2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-450, ritonavir, ABT-267, ABT-333, ribavirin		
Name of Active Ingredient: <u>ABT-450:</u> (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]diazacyclo pentadecine-14a(5H)-carboxamide hydrate <u>Ritonavir:</u> [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 <u>ABT-267:</u> Dimethyl ([(2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate <u>ABT-333:</u> (sodium N-{6-[3-*tert*-butyl-5-(2,4-dioxo-3,4 dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl]naphthalen-2-yl}methanesulfonamide) <u>Ribavirin:</u> 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide		

Title of Study:

A Randomized, Open-Label Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered With and Without Ribavirin Compared to Telaprevir Co-administered with Pegylated Interferon α-2a and Ribavirin in Treatment-Naïve Adults with Chronic Hepatitis C Genotype 1 Virus Infection (MALACHITE I)

Coordinating Investigator:

Brygida Knysz, MD

Study Sites:

43 investigative sites in Argentina, Australia, Canada, Chile, Finland, Hungary, Norway, Poland, Romania, and Slovakia

Publications: 2

Studied Period (Years):	**Phase of Development:** 3b
First Subject First Visit: 28 March 2013 Last Subject Last Visit: 16 July 2015	

Objectives:

The primary objectives of this study were to demonstrate that treatment with ABT-450/r/ABT-267 and ABT-333 administered with or without ribavirin (RBV) has noninferior efficacy (the percentage of subjects achieving SVR_{12}, hepatitis C virus [HCV] RNA < lower limit of quantitation [LLOQ] 12 weeks following treatment) compared to treatment with telaprevir (TPV) and pegylated interferon (pegIFN)/RBV and to compare the safety of the regimens in treatment-naïve HCV genotype (GT) 1a- and 1b-infected adults without cirrhosis.

The secondary objectives of this study were to compare the following between treatment with Arm A (3 direct-acting antivirals [DAAs] with RBV) and treatment with Arm B (TPV with pegIFN/RBV) within HCV GT1a, and between treatment with Arm C (3 DAAs with RBV) or D (3 DAAs without RBV), and treatment with Arm E (TPV with pegIFN/RBV) in HCV GT1b:

- change from baseline to the Final Treatment Visit in general health-related quality of life (HRQoL) using the Short-Form 36 Health Survey (SF-36) Mental Component Summary (superiority);
- change from baseline to the Final Treatment Visit in general HRQoL using the SF-36 Physical Component Summary scores (superiority);
- the percentage of subjects achieving SVR_{12} (superiority); and
- the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment.

In addition, the percentage of subjects with SVR_{12} among subjects with HCV GT1b was compared between the arm not selected for primary comparison (Arm C) and Arm E (noninferiority and superiority).

Methodology:

This was a Phase 3b, randomized, open-label, parallel-arm, multicenter study in 2 parts, a Treatment Period and Post-Treatment Period. In the Treatment Period, eligible subjects were randomized into 5 treatment arms and received treatment accordingly. Randomization was stratified by interleukin 28B (IL28B) genotype (CC versus non-CC). Approximately 99 HCV GT1a-infected, treatment-naïve, noncirrhotic adults were to be randomized to Arm A and Arm B in a 2:1 ratio:

- Arm A: ABT-450/r/ABT-267 150 mg/100 mg/25 mg once daily (QD) and ABT-333 250 mg twice daily (BID) and weight-based RBV for 12 weeks (3-DAA + RBV in GT1a);
- Arm B: TPV 750 mg every 8 hours and pegIFN 180 µg subcutaneously (SC) weekly and weight-based RBV for 12 weeks followed by an additional 12 or 36 weeks of pegIFN and weight-based RBV according to response-guided therapy per the prescribing information for TPV (TPV/PR in GT1a).

Approximately 215 HCV GT1b-infected, treatment-naïve, noncirrhotic adults were to be randomized to Arms C, D, and E in a 2:2:1 ratio.

- Arm C: ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD and ABT-333 250 mg BID and weight-based RBV for 12 weeks (3-DAA + RBV in GT1b);
- Arm D: ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD and ABT-333 250 mg BID for 12 weeks (3-DAA in GT1b);
- Arm E: TPV 750 mg every 8 hours and pegIFN 180 µg SC weekly and weight-based RBV for 12 weeks followed by an additional 12 or 36 weeks of pegIFN and weight-based RBV according to response-guided therapy per the prescribing information for TPV (TPV/PR in GT1b).

