

2.0 Synopsis

<p>AbbVie Inc.</p>	<p>Individual Study Table Referring to Part of Dossier:</p>	<p>(For National Authority Use Only)</p>
<p>Name of Study Drug: ABT-493, ABT-530, ABT-450/r/ ABT-267, ABT-333, ribavirin</p>	<p>Volume:</p>	
<p>Name of Active Ingredient:</p> <p>ABT-493: (3<i>aR</i>,7<i>S</i>,10<i>S</i>,12<i>R</i>,21<i>E</i>,24<i>aR</i>)-7-<i>tert</i>-butyl-<i>N</i>-[(1<i>R</i>,2<i>R</i>)-2-(difluoromethyl)-1-{(1-methylcyclopropyl)sulfonyl} carbamoyl] cyclopropyl]-20,20-difluoro-5,8-dioxo-2,3,3<i>a</i>,5,6,7,8,11,12,20,23,24<i>a</i>-dodecahydro-1<i>H</i>,10<i>H</i>-9,12-methanocyclopenta[18,19][1,10,17,3,6] trioxadiazacyclononadecino[11,12-<i>b</i>]quinoxaline-10-carboxamide</p> <p>ABT-530: methyl {(2<i>S</i>,3<i>R</i>)-1-[(2<i>S</i>)-2-{5-[(2<i>R</i>,5<i>R</i>)-1-{3,5-difluoro-4-[4-(4-fluorophenyl) piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2<i>S</i>)-1-[<i>N</i>-(methoxycarbonyl)-<i>O</i>-methyl-L-threonyl]pyrrolidin-2-yl}-1<i>H</i>-benzimidazol-5-yl) pyrrolidin-2-yl]-6-fluoro-1<i>H</i>-benzimidazol-2-yl} pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl} carbamate</p> <p>ABT-450: (2<i>R</i>,6<i>S</i>,12<i>Z</i>,13<i>aS</i>,14<i>aR</i>,16<i>aS</i>)-<i>N</i>-(cyclopropylsulfonyl)-6-{(5-methylpyrazin-2-yl)carbonyl}amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13<i>a</i>,14,15,16,16<i>a</i>-tetradecahydrocyclopropa[<i>e</i>] pyrrolo[1,2<i>a</i>][1,4]diazacyclopentadecine-14<i>a</i>(5<i>H</i>)-carboxamide dihydrate</p>	<p>Page:</p>	

<p>Name of Active Ingredient (Continued): Ritonavir: 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, [5S-(5R*,8R*,10R*,11R*)]</p> <p>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</p> <p>ABT-333: Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)</p> <p>Ribavirin: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide</p>		
<p>Title of Study: A Randomized, Open-Label, Dose Ranging Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of Multiple Doses of ABT-493 and ABT-530 in Adult Subjects with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection</p>		
<p>Coordinating Investigator: ██████████</p>		
<p>Study Sites: 13 investigative sites in the United States (US)</p>		
<p>Publications: 3 abstracts</p>		
<p>Studied Period (Years): First Subject First Visit: 18 November 2013 Last Subject Last Visit: 10 July 2015</p>	<p>Phase of Development: 2a</p>	

Objectives:

The primary objective of Study M13-595 was to assess the safety, tolerability, pharmacokinetics, and antiviral activity of multiple doses levels of ABT-493 and ABT-530 administered as monotherapy for 3 days in treatment-naïve adults with chronic HCV genotype 1 (GT1) infection with and without compensated cirrhosis.

The secondary objectives were to assess the safety and SVR₁₂ (percentage of subjects achieving sustained virologic response 12 weeks following treatment, defined as HCV ribonucleic acid [RNA] < lower limit of quantification [LLOQ]) of coformulated ABT-450, ritonavir, ABT-267 (ABT-450/r/ABT-267), and ABT-333 coadministered with ribavirin (RBV) for 12 weeks. The percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post treatment were also assessed.

