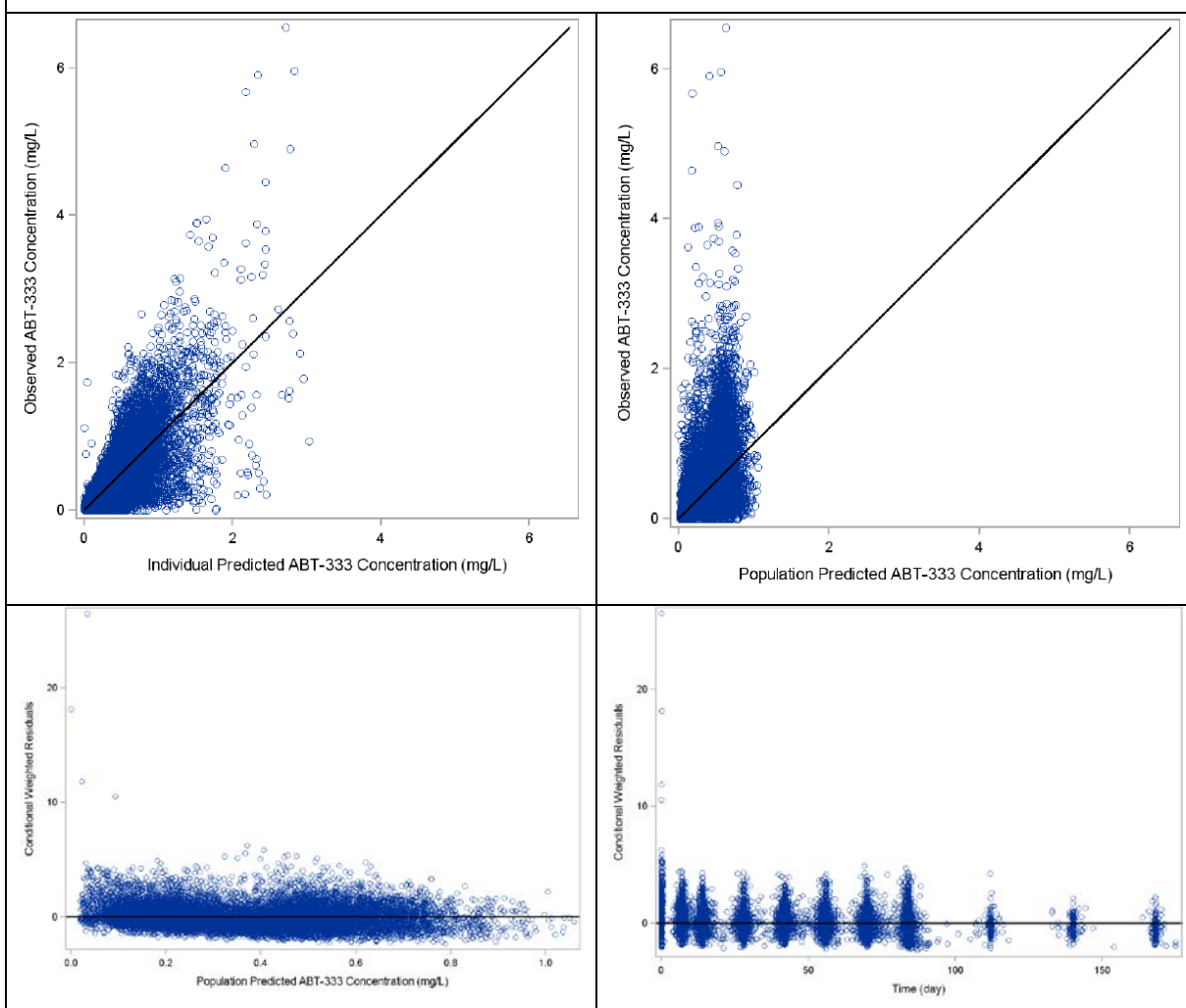
The goodness of fit (Observed vs individual predicted concentrations etc.) plots are provided in **Figure 2**.

