

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333, ribavirin	Volume:	
Name of Active Ingredient: ABT-450: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-[[[(5-methylpyrazin-2-yl)carbonyl]amino]-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate ritonavir: [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester ABT-267: Dimethyl [(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbonyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}biscarbamate hydrate ABT-333: (sodium N-{6-[3-tert-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide hydrate) Ribavirin: 1-β-D-ribofuranosyl-1 <i>H</i> -1,2,4-triazole-3-carboxamide	Page:	
Title of Study: A Multipart, Open-label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir with and without Dasabuvir Coadministered with and without Ribavirin in Adults with Genotype 1 or 4 Chronic Hepatitis C Virus Infection and Human Immunodeficiency Virus, Type 1 Coinfection (TURQUOISE-1)		
Coordinating Investigator: Jürgen Rockstroh, Prof. Dr. Med.		
Study Sites: 61 investigative sites enrolled subjects in Australia, Canada, France, Germany, Italy, Russia, Spain, United Kingdom, New Zealand and the United States, including Puerto Rico.		
Publications: 2 manuscripts and 4 abstracts		

<p>Studied Period (Years): First Subject First Visit: 30 August 2013 Last Subject Last Visit: 25 October 2016</p>	<p>Phase of Development: 2/3</p>
<p>Objectives:</p> <p>The primary objectives of this study were to assess the safety of ombitasvir/paritaprevir/ritonavir (ABT-450/r/ABT-267) with and without dasabuvir (ABT-333) coadministered with and without ribavirin (RBV) for 12 and 24 weeks in hepatitis C virus (HCV) genotype 1 (GT1)- or genotype 4 (GT4)-infected subjects with human immunodeficiency virus (HIV)-1 coinfection and to evaluate the percentage of subjects achieving a 12-week sustained virologic response, SVR₁₂ (HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ] 12 weeks following treatment). These objectives were assessed separately within each part of the study. For Part 1a, the 12- and 24-week treatment arms were assessed separately. For Part 1b, the darunavir (DRV) once daily (QD) and twice daily (BID) arms were assessed separately as well as in combination. For Part 2, the GT1-infected subjects were assessed separately from the GT4-infected subjects, and the percentage of subjects in the GT1 Analysis Group (i.e., GT1 subjects enrolled in Arms E, F, H, I and J) achieving SVR₁₂ was compared to a threshold based on the historical SVR₁₂ rate of sofosbuvir plus RBV. The secondary objectives were to assess the percentage of subjects with on treatment HCV virologic failure, the percentage of subjects with HCV virologic relapse, and the percentage of subjects with plasma HIV-1 viral suppression at the end of treatment and at Post-Treatment Week 12 within each part of the study, and to compare the SVR₁₂ rates between treatment arms in Part 1a and Part 1b of the study.</p>	
<p>Methodology:</p> <p>This was a Phase 2/3, multipart, open-label, multicenter study evaluating the safety and efficacy of ABT-450/r/ABT-267 with and without ABT-333 coadministered with and without RBV for 12 or 24 weeks in adults with HCV GT1 or GT4/HIV-1 coinfection who were HCV treatment-naïve or HCV treatment-experienced with and without compensated cirrhosis. This study consisted of a Phase 2 pilot cohort (Part 1a and Part 1b) and a Phase 3 cohort (Part 2). Both Part 1 and Part 2 of this study consisted of a Treatment Period and a Post-Treatment Period. In addition, Part 1b consisted of a lead-in period (Pre-Treatment Period) for approximately 2 weeks prior to the initiation of the Treatment Period. Subjects with unquantifiable plasma HIV-1 RNA and a CD4+ count ≥ 200 cells/mm³ (Part 1 only) or CD4+% $\geq 14\%$ (Part 1 only) while on a stable atazanavir (ATV)-, raltegravir (RAL)-, dolutegravir (DTG)-, or DRV (Part 1b and Part 2 GT4 subjects only)-containing HIV-1 ART regimen were eligible. Approximately 60 eligible subjects in Part 1a were to be randomized in a 1:1 ratio to either:</p> <ul style="list-style-type: none"> • Arm A: ABT-450/r/ABT-267 150/100/25 mg once daily (QD) + ABT-333 250 mg BID + RBV for 12 weeks; or • Arm B: ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV for 24 weeks <p>RBV was administered weight-based 1,000 or 1,200 mg divided BID.</p>	