Methodology:

This was a Phase 2a, randomized, open-label, multicenter dose-ranging study that explored the safety, tolerability, pharmacokinetics, and antiviral activity of ABT-493 and ABT-530 administered as monotherapy for 3 days in HCV GT1-infected treatment-naïve adults with and without compensated cirrhosis. Monotherapy was to be followed by 12 or 24 weeks of combination treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV. And, per protocol, subjects could have been offered pegIFN during the Combination Treatment Period. Of note, no subjects were offered add-on pegIFN/RBV treatment, and treatment duration was not extended to 24 weeks for any of the study subjects.

This study comprised 2 substudies, each to have up to 6 arms and a target of 48 subjects. The opened arms were as follows:

- Substudy 1
 - Arms 1 – 4 and Arm 11 each evaluated the safety, pharmacokinetics and antiviral effect of a single dose level of ABT-493 (100, 200, 300, 400, and 700 mg) in 8 treatment-naïve, HCV genotype 1 infected subjects without cirrhosis for 3 days, followed by 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.
 - Arm 5 evaluated the safety, pharmacokinetics and antiviral effect of ABT-493 200 mg in 8 treatment-naïve, HCV genotype 1-infected subjects with compensated cirrhosis for 3 days, followed by 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.
- Substudy 2
 - Arms 6 – 9 each evaluated the safety, pharmacokinetics and antiviral effect of a single dose level of ABT-530 (15, 40, 120, and 400 mg) in 8 treatment-naïve, HCV genotype 1-infected subjects without cirrhosis for 3 days, followed by 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.
 - Arm 10 evaluated the safety, pharmacokinetics and antiviral effect of ABT-530 120 mg in 8 treatment-naïve, HCV genotype 1-infected subjects with compensated cirrhosis for 3 days, followed by 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV.

Methodology (Continued):

Subjects who met the eligibility criteria were to be enrolled at approximately 20 sites until approximately 96 subjects were enrolled. At the start of the trial, the first 24 subjects in each substudy were randomized to Arms 1 through 3 or 6 through 8. Subjects at sites participating in Substudy 1 were randomized in a 1:1:1 ratio to Arms 1, 2, or 3. Subjects at sites participating in Substudy 2 were randomized in a 1:1:1 ratio to Arms 6, 7, or 8. After available safety, efficacy, and pharmacokinetic data from Arms 1 through 3 were reviewed, Arms 4, 5, and 11 were opened for enrollment. And, after available safety, efficacy, and pharmacokinetic data from Arms 6 through 8 were reviewed, Arms 9 and 10, but not 12, were opened for enrollment. Subjects without cirrhosis at sites in Substudy 1 were assigned to Arms 4 and 11, and subjects with compensated cirrhosis at sites in Substudy 1 were assigned to Arm 5. Similarly, subjects without cirrhosis at sites in Substudy 2 were assigned to Arm 9, and subjects with compensated cirrhosis at sites in Substudy 2 were assigned to Arm 10.

This study consisted of a Monotherapy Period, Combination Treatment Period, and a Post-Treatment Period. All subjects dosed with study drug who completed or prematurely discontinued study drug were to be followed for 48 weeks in the Post-Treatment Period to monitor safety, HCV RNA, and the emergence and persistence of viral variants.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 96 subjects (8 per Arm)

Analyzed: 89 subjects were enrolled and received at least 1 dose of study drug

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female and age was between 18 and 70 years, inclusive, at time of Screening.
2. Chronic HCV-infection defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV Ab at the time of Screening;
 - Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic hepatitis C disease).
3. Screening laboratory result indicating HCV GT1 infection.
4. Subject has plasma HCV RNA level > 10,000 IU/mL at Screening.
5. Per local standards, subjects were considered to be non-cirrhotic or to have compensated cirrhosis.