**Figure 2: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Models**



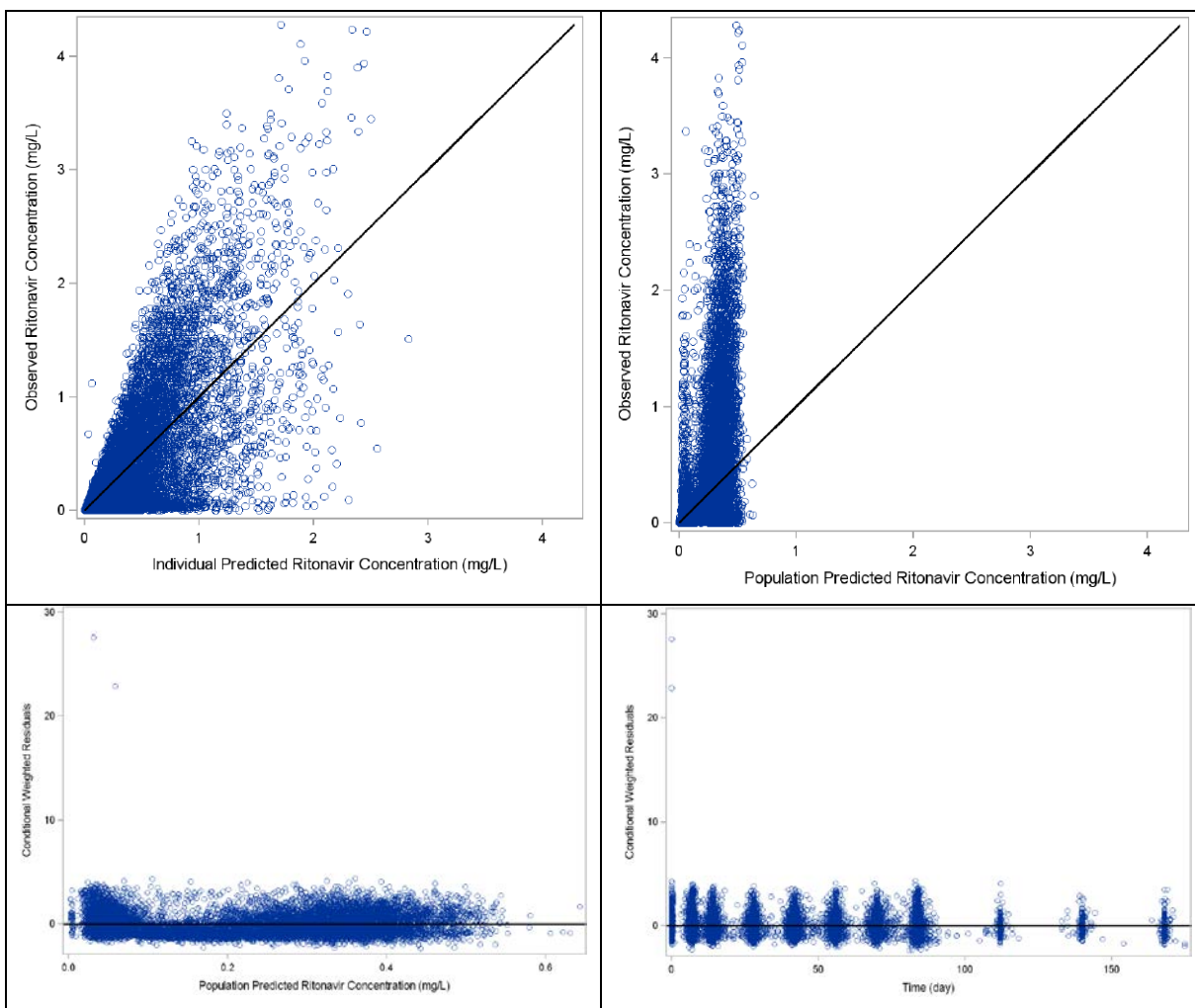


### ABT-333

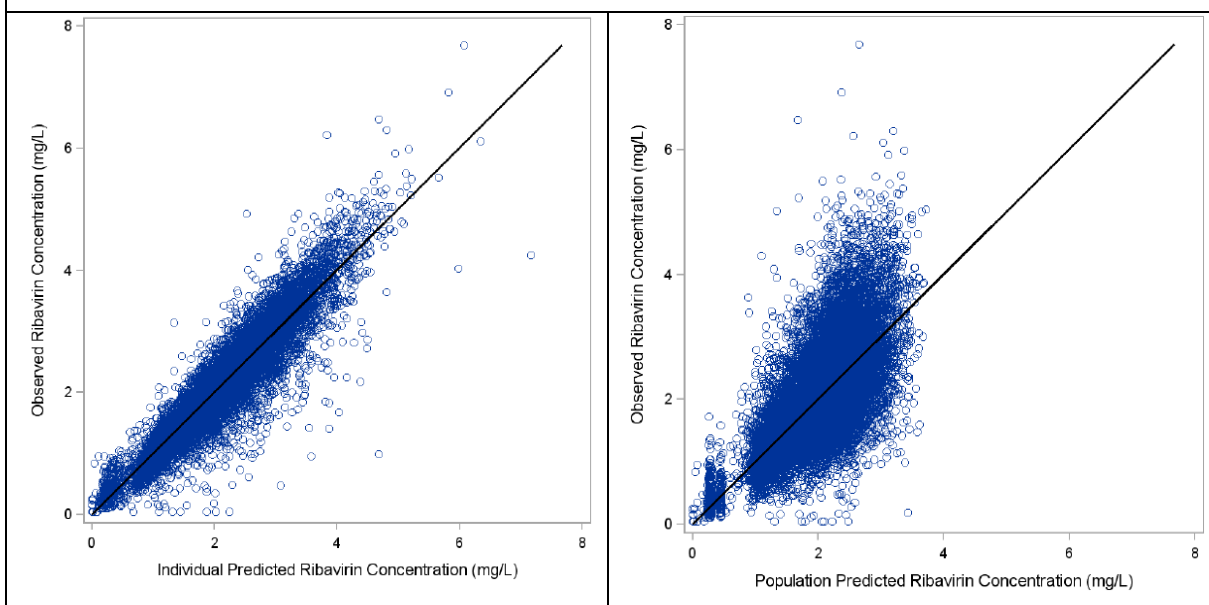


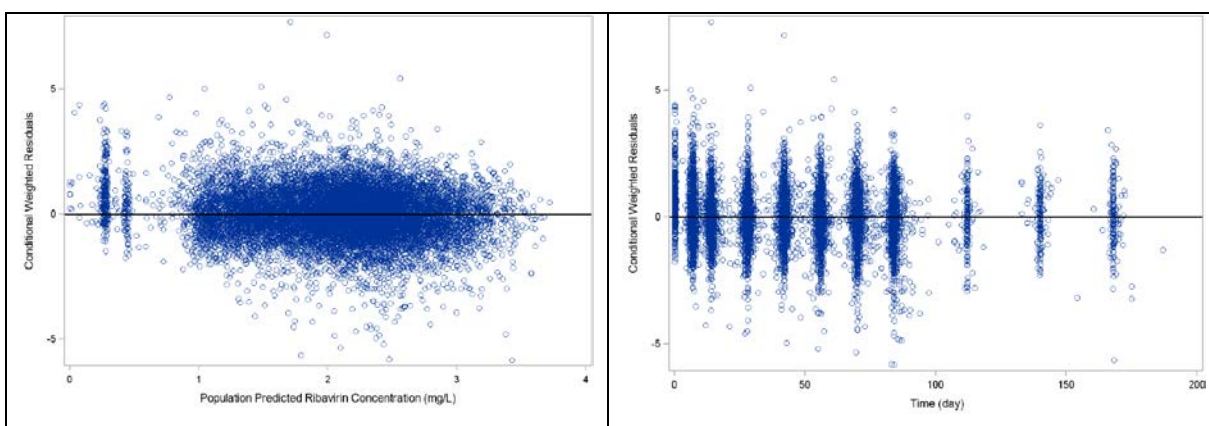
### Ritonavir





### RBV





Source: Sponsor's Population PK Study Report, Figure 14.7\_\_1.1, Figure 14.7\_\_2.1, Figure 14.7\_\_3.1, Figure 14.7\_\_4.1, and Figure 14.7\_\_5.1

*Reviewer's comments: The sponsor's Pop-PK model provides reasonable description of drug concentrations for individual predictions (observed vs. individual predicted concentrations). Of note, separate Pop-PK models were developed for each of the drugs in the regimen. Visual inspection shows that the model reasonably predicts individual data over a range of concentrations with some under-prediction at higher observed concentrations for a limited number of observations for ABT-450, ABT-267, ABT-333 and ritonavir. As the exposure-response analyses focused on  $C_{trough}$  or AUC values, the under prediction of  $C_{max}$  does not impact the subsequent analyses.*

### 3.3 Exposure-Response Analysis

Brief synopses of sponsor's exposure-response (E-R) analyses for efficacy and safety with exposures to different constituents of the 3-DAA (ABT-450/ritonavir, ABT-267, ABT-33)  $\pm$  RBV regimen are given below (source: excerpted from Sponsor's Exposure-Viral Load Response ( $SVR_{12}$ ) Relationship Report R&D/14/0049 and Exposure-Safety Response Relationship Report R&D/14/0048):