Methodology (Continued):

Randomized subjects in Part 1a were stratified by prior HCV treatment history (treatment-naïve versus treatment-experienced) and by presence of cirrhosis (cirrhotic or noncirrhotic). Treatment-naïve subjects were also stratified by interleukin 28B (IL28B) genotype (CC versus non-CC).

PegIFN/RBV-experienced subjects were also stratified by type of previous response to pegIFN/RBV (null responder, partial responder, or relapser). HCV GT1/HIV-1 coinfecting adults with compensated cirrhosis were eligible for enrollment in the study. The Part 1a cohort consisted of 2 HIV-1 ART regimen subgroups (ATV and RAL), each containing at least 20 subjects. Subjects were to be followed for 48 weeks after the end of treatment.

In Part 1b, approximately 30 subjects on a stable QD DRV-containing HIV-1 ART regimen were to be randomized to either continue to receive DRV 800 mg QD or to switch to DRV 600 mg BID administration during a pretreatment period. All subjects in Part 1b were to receive ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV for 12 weeks during the treatment period and be followed for 24 weeks after the end of treatment. Randomized subjects in Part 1b were stratified by prior HIV treatment history (previously protease inhibitor (PI)-naïve subjects [i.e., no PI exposure other than DRV] and previously PI-experienced subjects [i.e., received non-DRV PI prior to current DRV treatment]).

Part 2, the Phase 3 cohort, was designed together with Part 1 to evaluate the safety and efficacy of ABT-450/r/ABT-267 and ABT-333 coadministered with and without RBV or ABT-450/r/ABT-267 with RBV for 12 and 24 weeks. Approximately 230 subjects were planned for Part 2. Approximately 210 HCV GT1/HIV-1 coinfecting, HCV treatment-naïve and HCV treatment experienced adults were randomly assigned (Arms F and G) or allocated (Arms E, H, I, and J) to receive ABT-450/r/ABT-267 and ABT-333 coadministered with and without RBV for 12 or 24 weeks. Subjects in Part 2 were to be followed for 24 weeks. Approximately 20 HCV GT4/HIV-1 coinfecting, HCV treatment-naïve and HCV treatment experienced adults were allocated to receive ABT-450/r/ABT-267 with RBV for 12 or 24 weeks (Arms K and L). HCV GT1 and GT4 subjects on a stable ATV, RAL, or DTG containing HIV-1 ART regimen were eligible in Part 2. In addition, subjects with HCV GT4 on a stable DRV QD containing HIV-1 ART regimen were also eligible.

Interim analyses occurred after all randomized subjects in Part 1a (N = 63) completed Post-Treatment Week 4 and Post-Treatment Week 12, respectively, or prematurely discontinued from the study, and an additional interim analysis of data from subjects in Part 1b occurred after all randomized subjects in Part 1b had completed the Treatment Period through Post-Treatment Week 12 or had prematurely discontinued from the study. The primary analysis was the analysis of SVR₁₂ in GT1 subjects from Part 2 of the study and is included in the final clinical study report.

Number of Subjects (Planned and Analyzed):

Approximately 320 subjects were planned to be enrolled (approximately 60 subjects in Part 1a, approximately 30 in Part 1b, and approximately 230 in Part 2).

63 subjects were enrolled in Part 1a of the study and received at least 1 dose of study drug.

22 subjects were enrolled in Part 1b of the study and received at least 1 dose of study drug.