Main Exclusion Criteria:

1. History of severe, life-threatening, or other significant sensitivity to any drug.
2. Positive test result for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab).
3. Prior therapy for the treatment of HCV.
4. Any current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites (noted on physical exam), variceal bleeding, or hepatic encephalopathy.
5. Any cause of liver disease other than chronic HCV infection.

Test Product, Dose/Strength/Concentration, Mode of Administration, and Lot Number:			
Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-493	AbbVie	100 mg tablet/Oral	13-003615
ABT-530	Abbott/AbbVie	15 mg tablet/Oral	12-005319
ABT-530	AbbVie	40 mg tablet/Oral	13-002662
ABT-333	Abbott/AbbVie	250 mg tablet/Oral	13-000242
ABT-450/ritonavir/ ABT-267	Fournier Laboratories Ireland Limited	75 mg/50 mg/12.5 mg tablet/Oral	12-008149
Ribavirin (Ribasphere [®])	Generic manufacturer	200 mg tablet/Oral	13-003287
Duration of Treatment: Subjects were to receive single doses of ABT-493 (100 mg – 700 mg) or ABT-530 (15 mg – 400 mg) for 3 days in the Monotherapy Period, followed by ABT-450/r/ABT-267 150/100/25 mg QD + ABT-333 250 mg BID + RBV weight-based, beginning on Study Day 4, for 12 weeks in the Combination Treatment Period.			
Reference Therapy, Dose/Strength/Concentration, Mode of Administration, and Lot Number: Not applicable.			
Criteria for Evaluation			
Efficacy: HCV RNA in IU/mL was assessed at study visits during the Treatment Period and Post-Treatment Period. Virologic response (HCV RNA) decrease from baseline in log ₁₀ IU/mL was assessed on Study Day 1 through prior to the morning dose on Study Day 4.			
Resistance: For subjects who received study drugs who did not achieve SVR, the following information was tabulated and summarized: (1) the variants at each amino acid position at baseline identified by population nucleotide sequencing compared to the appropriate prototypic reference sequence, (2) the amino acid variants at available post-baseline time points at signature resistance-associated positions identified by population and/or clonal nucleotide sequencing compared to baseline and the appropriate prototypic reference standard sequences, (3) the most prevalent amino acid variants found at signature resistance-associated amino acid positions by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype, and (4) the persistence of viral resistance.			
Pharmacokinetic: Plasma concentrations and pharmacokinetic parameters values for ABT-493, ABT-530, ABT-450, ABT-267, ritonavir, ABT-333, ABT-333 M1 metabolite, and RBV were tabulated and summarized.			
Safety: Safety and tolerability was assessed by monitoring adverse events (AE), physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECG), and vital signs.			

Statistical Methods

Efficacy:

The primary efficacy endpoint was the maximal decrease from baseline in \log_{10} HCV RNA levels during ABT-493 or ABT-530 monotherapy treatment (through prior to first dose of the combination DAA regimen on Study Day 4). The maximal \log_{10} decreases in HCV RNA level were compared between doses within a substudy (comparing ABT-493 100 mg to each of the higher doses of ABT-493 and comparing ABT-530 15 mg to each of the higher doses of ABT-530) using an analysis of covariance (ANCOVA) with the baseline \log_{10} HCV RNA value as a covariate and factors for dose (as appropriate for each substudy), HCV genotype subtype (1a or non-1a), and presence or absence of cirrhosis.

The secondary efficacy endpoints for ABT-450/r/ABT-267 and ABT-333 plus RBV were:

- percentage of subjects with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug with no confirmed post-treatment HCV RNA \geq LLOQ before or during the SVR₁₂ window);
- percentage of subjects with on-treatment virologic failure during the Combination Treatment Period (defined as virologic breakthrough or rebound or failing to suppress at the end of treatment after receiving at least 6 weeks of combination treatment);
- percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed combination treatment and with HCV RNA < LLOQ at the end of treatment).