#### **Exposure-Efficacy analyses:**



<b>Name of Study Drug:</b> ABT-450/r, ABT-267 and ABT-333
<b>Name of Active Ingredient:</b> ABT-450/r, ABT-267 and ABT-333
<b>Title of Study:</b> Exposure-Viral Load Response (SVR <sub>12</sub> ) Relationship for ABT 450/Ritonavir, ABT-267, ABT-333 and Ribavirin in Hepatitis C Genotype 1 Virus-Infected Subjects – Analyses of Data from Six Phase 3 Studies and One Phase 2 Study
<p><b>Objectives:</b></p> <p>The objective of this report is to describe the relationships between DAA and RBV steady-state exposure (area under the curve [AUC] and the plasma trough concentration [C<sub>trough</sub>]) and pharmacodynamic response (SVR<sub>12</sub>) following administration of the 3-DAA regimen of ABT-450/r/, ABT-267 and ABT-333 with and without ribavirin in HCV genotype 1-infected subjects in six Phase 3 studies and one Phase 2 study.</p>
<p><b>Methodology:</b></p> <p>Pharmacokinetic parameters (AUC and C<sub>trough</sub>) of DAAs and RBV at steady state estimated for each subject based on the population-pharmacokinetic models (the empirical Bayes post-hoc estimates) were used for exposure-response analyses. Graphical and quantitative multivariate logistic regression analyses were performed.</p> <p>Graphically the relationship between ABT-450, ABT-267, ABT-333 and ribavirin exposures (AUC and C<sub>trough</sub>) values and % SVR<sub>12</sub> was explored using quartiles plots. Graphic analyses were performed for different sub-populations of HCV infected subjects included in the dataset, such as GT1a and GT1b, subjects with and without compensated cirrhosis, prior pegIFN/RBV treatment-naïve and -experienced. Multivariate logistic-regression analyses were performed only using the data from GT1a-infected subjects (as &gt; 99% of GT1b-infected subjects achieved SVR<sub>12</sub>). Logistic regression was performed using generalized linear regression with PROC LOGISTIC in SAS 9.3 on a 64 bit Windows 7 workstation. In the logistic-regression analysis, the predictor variables were steady-state exposure (AUC or C<sub>trough</sub>) for ABT-450, ABT-267, ABT-333, and ribavirin and subject-specific covariates, such as demographic variables (age, body mass index [BMI], sex, ethnicity [Hispanic/Latino versus non-Hispanic/Latino] and race [Black versus non-Black]), baseline HCV viral load, IL28B genotype, prior pegIFN/RBV treatment experience, and compensated liver cirrhosis (Child-Pugh A). These covariates were evaluated in the logistic regression model using forward selection procedure at the alpha level of 0.05.</p>
<p><b>Study Subjects:</b></p> <p>HCV genotype-1 infected adult male and female subjects (N = 2060) enrolled in Studies M11-646, M13-098, M13-099, M13-389, M13-96, M14-002 and M14-103 were included for graphical analysis. HCV GT1a-infected subjects (N = 1064) from the studies noted above were included in the multivariate logistic regression exposure-response analysis.</p>

**Exposure-Response Results Summary and Conclusions:****Graphical Analysis (Quartile Plots)**

- No trend was observed between ABT-450, ABT-333, ABT-267 or RBV AUC and % SVR<sub>12</sub> for all GT1b-infected subjects.
- HCV GT1a-infected subjects (naïve and experienced) with or without cirrhosis (Child-Pugh A) receiving the 3 DAA + RBV regimen in Phase 3 and Phase 2 Studies included in the dataset showed no apparent relationship between ABT 333 AUC and % SVR<sub>12</sub>, but a shallow trend was observed for ABT-450, ABT-267 and RBV AUC.
  - Naïve and experienced subjects when plotted separately (within subjects with or without cirrhosis) showed a shallow trend generally similar to when they were combined together, except for experienced subjects without cirrhosis, who do not show a trend for ABT-450 and ABT-267 AUC.
  - Male and female subjects when plotted separately when plotted separately (within subjects with or without cirrhosis), showed no trend between DAA and RBV AUC and % SVR<sub>12</sub> for female subjects, but a shallow trend between ABT-450, ABT-267 and RBV AUC and % SVR<sub>12</sub> was observed for GT1a-infected male subjects.
- For GT1a-infected, naïve subjects without cirrhosis receiving 3-DAA regimen, a shallow trend was observed between ABT-450 and ABT-267 AUC and % SVR<sub>12</sub>, but not for ABT-333 AUC and % SVR<sub>12</sub>.

Results from graphical analysis using C<sub>trough</sub> as a measure of exposure were consistent with AUC.

**Multivariate Logistic Regression**

The estimates of logistic regression model parameters from the final model are listed in table below.

Predictor Variable	$\beta$	SE	p-value
Intercept	10.3425	2.2469	< 0.0001
Log ABT-267 AUC	1.4878	0.3607	< 0.0001
Log Ribavirin AUC (centered at geometric mean)	2.1984	0.7632	0.0040
Absence of RBV	-1.5983	0.3773	< 0.0001
Baseline VL	-0.9752	0.3287	0.0030
IL28B (CC)	1.1381	0.4666	0.0147
Ethnicity (Hispanic/Latino)	-0.9467	0.4354	0.0297

The estimates of odds ratios for covariates in the final model are summarized in the table below.

Effect	Odds Ratio Estimates		
	Point Estimate	95% Wald Confidence Limits	
Log ABT-267 AUC	4.428	2.183	8.979
Log RBV AUC (centered at geometric mean)	9.101	2.019	40.212
Baseline VL	0.377	0.198	0.718
Ethnicity (Hispanic/Latino)	0.388	0.165	0.911
IL28B (CC)	3.121	1.251	7.787
Absence of RBV	0.202	0.097	0.424

Based on the these results, a 50% decrease in ABT-267 AUC is predicted to result in a 3.4% decrease in SVR<sub>12</sub> and a 100% increase in ABT-267 AUC is predicted to result in a minimal 1.3% increase in SVR<sub>12</sub> for the reference population comprised of subjects with IL28B non-CC genotype, non-Hispanic/Latino ethnicity.