233 subjects were enrolled in Part 2 of the study and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:					
Male or female subjects at least 18 years of age at time of screening					
In Part 1a and Part 1b, HCV GT1/HIV-1 coinfecting adults with and without compensated cirrhosis who were on a stable HIV-1 ART regimen and who were HCV treatment-naïve or pegIFN alfa-2a or alfa-2b/RBV-experienced.					
In Part 2, HCV GT1 or GT4/HIV-1 coinfecting adults with and without compensated cirrhosis who were either HCV treatment-naïve or HCV treatment-experienced and who were HIV-1 virologically suppressed on a stable ART regimen containing ATV, RAL, DTG, or DRV (GT4 only).					
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:					
Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
ABT-450/r/ABT-267	AbbVie ^a	Oral	Tablet	75 mg/	12-005439
				50 mg/	12-006474
				12.5 mg	13-004118
					13-005537
					13-005535
				15-000397	
ABT-333	AbbVie ^a	Oral	Tablet	250 mg	12-005683
					14-000610
					14-001347
RBV	Roche or Generic Manufacturer Kadmon	Oral	Tablet	200 mg	12-004860
					13-003287
					13-005533
					13-004079
					13-004080
					14-003370
a. Abbott Laboratories at the time of production.					
Duration of Treatment:					
GT1/HIV-1 coinfecting subjects received ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 or 24 weeks.					
GT4/HIV-1 coinfecting subjects received ABT-450/r/ABT-267 with RBV for 12 or 24 weeks in Part 2 (Arms K and L, respectively).					
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:					
Not applicable.					

Criteria for Evaluation

Efficacy:

Plasma HCV RNA (IU/mL) was assessed at each Treatment and Post-Treatment Visit.

Resistance:

For subjects receiving at least 1 dose of study drugs who did not achieve SVR₁₂: the variants at each amino acid position by population nucleotide sequencing at baseline compared to the appropriate prototypic reference sequence, the variants at signature resistance-associated amino acid positions at available post-baseline time points by population and/or deep nucleotide sequencing compared to the appropriate prototypic reference sequence, and the variants at each amino acid position by population and/or deep nucleotide sequencing at available post-baseline time points compared to the baseline sequence were tabulated and summarized.

HIV-1 drug resistance genotyping for protease, reverse transcriptase, and integrase, as appropriate, could have been performed for protocol-defined eligible specimens.

Patient-Reported Outcomes (PROs):

The change in PROs was measured using several instruments. Non-disease-specific health-related quality-of-Life (HRQoL) was assessed using the Short-Form 36 Health Survey – Version 2 (SF-36v2) questionnaire. Health State Utility was measured using the EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L). HCV-specific function and wellbeing was assessed using the HCV Patient Reported Outcomes instrument (HCVPRO [Parts 1a and 1b only]).

Pharmacokinetic:

Individual plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were determined at each study visit in the Treatment Period of Part 1a, Part 1b and Part 2. Plasma concentrations of DRV were determined for all subjects in Part 1b.

Safety:

Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and vital signs.

Statistical Methods

Analyses were performed separately for each part of the study (Part 1a, Part 1b, Part 2).

Efficacy:

The primary efficacy endpoint was the percentage of GT1 subjects enrolled in Arms E, F, H, I, and J in Part 2 (GT1 Analysis Group) achieving SVR₁₂ compared to the historical SVR₁₂ rate for sofosbuvir plus RBV as reported in the PHOTON-1 study. The percentage of subjects achieving SVR₁₂ was calculated and a 2-sided 95% confidence interval (CI) of the percentage was computed using Wilson score method for the binomial proportion. The lower confidence bound of the 2-sided 95% CI for the percentage of subjects achieving SVR₁₂ had to exceed 74% to achieve noninferiority.