The duration of the study was planned to be up to 96 weeks (not including a Screening Period of up to 35 days). All subjects administered study drugs were followed for 48 weeks post-treatment to monitor safety, perform patient-reported outcome (PRO) assessments, and test for durability of antiviral response on HCV RNA (SVR) and emergence or persistence of resistance to DAAs.

The primary analysis occurred after all subjects completed through Post-Treatment Week 12 or prematurely discontinued the study.

Number of Subjects (Planned and Analyzed):

A total of 314 subjects were planned to be enrolled; 311 subjects (69 in Arm A, 34 in Arm B, 84 in Arm C, 83 in Arm D, and 41 in Arm E) were enrolled and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Subjects were HCV GT1a- or 1b-infected, treatment-naïve adults (18 to 65 years of age, inclusive), with a body mass index ≥ 18 to < 38 kg/m^2. Females were either practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), postmenopausal for at least 2 years, surgically sterile, or of childbearing potential and practicing 2 effective forms of birth control starting with Day 1 and for 7 months after stopping study drug (or as directed by the local RBV prescribing information) or sexually active with female partners only. Males must have been surgically sterile or agreed to practice 2 effective methods of birth control starting with Day 1 and for 7 months after stopping study drug (or as directed by the RBV prescribing information) or sexually active with male partners only. Subjects had a chronic HCV infection, a plasma HCV RNA > 10,000 IU/mL, a liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis (e.g., a Metavir score of 3 or less or an Ishak score of 4 or less) or FibroTest® score ≤ 0.72 and aspartate aminotransferase (AST) to platelet ratio index ≤ 2, or FibroScan® result < 9.6 kPa.

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/Ritonavir/ ABT-267	AbbVie[a]	Oral	Tablet	75 mg/50 mg/ 12.5 mg	12-006414
ABT-333	AbbVie[a]	Oral	Tablet	250 mg	12-006334
Ribavirin	Roche	Oral	Tablet	200 mg	12-008082 12-005722 12-006117

a. Abbott Laboratories at time of production.

Duration of Treatment:

Subjects in Arms A, C, and D were dosed for 12 weeks. Subjects in Arms B and E received TPV with pegIFN and RBV for 12 weeks followed by response-guided therapy with pegIFN and RBV for an additional 12 or 36 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ribavirin	Roche	Oral	Tablet	200 mg	12-008082 12-005722 12-006117
Telaprevir	Janssen-Cilag	Oral	Film-coated Tablet	375 mg	12-008115 12-007829 13-001428
Pegylated Interferon-α2a	Roche	SC injection	Syringe	180 µg/0.5 mL	12-006583 12-006672 12-007212 12-007701 12-007211 13-001532 12-003160

Criteria for Evaluation

Efficacy:

HCV RNA in IU/mL was evaluated at all Treatment Period Visits and at all Post-Treatment Visits (through 48 weeks after completion of treatment).

Resistance:

For subjects in Arms A, C, and D who experienced virologic failure (on-treatment rebound or post-treatment relapse subsequent to study drug duration of at least 77 days) and had resistance data available, the variants at signature resistance-associated amino acid positions by population nucleotide sequencing at baseline were compared with the appropriate prototypic reference sequence, and the variants at each amino acid position by population nucleotide sequencing at available postbaseline time points were compared with baseline and the appropriate prototypic reference sequences were tabulated and summarized.

Patient-Reported Outcomes:

The impact on general HRQoL was assessed using the SF-36 version 2 (SF-36v2) non-disease specific HRQoL instrument. The change in disease-specific function and well-being was assessed using the HCV Patient Reported Outcomes (HCV-PRO) instrument. Health Utility was measured using the EuroQol-5 Dimensions-5 Levels Health State Instrument (EQ-5D-5L) with visual analogue scale (VAS). Additional PRO assessments included the Work Productivity and Activity Impairment specific for HCV (WPAI-HCV) and the HCV Treatment Satisfaction Instrument (HCVTSat).

Pharmacokinetic:

Subjects randomized to Arms A, C, and D had individual plasma concentrations of ABT-267, ABT-333, ABT-333 M1, ABT-450, RBV (Arms A and C), and ritonavir determined at all study visits up to Week 12. Subjects randomized to Arms B and E may have had plasma concentrations for TPV and RBV and serum concentrations for pegIFN determined at all study visits up to Week 12. Subjects who had the premature treatment termination visit prior to Week 12 also had a pharmacokinetic sample collected.