In summary, following multivariate logistic regression analysis, ABT-267 and RBV exposure were statistically significant predictors of the probability of SVR<sub>12</sub> success. In addition, absence of RBV, baseline VL, IL28B genotype and Hispanic/Latino ethnicity were also significant predictors of the probability of SVR<sub>12</sub> success. Subject-specific covariates that were tested in logistic regression analysis, but were not statistically significant, includes prior pegIFN/RBV treatment experience (Naive versus experienced), compensated cirrhosis (presence [Study M13-099] versus absence), race (Blacks versus Non-Blacks), BMI and sex. Although ABT-267 exposure variables were statistically significant predictors of the probability of achieving SVR<sub>12</sub>, the changes in model predicted SVR<sub>12</sub> were limited: a 50% reduction in ABT-267 AUC values was predicted to result in a 3.4% decrease in SVR<sub>12</sub>, and a 100% increase in ABT-267 AUC values was predicted to result in a 1.3% increase in SVR<sub>12</sub>. The change in SVR<sub>12</sub> associated with relatively large magnitude of changes in ABT-267 AUC values (0.5-fold to 2-fold changes) are of limited clinical significance.

### **Exposure-Safety analyses:**



<b>Name of Study Drugs:</b> ABT-450/ritonavir, ABT-267, ABT-333 and ribavirin
<b>Title of Study:</b> Exposure-Safety Response Relationship for ABT-450/Ritonavir, ABT-267, ABT-333 and Ribavirin in Hepatitis C Genotype 1 Virus-Infected Subjects – Analyses of Safety Data from One Phase 2 and Six Phase 3 Studies
<b>Objective:</b> The objective of this report was to describe the relationships of ABT-450, ritonavir, ABT-267, ABT-333 and ribavirin exposures and clinical safety parameters, including adverse events and laboratory parameters, following administration of the direct-acting antiviral agents (DAAs), ABT-450 with ritonavir (ABT-450/r), ABT-267 and ABT-333 as 3-DAA combinations with or without ribavirin (RBV), in six Phase 3 and one Phase 2 clinical trials in hepatitis C virus (HCV)-infected subjects.
<p><b>Methodology</b></p> <p><b>Exposure-Safety Response</b></p> <p>The steady-state area under the plasma concentration-time curve (AUC) was obtained using post-hoc estimations for the individual subjects from the population pharmacokinetic analyses for each DAA and ritonavir and ribavirin. The response variables were based on the treatment-emergent adverse events of special interest identified in the Integrated Summary of Safety (ISS).</p> <p>The relationship between adverse events or laboratory abnormalities and drug (ABT-450, ritonavir, ABT-267, ABT-333 or ribavirin) exposure were evaluated graphically and by multivariate logistic regression exposure-response analyses. Three sets of graphical evaluations of the relationships between adverse events or laboratory abnormalities and drug exposures were performed: ABT-450, ritonavir, ABT-267, ABT-333 and ribavirin AUCs were plotted against (1) the various severities/grades of adverse events, (2) the shifts in grade from baseline in laboratory abnormalities, and (3) the incidences of safety events.</p> <p>In the analyses, the predictor variables were logarithmically-transformed values of the steady-state AUCs for ABT-450, ABT-267, ABT-333, ritonavir and ribavirin derived from population pharmacokinetic analyses, treatment effects (placebo versus active treatment, presence or absence of ribavirin), and covariates including sex, age, weight, race, study effects, use of estrogen or progesterone containing medication, and baseline laboratory abnormality grades of the safety variable. Multivariate logistic regression analyses were performed to evaluate the relationships between logarithmic AUCs and safety events, while accounting for the effects of covariates and baseline status. The grouping of the categories of response variables (adverse events and laboratory abnormalities) in the logistic regression analyses were based on available data (frequency of events) and clinical relevance.</p> <p><b>Study Subjects</b></p> <p>HCV genotype 1 virus-infected subjects (N = 2346) enrolled in Studies M11-646, M13-098, M13-099, M13-389, M13-961, M14-002, and M14-103 were included in this report. A total of 2093 subjects received the 3-DAA regimens with/without ribavirin, including 509 subjects who received ABT-450/r + ABT-267 +ABT-333 without RBV and 1584 subjects who received ABT-450/r + ABT-267 +ABT-333 with RBV. A total of 253 subjects received the placebo regimen in the double blind period in Studies M11-646 and M13-098. The treatment durations were up to 24 weeks.</p>



## **Criteria for Evaluation**

### **Exposure Clinical Response for Safety:**

The relationship between safety events and exposure were evaluated graphically and by multivariate logistic regression. The graphic presentations were created using R Package ggplot2 in R (v. 3.0.1). Exposure-safety response analyses using multivariate logistic regression model were performed with generalized linear regression function (*glm*) in R.