Statistical Methods (Continued)

Efficacy (Continued):

The secondary endpoints were:

- The percentage of Part 1a subjects achieving SVR₁₂ in the 24-week treatment arm (Arm B) compared to the 12-week treatment arm (Arm A);
- The percentage of Part 1b subjects achieving SVR₁₂ in the DRV QD arm (Arm C) compared to the DRV BID arm (Arm D);
- The percentage of Part 1b subjects achieving SVR₁₂;
- The percentages of Part 2 GT1b cirrhotic subjects achieving SVR₁₂ in Arm F and in Arm G;
- The percentage of GT4 subjects in Part 2 achieving SVR₁₂ by arm and overall;
- The percentage of subjects with on-treatment HCV virologic failure during the Treatment Period for the 12-week and 24-week treatment arms in Part 1a, the DRV QD and BID arms separately and combined in Part 1b, the GT1 Analysis Group and the GT4 Analysis Group in Part 2 by arm and overall;
- The percentage of subjects with post-treatment relapse (analyses performed as described for the percentage of subjects with on-treatment HCV virologic failure);
- The percentage of subjects with plasma HIV-1 RNA suppression at the end of treatment and at Post-Treatment Week 12 using the FDA Snapshot Algorithm (analyses performed as described for the percentage of subjects with on treatment HCV virologic failure).

Resistance:

The following resistance information was analyzed for subjects receiving study drugs who did not achieve SVR₁₂ regardless of the reason (and who had HCV RNA \geq 1,000 IU/mL):

- 1) the amino acid variants at signature amino acid positions at baseline identified by population nucleotide sequencing and comparison to the appropriate prototypic reference sequence,
- 2) the amino acid variants in available post-baseline samples at signature amino acid positions identified by population and/or next generation sequencing and comparison to the appropriate reference sequence,
- 3) the amino variants in available post-baseline samples identified by population and/or next generation sequencing and comparison to the baseline sequences, variants found at signature amino acid positions and variants at any amino acid position that emerge or become enriched in isolates from at least 2 subjects of the same subtype were summarized.

HIV-1 drug resistance genotyping for protease, reverse transcriptase, and integrase, as appropriate, were performed for protocol-defined eligible specimens.

PROs:

The change in non-disease-specific HRQoL, health state utility, and HCV-specific function and wellbeing were measured using the SF-36v2, EQ-5D-5L, and HCVPRO instruments (Part 1a and Part 1b only), respectively. SF-36v2 and HCVPRO were analyzed by their component/total scores, as appropriate. The EQ-5D-5L was analyzed by health index (i.e., utility) score and by visual analogue scale response. Change from baseline in the PRO summary measures was summarized and compared between treatment arms in Part 1a using analysis of covariance models with a treatment group factor and the baseline score as a covariate.

Statistical Methods (Continued)

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ABT-333, ABT-333 M1 metabolite, ritonavir, and RBV were tabulated. Summary statistics were computed for each time point (for intensive PK data) or binned time interval (for all available PK data after Week 2) in the Treatment Period. Plasma concentrations of DRV from Part 1b were also summarized.

For the intensive PK data in Part 1b, pharmacokinetic parameters of DRV and ritonavir were compared between Week 4 (DRV coadministered with direct-acting antiviral agents [DAAs]) and Day –1 (DRV administered alone).

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Comparisons between treatment arms were performed using Fisher's exact test for Part 1a only. Additional tabulations were provided in which the number of subjects reporting an adverse event (MedDRA preferred term) was presented by severity and relationship to study drug(s).

Changes from baseline in laboratory tests and vital sign measurements to each time point of collection were summarized descriptively. Laboratory test and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified and summarized, and comparisons between the treatment arms in Part 1a were made using Fisher's exact test. For Part 2, safety analyses were performed on the GT1 Analysis Group, Arm F, Arm G, the GT4 Analysis Group, Arm K, and Arm L.