The number and percentage of subjects meeting each endpoint were summarized by treatment arm. In addition, each of the secondary efficacy endpoints was summarized for all subjects without cirrhosis combined (Arms 1 through 4 + Arm 11 + Arms 6 through 9 + Arm 12) and for all subjects with compensated cirrhosis combined (Arms 5 + 10) with percentages and exact 2-sided 95% confidence intervals (CI).

Additional efficacy endpoints were:

- For subjects dosed in the Monotherapy Period: change from baseline in \log_{10} HCV RNA levels to each post-baseline time point on Study Days 1 – 4.
- For subjects dosed in the Combination Treatment Period:
 - percentage of subjects with HCV RNA < LLOQ at each Combination Treatment Period visit;
 - percentage of subjects with virologic breakthrough or rebound during the Combination Treatment Period;
 - percentage of subjects receiving at least 6 weeks of combination therapy who failed to suppress (never achieving HCV RNA < LLOQ) during the Combination Treatment Period;
 - percentage of subjects with SVR₄;
 - percentage of subjects with SVR₂₄.

Statistical Methods (Continued)

Efficacy (Continued):

Each endpoint was summarized descriptively by treatment arm. In addition, each of the additional efficacy endpoints was summarized for all subjects without cirrhosis combined (Arms 1 through 4 + Arm 11 + Arms 6 through 9 + Arm 12) and for all subjects with compensated cirrhosis combined (Arms 5 + 10).

SVR₁₂ rates also were summarized by HCV GT1 subtype (1a, 1b, or other), IL28B genotype (CC, CT, or TT), and the combination of HCV GT1 subtype and presence or absence of cirrhosis.

Resistance:

The following resistance information was analyzed for subjects receiving study drugs in monotherapy arms: 1) the variants at signature resistance-associated amino acid position at baseline identified by population nucleotide sequencing were compared to the appropriate prototypic reference sequence, 2) the variants at available post-baseline time points identified by population/clonal nucleotide sequencing were compared to baseline sequences, and, 3) the most prevalent amino acid variants found by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype.

The following resistance information was analyzed for subjects receiving combination therapy who did not achieve SVR and had HCV RNA \geq 1000 IU/mL: 1) the variants at available post-baseline time points identified by population/clonal nucleotide sequencing were compared to baseline sequences, 2) the most prevalent amino acid variants found by population sequencing and amino acid variants that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype, and 3) the persistence of viral resistance.

Pharmacokinetic:

Plasma concentrations of ABT-493, ABT-530, ABT-450, ritonavir, ABT-267, ABT-333, ABT-333 M1 metabolite, and RBV were tabulated for each subject and group at each study visit up to 12 weeks. Pharmacokinetic parameter values of ABT-493 and ABT-530 on Monotherapy Day 1 were tabulated for each subject and group. Results were tabulated for each subject and summary statistics were computed for each sampling time within each arm. Individual plasma concentrations of ABT-450, ritonavir, ABT-333, ABT-333 M1 metabolite, ABT-267, and RBV were tabulated in relation to time of the last drug dose and summarized by liver condition (cirrhosis vs. non-cirrhosis).

Safety:

The number and percentage of subjects in each treatment arm with treatment-emergent adverse events (TEAEs) were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Tabulations were also provided for the number and percentage of subjects with TEAEs by grade (Grades 1 – 5) and relationship to study drug. Changes from baseline in laboratory tests and vital sign measurements to each time point of collection were summarized by arm. The number and percentage of subjects with post-baseline values meeting pre-specified criteria for potentially clinically significant (PCS) laboratory and vital sign values during treatment were summarized.

Summary/Conclusions

Efficacy Results:

During 3 days of monotherapy, maximal decrease in mean HCV plasma RNA viral load from baseline was similar for all ABT-493 dose groups between 100 mg and 700 mg, and for ABT-530 was higher in the 40 mg QD to 400 mg QD dose groups compared with the 15 mg dose ($P < 0.01$ for each comparison; data shown in the table below). The decline in HCV viral load was immediate and substantial on Study Day 1 for all dose groups of ABT-493 and for the 40 mg, 120 mg, and 400 mg doses of ABT-530.