## **Statistical Methods**

### **Exposure-Safety Response:**

Exposure-safety response analyses were performed using the estimated individual steady-state pharmacokinetic exposure (AUC) and safety data (adverse events and laboratory abnormalities with highest grade developed within the treatment period). Multivariate logistic regression analyses were performed to evaluate the relationships between safety events and pharmacokinetic exposures, treatment effects, and covariates including sex, age, weight, race, study effects, use of estrogen or progesterone containing medication, and baseline laboratory abnormality grades of the safety variable.

## **Summary and Conclusions**

The relationship between adverse events or laboratory abnormalities and drug exposure (ABT-450, ritonavir, ABT-267, ABT-333 or ribavirin) were evaluated graphically and by multivariate logistic regression exposure-response analyses.

### **Graphical Evaluation**

Graphical evaluation suggested that events in the drug-induced rash company medical dictionary for regulatory activities (MedDRA) query (CMQ), alanine aminotransferase (ALT) elevations, total bilirubin elevations and hemoglobin reductions appeared to be associated with increases in ABT-450 AUC, while total bilirubin elevations and hemoglobin reductions appeared to be associated with increases in ABT-333 and ribavirin AUCs.

In addition, plots exploring incidence of drug-induced rash or laboratory abnormalities versus AUCs (using Quartile plots) indicated that all DAAs, ritonavir and ribavirin appeared to be associated with drug-induced rash. ABT-450 AUC appeared to be associated with ALT elevations. ABT-450, ABT-333, ritonavir and RBV AUCs appeared to be associated with total bilirubin elevations, and RBV AUC appeared to be associated with hemoglobin reduction.

### **Exposure-Response Modeling by Multivariate Logistic Regression**

Exposure-response modeling was conducted using multivariate logistic regression. In addition to AUC values, treatment effects (placebo versus active treatment, presence or absence of ribavirin), covariates (including sex, age, weight, race, study effect, use of estrogen or progesterone containing medication), and baseline status were evaluated in the model to characterize associations between adverse events or laboratory abnormalities and pharmacokinetic exposures.

### **Drug-Induced Rash CMQ (Moderate/Severe)**

Incidence of drug-induced rash was higher with active treatment compared to placebo. Inclusion of RBV in the regimen was a significant predictor of rash. The incidence in events in the drug-induced rash was also associated with higher ABT-450 AUC.

## Summary and Conclusions (Continued)

### ALT Elevations

ABT-450 AUC and baseline ALT levels were associated with post-baseline  $\geq$  Grade 3 ALT elevations. Increasing ABT-450 exposure by 2-fold is predicted to increase the odds of  $\geq$  Grade 3 ALT elevations to 1.6-fold. Given the observed ALT elevation incidence of 0.91%, a 2-fold increase in ABT-450 exposure is predicted to increase the incidence of  $\geq$  Grade 3 ALT elevations to 1.4%.

### Bilirubin Elevations

Treatment effect (no RBV versus RBV) was associated with  $\geq$  Grade 3 total bilirubin elevation. Only 2 out of 509 subjects (0.39%) had  $\geq$  Grade 3 total bilirubin elevations in the absence of RBV with the treatment regimen compared to 81 out of 1584 subjects (5.1%) who had  $\geq$  Grade 3 total bilirubin elevations in the presence of RBV with the regimen. ABT-450 and ribavirin AUCs as well as elevated baseline bilirubin levels were associated with post-baseline  $\geq$  Grade 2/3 bilirubin elevations. Increasing ABT-450 exposure by 2-fold is predicted to increase the odds of  $\geq$  Grade 3 total bilirubin elevations to 1.5-fold. Thus given the observed  $\geq$  Grade 3 total bilirubin elevation incidence of 4.0%, a 2-fold increase in ABT-450 exposure is predicted to increase the incidence of  $\geq$  Grade 3 bilirubin elevation to about 6%.

### Decreases in Hemoglobin Levels

Decreases in hemoglobin levels ( $\geq$  Grade 2) were associated with presence of ribavirin and higher ribavirin exposures. Female sex, hemoglobin baseline status (baseline  $\geq$  Grade 1), and the presence of cirrhosis were covariates associated with decreases in hemoglobin levels.

Overall there was no association between ABT-333, ABT-267 or ritonavir exposures and adverse events or changes in laboratory values in the logistic regression analyses. While ABT-450 and ribavirin had some associations, the relationships were shallow. Given the very low incidences of adverse events across all Phase 3 studies, increases in ABT-450 exposure by up to 2 fold are not expected to adversely affect the safety profile of the regimen.