Safety:

The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, electrocardiogram, and laboratory test assessments.

Statistical Methods

Efficacy:

In order to control the Type I error rate, a fixed-sequence testing procedure was used to proceed through the primary and first 5 secondary endpoints in the order numbered below.

The primary efficacy endpoint was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

To show noninferiority in SVR_{12} rates of the DAA regimen(s) to the TPV/PR regimen, the simple percentage of subjects achieving SVR_{12} was calculated for each arm and a 2-sided 95% confidence interval (CI) for the difference in SVR_{12} rates (Arm A minus Arm B in GT1a, and Arm D minus Arm E in GT1b) was calculated using normal approximation to the binomial distribution. If the lower bound of the 2-sided 95% CI for the difference was above the noninferiority margin of –10.5%, the test arm was considered noninferior to the active control arm in the respective HCV subgenotype.

Statistical Methods (Continued)

Efficacy (Continued):

The secondary efficacy endpoints included in the fixed-sequence testing procedure were:

1. mean change from baseline to Final Treatment Visit in SF-36v2 Mental Component Summary score (superiority);
2. mean change from baseline to Final Treatment Visit in SF-36v2 Physical Component Summary score (superiority);
3. percentage of subjects with SVR_{12} (superiority);
4. percentage of subjects with SVR_{12} (noninferiority; applied within GT1b only, for the arm not selected for primary comparison [Arm C]); and
5. percentage of subjects with SVR_{12} (superiority; applied within GT1b only, for the arm not selected for primary comparison [Arm C]).

Two additional secondary endpoints were summarized outside the sequential testing procedure:

- the percentage of subjects with virologic failure during treatment (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment or confirmed HCV RNA ≥ LLOQ at the end of treatment); and
- the percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ among subjects completing treatment and with HCV RNA < LLOQ at the end of treatment).

Resistance:

The following HCV resistance variables were tabulated and summarized for the subjects who experienced virologic failure and who had resistance data available:

- the variants at each amino acid position by nucleotide population sequencing at baseline compared to the appropriate prototypic reference sequence;
- the variants at each amino acid position by nucleotide population for each postbaseline time point that was analyzed compared with baseline and the appropriate prototypic reference sequences; and
- the most prevalent amino acid variants by population sequencing that emerged or became enriched in isolates from at least 2 subjects of the same subgenotype.

Patient-Reported Outcomes:

In addition to the assessment of pre-specified PROs as of key secondary endpoints, exploratory analyses of PROs were performed, including but not limited to the following.

Summary statistics at each visit and for change from baseline to each visit by treatment arm and HCV subtype were provided for the HCV-PRO total score, the EQ-5D-5L health index and VAS scores, and the SF-36v2 Physical Component Summary and Mental Component Summary scores. For each of these scores, mean change from baseline to Final Treatment Visit and from baseline to Post-Treatment Week 12 was compared between treatment arms within each HCV subtype using an analysis of covariance model with treatment arm as a factor and baseline score and region as covariates.

Statistical Methods (Continued)

Patient-Reported Outcomes (Continued):

For HCV-PRO total score, EQ-5D-5L index score and VAS, and SF-36v2 Mental Component Summary and Physical Component Summary measures, continuous plots by treatment arm within each HCV subtype were provided with change from baseline on the horizontal axis and the cumulative percentage of subjects experiencing up to that change on the vertical axis. These plots were used to show change from baseline to Final Treatment Visit and change from baseline to Treatment Week 12.

The minimally important difference (MID) during treatment for the SF-36v2 was a decrease of 5 points from baseline for both the Physical Component Summary and Mental Component Summary scores. The MID during treatment was calculated for the HCV-PRO total score and the EQ-5D-5L health index using receiver operating characteristic curves with a change from baseline to Final Treatment Visit of –5 points in the SF-36v2 Physical Component Summary and Mental Component Summary measures as anchors (the calculated MIDs using SF-36 Physical Component Summary and Mental Component Summary scores as anchors were averaged). The percentage of subjects with a change from baseline to the Final Treatment Visit in each of these measures above the appropriate MID was compared between treatment arms within each HCV subtype using Fisher's exact tests.

The responses to HCVTSat were summarized by 2 scores: 1) a global measure of treatment satisfaction (final item scored 1 to 10) and 2) a composite index measure (average of 9 items scored 1 to 5). Summary statistics (n, mean, standard deviation, median, minimum and maximum) for each treatment arm were provided for the 2 summary scores at each applicable time point. Pairwise comparisons of the 2 summary scores between the treatment arms within each HCV subtype were performed using analysis of variance (ANOVA) with treatment arm as the factor.