Summary/Conclusions

Efficacy Results:

Primary Efficacy Endpoint:

For the primary efficacy endpoint, SVR₁₂ was achieved by 194/200 (97.0%) subjects in the GT1 Analysis Group in Part 2 (95% CI: 93.6% – 98.6%). The lower confidence bound of the 2-sided 95% CI exceeded 74%; therefore the noninferiority of DAAs compared to sofosbuvir plus RBV was demonstrated. The reasons for non-achievement of SVR₁₂ in the GT1 Analysis Group were on-treatment virologic failure (breakthrough), relapse by Post-Treatment Week 12, HCV reinfection, and missing SVR₁₂ data for 1 subject each, and premature discontinuation of study drug for 2 subjects.

Secondary Efficacy Endpoints:

Part 1a:

SVR₁₂ was achieved by 29/31 (93.5%) subjects in Arm A (95% CI: 79.3% – 98.2%) and by 29/32 (90.6%) subjects in Arm B (95% CI: 75.8% – 96.8%).

Based on Fisher's exact test comparing the percentage of subjects with SVR₁₂ in Arm A versus Arm B, the difference between treatment arms was not statistically significant ($P = 1.000$).

The on-treatment virologic failure rate was low. In Arm A, 1 (3.3%) subject experienced virologic failure; this subject experienced a relapse at Post-Treatment Week 4. One (3.2%) subject in Arm A prematurely discontinued study drug due to withdrawal of consent with their last reported HCV RNA below the LLOQ. In Arm B, 1 (3.1%) subject experienced on-treatment virologic failure and 2 (6.3%) subjects had evidence of HCV reinfection. The post-treatment relapse rate through Post-Treatment Week 12 among completers was low for Arm A (1 subject; 3.3%) and Arm B (no subjects).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Secondary Efficacy Endpoints (Continued):

Part 1a (Continued):

Plasma HIV-1 RNA suppression was evaluated using the FDA snapshot algorithm; HIV virologic success (HIV-1 RNA < 40 copies/mL) was achieved at the end of treatment for 29 (93.5%) subjects in Arm A and 29 (90.6%) subjects in Arm B. At Post-Treatment Week 12, 30 (96.8%) subjects in Arm A and 30 (93.8%) subjects in Arm B achieved HIV virologic success. No subjects in either treatment arm required a switch of their HIV-1 ART regimen due to loss of plasma HIV-1 RNA suppression.

Part 1b

SVR₁₂ was achieved by 10/10 (100%) subjects in Arm C and by 12/12 (100%) subjects in Arm D. HIV virologic success (HIV-1 RNA < 40 copies/mL) was achieved at the end of treatment for all (100%) subjects in Arm C and 10 (83.3%) subjects in Arm D. At Post-Treatment Week 12, 10/10 (100%) subjects in Arm C and 9/12 (75.0%) subjects in Arm D achieved HIV virologic success. No subjects in either treatment arm required a switch of their HIV-1 ART regimen due to loss of plasma HIV-1 RNA suppression.

Part 2:

SVR₁₂ was achieved by 3/4 (75.0%) subjects in Arm F and by 4/5 (80.0%) subjects in Arm G. The reasons for non-achievement of SVR₁₂ were on-treatment virologic failure (breakthrough) for 1 subject in Arm F and prematurely discontinuing study drug for 1 subject in Arm G.

SVR₁₂ was achieved by 27/28 (96.4%) subjects in the GT4 Analysis Group. The reason for non-achievement of SVR₁₂ for the 1 subject was premature discontinuation of study drug.

The on-treatment virologic failure rate and the post-treatment Relapse₁₂ rate among completers were low for the GT1 Analysis Group (0.5% each) and the GT4 Analysis Group (no subjects).

HIV virologic success (HIV-1 RNA < 40 copies/mL) was achieved at the end of treatment for 178 (89.0%) subjects in the GT1 Analysis Group and 24 (85.7%) subjects in the GT4 Analysis Group. At Post-Treatment Week 12, 186 (93.0%) subjects in the GT1 Analysis Group and 26 (92.9%) subjects in the GT4 Analysis Group achieved HIV virologic success. No subjects in either treatment arm required a switch of their HIV-1 ART regimen due to loss of plasma HIV-1 RNA suppression.