Primary Efficacy Endpoint: Maximal Decrease from Baseline in HCV RNA (\log_{10} IU/mL) with ABT-493 or ABT-530 During 3-Day Monotherapy (ITT Population)

Dose Group (Arm)	N	Baseline Mean	With-In Group Change from Baseline	Between Group Comparison to Arm 1 (ABT-493) or Arm 6 (ABT-530)		
			Mean \pm SD	LS Mean \pm SE	95% CI	P-value ^a
ABT-493						
100 mg QD (Arm 1)	8	6.6	-4.11 \pm 0.47			
200 mg QD (Arms 4 and 5)	16	6.6	-4.06 \pm 0.56	-0.0 \pm 0.26	(-0.56, 0.49)	0.899
300 mg QD (Arm 11)	8	6.3	-3.79 \pm 1.21	0.2 \pm 0.26	(-0.38, 0.69)	0.571
400 mg QD (Arm 2)	8	6.9	-4.02 \pm 0.66	0.3 \pm 0.27	(-0.26, 0.81)	0.313
700 mg QD (Arm 3)	9	6.9	-4.31 \pm 0.26	-0.0 \pm 0.26	(-0.56, 0.48)	0.877
ABT-530						
15 mg QD (Arm 6)	8	6.8	-3.38 \pm 0.77			
40 mg QD (Arm 9)	8	6.7	-4.08 \pm 0.45	-0.7 \pm 0.24	(-1.20, -0.21)	0.007
120 mg QD (Arms 7 and 10)	16	7.0	-4.21 \pm 0.42	-1.1 \pm 0.25	(-1.61, -0.62)	< 0.001
400 mg QD (Arm 8)	8	6.4	-4.25 \pm 0.49	-0.8 \pm 0.25	(-1.36, -0.32)	0.002

CI = confidence interval; HCV = hepatitis C virus; ITT = intent-to-treat; LS = least squares; QD = once daily; RNA = ribonucleic acid

a. P-value for difference between low dose and higher doses from ANCOVA with the baseline \log_{10} HCV RNA value as a covariate and factors for dose, HCV genotype subtype (1a or non-1a), and presence or absence of cirrhosis.

Note: Subjects who received at least 1 dose of ABT-493 or ABT-530 and had a baseline and at least 1 post-baseline measurement of HCV RNA during monotherapy are included.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

SVR₁₂ was achieved in 84 of 88 (95.5%) chronic HCV G1-infected, treatment-naïve subjects treated with the combination of ABT-450/r/ABT-267 and ABT-333 plus RBV for 12 weeks, including all 16 subjects with compensated cirrhosis and 68 of 72 (94.4%) subjects without cirrhosis. One subject (who was noncompliant with study drugs) did not achieve SVR₁₂ due to virologic failure at Week 4 during the Combination Treatment Period. One subject with HCV GT1a infection at Screening was determined to have been reinfected with HCV GT3a at the Post-Treatment Week 48 visit.

Resistance Results:

Monotherapy Period

Resistance analysis was conducted on all baseline samples from subjects receiving ABT-493 or ABT-530. None of the 40 genotype 1a- or the 7 genotype 1b-infected subjects who received ABT-493 and had baseline sequence data available had resistance-conferring variants in NS3 pre-existing at baseline. Among the 30 genotype 1a- and 5 genotype 1b-infected subjects with post-baseline sequence data during the ABT-493 monotherapy period, 1 genotype 1a-infected subject had a treatment-emergent A156T variant in NS3.