Pharmacokinetics:

Individual plasma concentrations of ABT-267, ABT-333, ABT-333 M1, ABT-450, RBV, and ritonavir were tabulated and summarized for subjects treated in Arms A, C, and D. Plasma concentrations of TPV, RBV and serum concentrations of pegIFN were tabulated and summarized for subjects treated in Arms B and E up to Week 12.

Safety:

All subjects who received at least 1 dose of study drug were included in the safety analyses. The safety variables were not expected to be different between HCV GT1a and GT1b. To increase the power to detect safety signals, treatments arms of the same regimen were combined across subgenotypes to form 3 safety groups: Arms A + C (3-DAA + RBV), Arm D (3-DAA), and Arms B + E (TPV/PR). All safety parameters were summarized for each of the 3 safety groups, and the comparisons were 3-DAA + RBV versus TPV/PR and 3-DAA versus TPV/PR.

The number and percentage of subjects in each safety group with treatment-emergent adverse events (i.e., any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by primary Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term and compared within the 2 pairwise comparisons using Fisher's exact tests. The tabulation of the number of subjects with treatment-emergent adverse events by severity rating and relationship to each study drug (AbbVie DAAs, RBV, TPV, or pegIFN) was also provided.

Statistical Methods (Continued)

Safety (Continued):

To account for different treatment durations, exposure-adjusted adverse event analyses and a Week 12 truncated adverse event analysis were conducted for each safety group.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection during the Treatment Period, including Final Treatment Visit, was summarized by safety group and compared within the 2 pairwise comparisons using an ANOVA model with treatment group as the factor. Laboratory and vital sign values that were potentially clinically significant (PCS), according to predefined criteria, were identified, and the percentage of subjects with PCS values during the Treatment Period was compared between groups within the 2 pairwise comparisons using Fisher's exact test.

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoint was the percentage of subjects with SVR_{12} (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). The 2 primary treatment arm comparisons were:

- subjects with HCV GT1a: 3-DAA + RBV versus TPV/PR
- subjects with HCV GT1b: 3-DAA versus TPV/PR

Among HCV GT1a-infected subjects, SVR_{12} was achieved by 67/69 (97.1%) subjects in the 3-DAA + RBV arm and 28/34 (82.4%) subjects in the TPV/PR arm. The lower bound of the 95% CI for the treatment arm difference was 1.3%, which was above the noninferiority margin of –10.5%.
Two (2.9%) subjects in the 3-DAA + RBV arm experienced on-treatment virologic failure, and no subject experienced post-treatment relapse, for a total of 2.9% (2/69) virologic failures. In the TPV/PR arm, 2 (5.9%) subjects experienced on-treatment virologic failure, and no subject experienced post-treatment relapse, for a total of 5.9% (2/34) virologic failures.

Among HCV GT1b-infected subjects, SVR_{12} was achieved by 81/83 (97.6%) subjects in the 3-DAA arm, and 32/41 (78.0%) subjects in the TPV/PR arm. The lower bound of the 95% CI for the treatment arm difference was 6.4%, which was above the noninferiority margin of –10.5%. One (1.2%) subject in the 3-DAA arm experienced on-treatment virologic failure, and no subject experienced post-treatment relapse, for a total of 1.2% (1/83) virologic failures. In the TPV/PR arm, 5 (12.2%) subjects experienced on-treatment virologic failure, and 2/32 (6.3%) subjects experienced post-treatment relapse, for a total of 17.1% (7/41) virologic failures.

Sensitivity analyses that evaluated alternative methods to impute missing post-treatment virologic results were consistent with the primary analysis. A test of heterogeneity was conducted within each treatment arm, which indicated no significant heterogeneity across the 2 randomization strata defined by IL28B (CC versus non-CC). Among HCV GT1a-infected subjects, the 95% CI based on the stratum-adjusted variance was 93.1% to 100.0% for the 3-DAA + RBV arm and 69.1% to 95.6% for the TPV/PR treatment arm, with the difference in SVR_{12} rates of 14.7% (95% CI: 1.3%, 28.2%). Among HCV GT1b-infected subjects, the 95% CI based on the stratum-adjusted variance was 94.3% to 100.0% for the 3-DAA arm and 65.6% to 90.5% for the TPV/PR treatment arm, with the difference in SVR_{12} rates of 19.5% (95% CI: 6.4%, 32.6%).