Resistance Results:

A phylogenetic analysis of NS3/4A, NS5A and NS5B nucleotide sequences from 9 subjects experiencing virologic failure from samples collected at baseline and the time of failure were compared.

Three GT1a-infected subjects (2 in Arm B and 1 in Arm I) were determined to be reinfected with a GT1a virus that was distinct from the one present at baseline. One subject in Arm I was determined to be reinfected with GT3a virus by LiPA assay and reinfection was confirmed by phylogenetic analysis.

Among the GT1a-infected virologic failures, one subject each had R155K or D168V in NS3, one subject each had M28T or Q30R in NS5A, and 2 subjects had S556G in NS5B at the time of failure. One GT1a-infected virologic failure subject had no baseline polymorphisms or treatment-emergent substitutions.

Among the 2 GT1b-infected virologic failures, Y56H + D168V in NS3 was detected in 1 subject, Y93H in NS5A was detected in both subjects, and C316N + S556G in NS5B was present at baseline and at the time of failure in both subjects. Treatment-emergent substitutions in NS5A and NS5B persisted through post-treatment Week 24, while R155K or D168V in NS3 were not detectable at post-treatment Week 24.

Summary/Conclusions (Continued)

Resistance Results (Continued):

One subject in Arm B met the criterion for HIV-1 resistance testing, but none of the HIV resistance-associated mutations detected in this subject's plasma are known to confer resistance to this subject's HIV-1 treatment regimen.

PRO Results:

The 3-direct-acting antiviral agent (DAA) + RBV regimen had minimal impact on HRQoL, function, or wellbeing at the end of treatment for subjects. After treatment, PRO scores were generally improved over baseline in each arm in Part 1a, Part 1b, and Part 2 of the study.

Pharmacokinetic Results:

In HCV/HIV-1 coinfecting non-cirrhotic and cirrhotic subjects on a stable HIV-1 ART regimen containing ATV, RAL, DTG, or DRV, exposures of the DAA regimens are consistent with the DDI results from healthy subjects and the population PK analysis results in HCV mono-infected subjects. Exposures of DRV are consistent with the DDI results from healthy subjects. Taken together with the safety and efficacy data from this study, it supports that no dose adjustment is needed when coadministering the DAA regimens with HIV-1 ART regimen containing ATV, RAL, DTG, or DRV.

Safety Results:

For each part of the study, the safety population included all randomized or enrolled subjects who received at least 1 dose of study drug.

In all parts of the study, the majority of subjects experienced at least 1 treatment-emergent adverse event. The majority of events were mild or moderate in severity. No statistically significant differences were observed for the percentage of subjects experiencing the various categories of treatment-emergent adverse events in Part 1a.

In Part 1a, treatment-emergent adverse events reported for $\geq 10.0\%$ of subjects overall were fatigue, insomnia, nausea, headache, upper respiratory tract infection, pruritus, and cough. No statistically significant difference in the percentage of subjects with any specific treatment-emergent adverse event was observed between treatment arms (except for statistically significantly higher RBV-related pruritus in Arm A [19.4%] versus Arm B [0%]). In addition, there were no new safety issues observed with a longer duration of treatment (24 versus 12 weeks) in HIV-1-coinfecting subjects.

In Part 1b, treatment-emergent adverse events reported for $\geq 20.0\%$ of subjects were fatigue, irritability, and hemoglobin decreased across both treatment arms, fatigue, bronchitis, irritability, cough, headache, and nausea in Arm C, and fatigue and hemoglobin decreased in Arm D.