### *Reviewer's comments:*

- *The results of reviewer's analysis of E-R relationship for efficacy are described in section 2.2.4.1 of the Clinical Pharmacology Question Based Review (QBR).*
- *Sponsor's analyses of E-R relationship for safety based on multiple logistic regression analyses were verified and are described in section 2.2.4.2 of the Clinical Pharmacology Question Based Review (QBR). Predicted safety risk (incidences) corresponding to 2-fold changes in exposure of ABT-450 and ABT-267 based on these models by the sponsor were verified and additional predictions of incidence of decrease in hemoglobin level with change in ABT-450 exposure were made (a 2-fold increase from mean in ABT-450 exposure is predicted to increase incidence of  $\geq$  Grade 2 hemoglobin decrease events from 5.21% to ~6.9%).*
- *Overall, from the E-R relationships for safety and efficacy, a change in exposure within the window of 0.5- to 2.0-fold from the population mean exposures for ABT-450, ABT-267 or ABT-333 are not anticipated to alter the benefit/risk profile to an extent which would necessitate any dosing changes.*

#### 4 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

**Table 7: Analysis Data Sets**

Study Number/Context	Name	Link to EDR
Integrated Summary of Efficacy	Adeffp3.xpt	\\cdsesub1\evsprod\NDA206619\0003\m5\datasets\rd13443\analysis\legacy\datasets\adeffp3 xpt
E-R analysis for efficacy	Svrpkcsv xpt	\\cdsesub1\evsprod\NDA206619\0003\m5\datasets\rd140049\analysis\legacy\datasets\svrpksv xpt
E-R analysis for safety	p3safety xpt	\\cdsesub1\evsprod\NDA206619\0003\m5\datasets\rd140048\analysis\legacy\datasets\p3safety.xpt

**Table 8: Codes and Output Files**

Description	File Name\Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ombitasvir_AB T450_r_Dasabuvir_NDA206619_DDM\ER_Analyses\codes\
E-R analysis for efficacy	ER_SVR12_P2P3.sas
Virological Failure analysis	VF_GT1a_naive.sas
E-R analysis for safety	ER_Safety.sas
PK in Cirrhotic vs Non-Cirrhotic patients	Cirrhosis_PK.sas
Efficacy in Cirrhotic patients	cirrhotic_efficacy_M13099.sas
PK comparison for methadone use, gender, bodyweight etc.	Methadone_PK.sas

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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  
09/19/2014

SEONG H JANG  
09/19/2014

DHANANJAY D MARATHE  
09/19/2014

JEFFRY FLORIAN  
09/19/2014

ISLAM R YOUNIS  
09/19/2014



# Office of Clinical Pharmacology

## New Drug Application Filing and Review Form

General information about the submission	
NDA/BLA Number	206619
OCP Division	DCP4
Medical Division	Division of Antiviral Products (DAVP)
OCP Reviewer	Vikram Arya, Ph.D., FCP
OCP Team Leader	Islam Younis, Ph.D.
Pharmacometrics Reviewer	Dhananjay Marathe, Ph.D.
Pharmacometrics Secondary Reviewer	Jeffrey Florian, Ph.D.
Pharmacogenomics Reviewer	Not Applicable
Pharmacogenomics Secondary Reviewer	Not Applicable
Date of Submission	April 21, 2014
OCP Review Estimated Due Date	August 22, 2014
Medical Division Due Date	September 21, 2014
PDUFA Due Date	December 21, 2014
Relevant IND Number	103526 (ABT-450), 108434 (ABT-267), 101636 (ABT-333).

General information about the drug/biologic	
Brand Name	Viekira Pak
Generic Name	Dasabuvir (ABT-333) , Norvir (Ritonavir) Veruprevir (ABT-450), and Ombitasvir (ABT-267)
Drug Class	NS3A Protease Inhibitor (ABT-450), HIV-1 Protease Inhibitor (Ritonavir), NS5A Inhibitor (ABT-267), NS5B Polymerase Inhibitor (ABT-333)
Indication(s)	Treatment of genotype 1 chronic Hepatitis C infection, including patients with cirrhosis
Dosage Form	Co-formulated tablets (ABT-450/r/267) co-packaged with ABT-333 tablets
Dosing Regimen	<p>Two 75/50/12.5 mg tablets once daily co-administered with one ABT-333 250 mg tablet twice daily and weight-based Ribavirin (1000 or 1200 mg total dose in divided doses BID).</p> <p>Of note, the duration of treatment and the need for ribavirin in the proposed regimen varies based on prior response to pegIFN and ribavirin and the presence or absence of cirrhosis.</p>
Route of administration	Oral