Since the lower boundaries of the 95% CI for SVR_{12} rate differences in both cases were above the noninferiority threshold of –10.5%, noninferiority to TPV/PR in SVR_{12} was demonstrated for 3-DAA + RBV among HCV GT1a-infected subjects and for 3-DAA among HCV GT1b-infected subjects.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Among the secondary endpoints, within the HCV GT1a population, mean change from baseline to the Final Treatment Visit in SF-36v2 Mental Component Summary score between the 3-DAA + RBV and TPV/PR arms was not statistically significantly different; the other secondary endpoints were not tested per sequential testing criteria. Within the HCV GT1b population, each secondary endpoint met the sequential testing criteria for statistical significance. Key findings for each secondary endpoint were:

- Mean change from baseline to the Final Treatment Visit SF-36v2 Mental Component Summary score: Among HCV GT1b-infected subjects, a statistically significant difference was observed between the 3-DAA and TPV/PR arms (mean change from baseline of –0.1 and –6.4, respectively, $P = 0.002$).
- Mean change from baseline to the Final Treatment Visit in SF-36v2 Physical Component Summary score: Among HCV GT1a-infected subjects, a statistically significant difference was observed between the 3-DAA + RBV and TPV/PR arms (mean change from baseline of 0.5 and –5.5, respectively, $P < 0.001$); however, the treatment arm difference was not considered statistically significant per the sequential testing procedure. Among HCV GT1b-infected subjects, a statistically significant difference was observed between the 3-DAA and TPV/PR arms (mean change from baseline of 2.2 and –5.5, respectively, $P < 0.001$).
- Percentage of subjects with SVR_{12}: Among HCV GT1a-infected subjects, the adjusted odds ratio for 3-DAA + RBV versus TPV/PR was 7.2 (95% CI: 1.4, 38.0), with $P = 0.021$; however, the treatment arm difference was not considered statistically significant per the sequential testing procedure. Among HCV GT1b-infected subjects, the proportion of subjects achieving SVR_{12} was statistically significantly greater in the 3-DAA arm than the TPV/PR arm ($P = 0.005$), demonstrating superiority of 3-DAA versus TPV/PR for SVR_{12}.
- Percentage of subjects with SVR_{12} (noninferiority; applies within HCV GT1b only, for 3-DAA + RBV versus TPV/PR): Among HCV GT1b-infected subjects, SVR_{12} was achieved by 83/84 (98.8%) subjects in the 3-DAA + RBV arm and 32/41 (78.0%) subjects in the TPV/PR arm. The lower bound of the 95% CI for the treatment arm difference was 7.9%, which was above the noninferiority margin of –10.5%.
- Percentage of subjects with SVR_{12} (superiority; applies within HCV GT1b only, for 3-DAA + RBV versus TPV/PR): Among HCV GT1b-infected subjects, the adjusted odds ratio for 3-DAA + RBV versus TPV/PR was 28.2 (95% CI: 3.3, 241.1), with $P = 0.002$, demonstrating superiority of 3-DAA + RBV versus TPV/PR for SVR_{12}.

Results for the additional efficacy endpoint of sustained virologic response 24 weeks postdosing were consistent with the primary efficacy results with 100% agreement between SVR_{12} and SVR_{24} for all treatment arms except 3-DAA + RBV in GT1a (98.6%) and 3-DAA + RBV in GT1b (98.8%) due to 1 subject in each treatment arm with missing SVR_{24} data.

Summary/Conclusions (Continued)

Resistance Results:

Resistance analyses of subjects in the PVF population comprised 3 subjects (2 subjects in the 3-DAA + RBV in GT1a arm and 1 subject in the 3-DAA in GT1b arm). One additional subject who experienced virologic failure in the 3-DAA + RBV in GT1b arm was determined to have HCV GT2a infection based on phylogenetic analysis of the baseline NS5B sequence and was therefore excluded from the PVF population. Variants F43L, Y56H, R155K, and D168V/Y in NS3, M28T and Q30R in NS5A, and S556G in NS5B were detected in 1 or both of the GT1a-infected subjects at the time of virologic failure. The GT1b-infected subject had Y56H + D168V in NS3 at the time of failure, while Y93H in NS5A and S556G in NS5B were present at both baseline and at the time of failure. At the follow-up time points, NS3 variant R155K was detected at Post-Treatment Week 24 in 1 GT1a-infected subject, while D168 variants were not detected at Post-Treatment Week 24 or 48 in the 2 GT1a- or 1 GT1b-infected subjects. Treatment-emergent NS5A and NS5B variants persisted through Post-Treatment Week 24 or 48.