Among the 33 genotype 1a- and 7 genotype 1b-infected subjects who received ABT-530 and had baseline sequence data available, 5 genotype 1a-infected subjects had M28V, Q30R, H58P, Y93N, and/or Y93C/S and 3 genotype 1b-infected subjects had L31M, P58S, and/or Y93H at baseline. Post-baseline sequence analysis was conducted on 14 genotype 1a- and 5 genotype 1b-infected subjects. Three genotype 1a-infected subjects with pre-existing variants in NS5A at baseline had multiple treatment-emergent variants in NS5A during monotherapy. None of the other 11 genotype 1a- or the 5 genotype 1b-infected subjects who received ABT-530 had treatment-emergent variants at signature amino acid positions in NS5A.

Combination Treatment Period

One HCV GT1a-infected subject experienced on-treatment virologic failure. This subject had no pre-existing resistance-associated variants in NS3, NS5A, or NS5B. Treatment-emergent resistance-associated variants were not detected in NS3, while M28V and Q30R were detected in NS5A. In NS5A, M28V persisted through Post-Treatment Week 48.

Pharmacokinetic Results:

In subjects with HCV-infection, increase in ABT-493 exposure was more than dose-proportional over the 100 mg to 700 mg range. ABT-493 exposures following 200 mg QD dosing in cirrhotic subjects were between the exposure of 200 mg QD and 300 mg QD in non-cirrhotic subjects with HCV infection in this study. In subjects with HCV infection, the increase in ABT-530 exposure was more than dose-proportional over the 15 mg to 120 mg range and less than dose-proportional between the 120 and 400 mg doses. ABT-530 exposures were similar in non-cirrhotic and cirrhotic subjects with HCV infection in this study.

Summary/Conclusions (Continued)

Safety Results:

The safety population included all 89 subjects who received at least 1 dose of study drug. The study population comprised 74.2% male and 89.9% white subjects. The IL28B genotype was CT for 58.4% of subjects, CC for 25.8%, and TT for 15.7%.

Monotherapy Period

Treatment-emergent adverse events (TEAE) were reported for 22 of the 49 (44.9%) subjects treated with ABT-493 monotherapy, the most common being headache (22.4%), abdominal discomfort (6.1%), diarrhea (6.1%), fatigue (6.1%), and pruritus (6.1%).

Treatment-emergent AEs were reported for 10 of the 40 (25.0%) subjects treated with ABT-530 monotherapy, the most common being headache (10.0%), constipation (5.0%), and nausea (5.0%).

The type and frequency of TEAEs does not appear to be influenced by ABT-493 dose or ABT-530 dose. All TEAEs reported in the Monotherapy Period during treatment with either ABT-493 or ABT-530 were Grade 1 (mild) or Grade 2 (moderate) in severity and nonserious. No deaths were reported.

One subject (randomized to ABT-493) discontinued study drug on Study Day 2 due to an AE of drug (heroin) withdrawal syndrome, which the investigator considered as having no reasonable possibility of being related to study drug.

Most hematology values measured during ABT-493 monotherapy and ABT-530 monotherapy were within the reference range. None of the subjects had hemoglobin values > Grade 1 during monotherapy. No PCS results were observed for hematology parameters, and no subject had a TEAE related to an abnormal hematology value.

Most chemistry values measured during ABT-493 monotherapy and ABT-530 monotherapy were within the reference range, with the notable exception of high liver function test values. Elevated transaminase values on Study Day 1 (before the first dose of study drug) and the 2 days thereafter during the Monotherapy Period are consistent with HCV infection and associated hepatic inflammation with ongoing fluctuations; improvement in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels from baseline was not observed and is not expected after only 3 days of direct-acting antiviral agent (DAA) monotherapy. None of the subjects had liver function test values that met the criteria for Hy's law or other potential hepatotoxicity criteria. None of the subjects developed symptoms of worsening hepatic function (e.g., jaundice).

No PCS results were observed for chemistry parameters, with the exception of a PCS serum creatinine value for 1 subject in the ABT-493 400 mg arm with a history of chronic renal insufficiency. This abnormal chemistry value, and no other, was reported as an AE during the Monotherapy Period.