Sponsor	Abbvie Inc.
Priority Classification	Priority

Clinical pharmacology and biopharmaceutics information				
Study Type	Incl. at Filing	No. of Studies Submitted	No. of Studies Reviewed	Critical Comments
Table of Contents incl. reports, tables, data	<input checked="" type="checkbox"/>			
Tabular Listing incl. all human studies	<input checked="" type="checkbox"/>			
Human PK Summary	<input checked="" type="checkbox"/>			
Labeling	<input checked="" type="checkbox"/>			
Reference Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/>			
<b>I. CLINICAL PHARMACOLOGY</b>				
Mass Balance	<input checked="" type="checkbox"/>	3	3	
Isoenzyme Characterization (In Vitro)	<input checked="" type="checkbox"/>	23	23	Summary of results will be presented in a tabular format
Transporter Characterization (In Vitro)	<input checked="" type="checkbox"/>	31	31	Summary of results will be presented in a tabular format
Blood/Plasma Ratio	<input checked="" type="checkbox"/>	4	4	
Plasma Protein Binding	<input checked="" type="checkbox"/>	5	5	
<b>Pharmacokinetics (e.g. Phase 1)</b>				
<i>Healthy Volunteers</i>				
Single Dose	<input checked="" type="checkbox"/>	3	1	
Multiple Dose	<input checked="" type="checkbox"/>	2	0	
<i>Patients</i>				
Single Dose	<input type="checkbox"/>			
Multiple Dose	<input checked="" type="checkbox"/>			Trials have been counted under Proof-of Concept, Phase 2 and Phase 3 trials.
<i>Dose Proportionality – Fasting/Non-Fasting</i>				
Single Dose	<input checked="" type="checkbox"/>			Trials have been counted under single dose and multiple dose trials
Multiple Dose	<input checked="" type="checkbox"/>			

<i>Drug-Drug Interaction Studies</i>				
In Vivo Effects on Primary Drug	<input checked="" type="checkbox"/>	27	25	Trials M10-687 and M11-603 will not be reviewed as more clinically relevant information can be derived from other trials.
In Vivo Effects of Primary Drug	<input checked="" type="checkbox"/>			See “ In Vivo Effects on Primary Drug” section
In Vitro	<input checked="" type="checkbox"/>			See “Isozyme Characterization” and “Transporter Characterization” sections
<i>Special Populations</i>				
Ethnicity	<input checked="" type="checkbox"/>	7	1	Only trial M12-221 will be reviewed as it provides the most clinically relevant information
Gender	<input type="checkbox"/>			Gender was evaluated as a covariate in the population pharmacokinetic analysis
Pediatrics	<input type="checkbox"/>			
Geriatrics	<input type="checkbox"/>			Age was evaluated as a covariate in the population pharmacokinetic analysis
Renal Impairment	<input checked="" type="checkbox"/>	1	1	
Hepatic Impairment	<input checked="" type="checkbox"/>	1	1	
<i>Pharmacodynamics</i>				
Phase 2	<input checked="" type="checkbox"/>	4	4	
Phase 3	<input checked="" type="checkbox"/>	6	6	
<i>Pharmacokinetics/Pharmacodynamics</i>				
Proof of Concept (Phase 1 or 2)	<input checked="" type="checkbox"/>	6	0	More clinically relevant information can be obtained from Phase 2 and Phase 3 trials.

Clinical Trial (Phase 3)	<input type="checkbox"/>			
<i>Population Analyses</i>				
Data-rich	<input checked="" type="checkbox"/>			
Data-sparse	<input checked="" type="checkbox"/>	3	3	
<b>II. BIOPHARMACEUTICS</b>				
<i>Bioavailability</i>				
Absolute Bioavailability	<input checked="" type="checkbox"/>	1	1	
Relative Bioavailability (solution as reference)	<input type="checkbox"/>			
Relative Bioavailability (alt. formulation as ref.)	<input checked="" type="checkbox"/>	9	3	M12-683, M13-391, and M13-331 will be reviewed by the Biopharm group
<i>Bioequivalence</i>				
Traditional Design (single/multiple dose)	<input checked="" type="checkbox"/>	1	1	M14-196 will be reviewed by the Biopharm group
Replicate Design (single/multiple dose)	<input type="checkbox"/>			
<i>Food-Drug Interaction</i>	<input checked="" type="checkbox"/>	3	2	
<i>Biowaiver Request (based on BCS class)</i>	<input type="checkbox"/>			
<i>Dissolution (alcohol-induced dose-dumping)</i>	<input type="checkbox"/>			Not relevant
<b>III. OTHER CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS</b>				
<i>Genotype/Phenotype</i>	<input type="checkbox"/>			
<i>Chronopharmacokinetics</i>	<input type="checkbox"/>			
<i>Pediatric Development Plan</i>	<input type="checkbox"/>			
<i>Literature References</i>	<input type="checkbox"/>			
<b>TOTAL NUMBER OF STUDIES</b>		140	115	

On <b><u>initial</u></b> review of the NDA/BLA application for filing:					
<b>Content Parameter</b>		<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2	Has the applicant provided metabolism and drug-drug interaction information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
5	Has a rationale for dose selection been submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12	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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
13	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"/>	<input type="checkbox"/>	<input type="checkbox"/>	
14	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 pharmacokinetics or pharmacodynamics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>General</b>					

18	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"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

☒ **Yes**      ☐ **No**

**If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.**

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

Vikram Arya, Ph.D, FCP	June 19, 2014
<b>Reviewing Clinical Pharmacologist</b>	<b>Date</b>

Islam Younis, Ph.D.	June 19, 2014
<b>Team Leader/Supervisor</b>	<b>Date</b>

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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  
06/19/2014

ISLAM R YOUNIS  
06/19/2014