Patient-Reported Outcomes Results:

Overall, compared with the TPV/PR regimen, the 3-DAA regimen (with RBV or without RBV) had less unfavorable impact on subjects' HRQoL, function, well-being, work productivity, or daily activity during or at the end of treatment, though some of the differences between the regimens did not reach statistical significance. Furthermore, the 3-DAA + RBV regimen had only minimal impact on work productivity and daily activity; in contrast, the TPV/PR regimen was associated with notable impairments in work productivity and daily activity during or at the end of treatment. Satisfaction with treatment with the 3-DAA regimen (with RBV or without RBV) was statistically significantly greater compared with the TPV/PR regimen. In general, sustained improvements in subjects' HRQoL, function, and well-being were observed at the Final Post-Treatment Visit for all regimens.

Pharmacokinetic Results:

Based on the binned C_{trough} values in the 3-DAA + RBV in GT1a, 3-DAA + RBV in GT1b, and 3-DAA in GT1b arms, the exposures achieved in HCV treatment-naïve subjects in the present study for ABT-450, ritonavir, ABT-267, ABT-333, and ABT-333 M1 were within the range of exposures achieved in previous Phase 3 studies conducted in treatment-naïve or treatment-experienced HCV GT1-infected adults. The geometric mean of RBV binned C_{trough} values was approximately 14% to 24% lower than previous Phase 3 studies; however, the geometric mean RBV binned C_{trough} value was comparable to values reported for RBV.

In the TPV/PR in GT1a and TPV/PR in GT1b arms, the binned C_{trough} arithmetic mean for TPV was 2-fold higher (approximately 104% difference) in the present study than reported values. The arithmetic mean of the binned C_{trough} values of RBV was within the range of values previously reported. The binned C_{trough} values for the serum concentrations of pegIFN (Week 12) reported in the present study were comparable (< 13% difference in the arithmetic means) to reported values.

Safety Results:

The safety population included all randomized subjects who received at least 1 dose of study drug (N = 311).

Summary/Conclusions (Continued)

Safety Results (Continued):

ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 weeks in treatment-naïve HCV GT1-infected adults without cirrhosis was well tolerated, as demonstrated by the low rate (0% – 0.7%) of treatment-emergent serious adverse events and treatment-emergent adverse events leading to premature discontinuation of any study drug. The TPV/PR regimen was not as well tolerated, with a higher frequency and severity of adverse events, and 12.0% and 8.0% of subjects experiencing serious adverse events and discontinuing treatment due to adverse events, respectively.

While most subjects experienced at least 1 adverse event during the Treatment Period, most of these adverse events were mild in the 3-DAA with or without RBV groups. In contrast, most subjects in the TPV/PR group experienced an event that was at least moderate in severity.

The most common treatment-emergent adverse events in the 3-DAA + RBV group were headache, nausea, fatigue, and pruritus. The most common treatment-emergent adverse event in the 3-DAA group was headache. These adverse events were comparable in nature and frequency to those reported in other studies utilizing the 3-DAA + RBV and/or 3-DAA regimens. The most common treatment-emergent adverse events in the TPV/PR group were anemia, nausea, pruritus, headache, fatigue, rash, decreased appetite, dizziness, pyrexia, asthenia, vomiting, neutropenia, diarrhea, myalgia, alopecia, anal pruritus, and cough. These events are consistent with the reported safety profiles of TPV, RBV, and/or pegIFN.

Of the treatment-emergent adverse events reported for ≥ 10.0% of subjects in any group, anemia, neutropenia, anal pruritus, nausea, vomiting, asthenia, fatigue, pyrexia, decreased appetite, myalgia, dizziness, alopecia, pruritus, and rash occurred statistically significantly more frequently ($P \leq 0.05$) in the TPV/PR group than in each of the other 2 groups. In addition, cough occurred statistically significantly more frequently ($P \leq 0.05$) in the TPV/PR group than in the 3-DAA group. These events are known to be associated with either RBV or pegIFN.