Summary/Conclusions (Continued)

Safety Results (Continued):

Combination Treatment Period

Treatment-emergent AEs were reported for the majority of subjects (74/88, 84.1%) treated with ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks, the most common being fatigue (27.3%) headache (11.4%), dizziness (10.2%), and insomnia (10.2%).

Most TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Single Grade 3 events of acute cholecystitis, AST increased, bipolar disorder, cholelithiasis, dental caries, diarrhea, mania, pneumonitis, and renal failure were reported. Four of these events (i.e., acute cholecystitis, mania, pneumonitis, and renal failure) and no others met the definition of serious. No TEAE leading to death was reported.

One subject discontinued study drug during the Combination Treatment Period due to an AE of Grade 3 bipolar disorder, a condition that predated the subject's enrollment in this study.

One study subject experienced an unrelated AE of hypoxic-ischemic encephalopathy in the post-treatment period (Study Day 350) with an outcome of death.

Substantial decreases in alanine ALT, AST, and gamma glutamyl transferase (GGT) were observed during the 12-week Combination Treatment Period. No subject had an interruption or discontinued from study drugs because of abnormal hemoglobin or liver function test results. None of the subjects had liver function test values that met the criteria for Hy's law.

No other clinically meaningful observations were noted for hematology, clinical chemistry, urinalysis, vital signs, or ECG assessments

Conclusions:

Major conclusions from this clinical study report are summarized below:

- An immediate and substantial decline in HCV viral load was observed on Study Day 1 for all dose groups of ABT-493 monotherapy and for the 40 mg, 120 mg, and 400 mg doses of ABT-530 monotherapy. During 3 days of monotherapy, maximal decrease in mean HCV plasma RNA viral load from baseline was similar for all ABT-493 dose groups between 100 mg and 700 mg (-3.8 to $-4.3 \log_{10}$ IU/mL), and for ABT-530 was statistically significantly higher in the 40 mg QD to 400 mg QD dose groups ($\sim -4 \log_{10}$ IU/mL) compared with the 15 mg dose in treatment-naïve adults with chronic HCV GT1 infection with and without compensated cirrhosis.
- SVR₁₂ was achieved in the majority (95.5%) of chronic HCV G1-infected, treatment-naïve subjects treated with the combination of ABT-450/r/ABT-267 and ABT-333 plus RBV for 12 weeks, including all 16 subjects with compensated cirrhosis and 68 of 72 subjects without cirrhosis, among whom 1 subject poorly compliant with combination treatment experienced virologic breakthrough at CTP Week 4 and 3 subjects failed to achieve SVR₁₂ for non-virologic reasons.

Summary/Conclusions (Continued)

Conclusions (Continued):

- Increase in ABT-493 exposure was more than dose proportional over the 100 mg to 700 mg range in this study of subjects with HCV infection. ABT-493 exposures following 200 mg QD dosing in cirrhotic subjects were between the exposure of 200 mg QD and 300 mg QD in non-cirrhotic subjects.
- Increase in ABT-530 exposure was more than dose-proportional over the 15 mg to 120 mg range and less than dose-proportional between the 120 and 400 mg doses in this study of subjects with HCV infection. ABT-530 exposures were similar between the non-cirrhotic and cirrhotic subjects.
- Monotherapy with ABT-493 or ABT-530 appeared to be safe and well-tolerated. The safety profiles of 3-day ABT-493 monotherapy (across doses of 100 mg to 700 mg) and 3-day ABT-530 monotherapy (across doses of 15 mg to 400 mg) in study subjects infected with HCV GT1 were similar to those in healthy volunteers.
- The safety profile of ABT-450/r/ABT-267 and ABT-333 plus RBV in this study was favorable: The regimen administered for 12 weeks was well tolerated by treatment-naïve chronic HCV GT1-infected subjects. No new safety signal was observed in this study.