In Part 2, treatment-emergent adverse events reported for $\geq 10.0\%$ of subjects in the GT1 Analysis Group were fatigue, nausea, diarrhoea, insomnia, headache, and pruritus, and in the GT4 Analysis Group were fatigue, headache, nausea, hemoglobin decreased, nasopharyngitis, abdominal pain upper, dyspepsia, asthenia, and vomiting.

Adverse events leading to RBV dose modification occurred infrequently. The majority of subjects who required a RBV dose modification experienced a single modification. All subjects experiencing a treatment-emergent adverse event that led to RBV dose modification completed study treatment except 1 subject in Arm J who prematurely discontinued due to other reason. All achieved SVR₁₂, except for 1 subject in Arm I (reinfection).

Summary/Conclusions (Continued)

Safety Results (Continued):

No treatment-emergent deaths were reported. No subjects discontinued study drug due to a treatment-emergent adverse event during the study. The incidence of serious adverse events was low, with treatment-emergent serious adverse events reported for 1 (8.3%) subject in Arm D, 9 (4.5%) subjects in the GT1 Analysis Group and 1 (3.6%) subject in the GT4 Analysis Group.

Analyses of hepatic-related events and liver function test values, rash-related events, and anemia-related events and hemoglobin values during this study showed no new or different pattern compared with other clinical studies of these same DAAs with RBV.

Although the ABT-450 exposures among subjects who were on an ATV-based HIV-1 ART regimen were higher than the exposures previously observed among HCV monoinfected subjects, there was no association of these higher exposures and aminotransferase elevations. One subject (Subject [REDACTED]) experienced a serum alanine aminotransferase (ALT) $> 5 \times$ ULN.

The mean increase from baseline in total bilirubin was similar to that seen in other clinical studies of AbbVie DAAs with RBV. In Part 1a of the study, the percentages of subjects with at least grade 3 total bilirubin (35.5% Arm A, 18.8% Arm B) were higher in this HCV/HIV-1 coinfecting population compared with HCV GT1-monoinfected populations in other studies. The percentages of subjects with at least grade 3 observed in Arm A was not reflected in Part 1b (0% of subjects with grade 3) or Part 2 (13.0% in the GT1 Analysis Group and 7.1% in the GT4 Analysis Group). Symptomatic hyperbilirubinemia was infrequent. No subjects in Part 1a or Part 1b and 3 subjects in Part 2 had ALT and total bilirubin values that met biochemical criteria for inclusion in Hy's law quadrant, and no subjects in Part 1a or Part 1b and 1 subject in Part 2 experienced a serum ALT $> 5 \times$ ULN (i.e., grade 3). In Part 1a, total bilirubin elevations occurred at a significantly greater frequency in Arm A than Arm B; however, this finding is likely explained by the greater proportion of subjects in Arm A on an ATV-inclusive HIV-1 ART regimen. These bilirubin elevations are consistent with the known inhibition of UDP-glucuronosyl transferase by ATV, the known inhibition of organic anion-transporting polypeptide 1B1 and organic anion-transporting polypeptide 1B3 by ABT-450 and RBV-induced hemolysis.

No clinically meaningful results of urinalysis, vital signs, or ECGs were observed in any part of the study.

Conclusions:

Treatment with a 12- or 24-week regimen of ABT-450/r/ABT-267 and ABT-333 coadministered with or without RBV resulted in a primary SVR₁₂ rate of 97.0% (95% CI: 93.6% – 98.6%) in GT1 HCV/HIV-1 coinfecting subjects, demonstrating noninferiority of this regimen to SOF plus RBV. In GT4 HCV/HIV-1 coinfecting subjects, SVR₁₂ was achieved by 27/28 (96.4%) subjects with no virologic failure.

ABT-450/r/ABT-267 with or without ABT-333 coadministered with or without RBV was generally well tolerated in GT1 and GT4 HCV/HIV-1 coinfecting subjects. Adverse events reported in this study were generally consistent with the established safety profile for RBV and those demonstrated for these DAAs and the combination of these DAAs with RBV in previous studies of subjects with and without cirrhosis.