No treatment-emergent deaths were reported. Two subjects (both in the 3-DAA + RBV group) died more than 30 days after the last dose of study drugs due to serious adverse events of cancer, which were considered by the investigator to have no reasonable possibility of relationship to any study drug. One subject in the 3-DAA + RBV group, none in the 3-DAA group, and 9 subjects in the TPV/PR group experienced treatment-emergent serious adverse events. Anemia (2 subjects) was the only treatment-emergent serious adverse event in the TPV/PR group experienced by more than 1 subject. The 1 serious adverse event in the 3-DAA + RBV group was considered by the investigator to have no reasonable possibility of relationship to any study drug. In contrast, 8 of the 9 subjects with treatment-emergent serious adverse events in the TPV/PR group had events considered by the investigator to have a reasonable possibility of relationship to any study drug.

Among the adverse events of interest, 3.9% of subjects in the 3-DAA + RBV group and no subjects in the 3-DAA or TPV/PR groups experienced at least 1 bilirubin-related adverse event. These results in the 3-DAA + RBV and 3-DAA groups are consistent with those of other Phase 3 clinical studies of 3-DAA + RBV. RBV-associated hemolysis can also result in hyperbilirubinemia. In addition, transient elevations in bilirubin are expected effects of ABT-450, a known inhibitor of OATP1B bilirubin transporters.

Summary/Conclusions (Continued)

Safety Results (Continued):

A greater percentage of subjects in the TPV/PR group than in the 3-DAA + RBV and 3-DAA groups experienced rash-related adverse events (62.7% versus 20.3% and 7.2%, respectively), anemia-related adverse events (49.3% versus 7.2% and 1.2%, respectively), and treatment-emergent adverse events of special interest for neutropenia (22.7% versus 0% and 0%, respectively), thrombocytopenia (2.7% versus 0% and 0%, respectively), and psychiatric disorders (24.0% versus 14.4% and 4.8%, respectively) based on standardized MedDRA query(SMQ)/company MedDRA query search criteria. These events were generally assessed as mild or moderate in severity. Anemia and rash are well-known side effects of TPV and RBV treatment, and neutropenia, thrombocytopenia, and serious neuropsychiatric disorders are risks of pegIFN treatment. The 12-week truncated and exposure-adjusted adverse event analyses showed a similar trend.

Review of the specific MedDRA search queries for rash revealed that events of rash and pruritus were statistically significantly more frequent in the TPV/PR group than in each of the other 2 groups. The events reported in each group were mainly mild in severity. One TPV/PR subject interrupted a study drug (RBV) and prematurely discontinued a study drug (TPV) due to rash. Another TPV/PR subject prematurely discontinued TPV due to rash pruritic. One TPV/PR subject experienced a treatment-emergent adverse event (toxic skin eruption) that met the severe cutaneous reactions SMQ (narrow search). This event was serious. No other subjects interrupted any study drug or prematurely discontinued any study drug due to a rash-related event.

Analysis of hematology parameters showed statistically significant differences in the mean change from baseline to the Final Treatment Visit in the TPV/PR group compared with the 3-DAA and 3-DAA + RBV groups for hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell (WBC) count, total neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, and activated partial thromboplastin time. The mean changes in monocytes, eosinophils, and basophils were small in each group. In the TPV/PR group, the mean decreases from baseline in platelet count, WBC count, total neutrophils, and lymphocytes were consistent with the known effects of pegIFN. There was a greater mean increase from baseline in reticulocyte count in the 3-DAA + RBV group than in the TPV/PR group. This difference is likely due to the fact that the 3-DAA regimen allows for reticulocytosis, as a compensatory mechanism, to occur in response to the anemia resulting from RBV, while pegIFN in the TPV/PR regimen suppresses any compensatory reticulocytosis in response to anemia.

The mean decrease in hemoglobin for the TPV/PR group was 7.7 g/L greater ($P \leq 0.001$) than in the 3-DAA + RBV group and 22.5 g/L greater ($P \leq 0.001$) than in the 3-DAA group at the Final Treatment Visit, suggesting a greater impact of TPV and pegIFN on hemoglobin than DAA therapy. One (0.7%) subject in the 3-DAA + RBV group, no subjects in the 3-DAA group, and 3 (4.1%) subjects in the TPV/PR group experienced a reduction from baseline to a grade 3 hemoglobin value.

No more than 2 (1.3%) subjects in the 3-DAA + RBV group and 1 (1.2%) subject in the 3-DAA group experienced a PCS value for any hematology parameter. Approximately half of the subjects (51.4%) in the TPV/PR group had PCS low total neutrophil values; 41.9% of subjects had PCS low WBC count, and 20.3% of subjects had PCS low lymphocyte count.

Summary/Conclusions (Continued)

Safety Results (Continued):

Analysis of chemistry parameters showed statistically significant differences in the mean change from baseline to Final Treatment Visit for the TPV/PR group compared with the 3-DAA and/or 3 DAA + RBV groups in ALT, AST, alkaline phosphatase, GGT, uric acid, chloride, triglycerides, thyroid-stimulating hormone, calculated creatinine clearance, inorganic phosphate, calcium, magnesium, potassium, bicarbonate, albumin, and cholesterol. However, with the exception of liver chemistry parameters, the mean changes from baseline during the Treatment Period in all of these chemistry parameters were small and not considered clinically meaningful.

PCS values for chemistry parameters were infrequent, with the most notable results observed for the percentage of subjects with PCS total bilirubin values (12.4% 3-DAA + RBV, 1.2% 3-DAA, and 14.9% TPV/PR). Six (3.9%) subjects in the 3-DAA + RBV group, no subjects in the 3-DAA group, and 2 (2.7%) subjects in the TPV/PR group had at least a grade 3 postbaseline total bilirubin. This suggests that the effect of the 3-DAA + RBV regimen and the TPV/PR regimen on total bilirubin is similar.

Mean decreases from baseline were observed in ALT and AST at both the Final Treatment Visit and the Post-Treatment Week 4 Visit, and Final Post-Treatment Visit. One (0.7%) subject in the 3-DAA + RBV group and no subjects in the 3-DAA or TPV/PR groups experienced postbaseline elevations in ALT to $> 5 \times$ ULN. This elevation improved without study drug interruption or discontinuation.
One (0.7%) 3-DAA + RBV subject and 1 (1.4%) TPV/PR subject had ALT and total bilirubin values that met biochemical criteria for inclusion in Hy's law quadrant of an eDISH plot, but evaluation of laboratory trends and clinical status led to the conclusion that these were not likely to be true Hy's law cases.

No clinically meaningful results of urinalysis, vital signs, or electrocardiograms were observed.

In summary, adverse event and laboratory safety data in this study demonstrate that the 3-DAA + RBV and 3-DAA regimens were better tolerated than the TPV/PR regimen in treatment-naïve, HCV GT1-infected subjects. Key differences in the safety profiles of the TPV/PR regimen versus the 3-DAA + RBV and 3-DAA regimens include a higher frequency and severity of adverse events in general and a greater frequency of drug-related adverse events, serious adverse events, and adverse events leading to premature treatment discontinuation in the TPV/PR group than in the 3-DAA with or without RBV groups. In addition, a higher frequency of rash-related adverse events, anemia-related adverse events, psychiatric disorder-related adverse events, and adverse events of neutropenia and thrombocytopenia occurred with the TPV/PR regimen.

Conclusions:

Treatment-naïve, HCV GT1a- and GT1b-infected adults without cirrhosis who were treated with a 12-week regimen of ABT-450/r/ABT-267 and ABT-333 with or without RBV achieved SVR_{12} rates of 97.1% to 98.8%, while subjects treated for 24 to 48 weeks with the TPV/PR regimen achieved SVR_{12} rates of 82.4% for GT1a and 78.0% for GT1b. These results are consistent with previous reports on the 3-DAA regimen and TPV/PR.

Summary/Conclusions (Continued)

Conclusions (Continued):

Overall, compared with the TPV/PR regimen, the 3-DAA regimen (with RBV or without RBV) had less unfavorable impact on subjects' HRQoL, function, well-being, work productivity, or daily activity during or at the end of treatment, though some of the differences between the regimens did not reach statistical significance. Furthermore, the 3-DAA + RBV regimen had only minimal impact on work productivity and daily activity; in contrast, the TPV/PR regimen was associated with notable impairments in work productivity and daily activity during or at the end of treatment. Satisfaction with treatment with the 3-DAA regimen (with RBV or without RBV) was statistically significantly greater compared with the TPV/PR regimen. In general, sustained improvements in subjects' HRQoL, function, and well-being were observed at the Final Post-Treatment Visit for all regimens.

The 12-week regimen of ABT-450/r/ABT-267 and ABT-333 with or without RBV was well tolerated, as shown by the low rate (< 1%) of treatment-emergent serious adverse events and treatment-emergent adverse events leading to premature discontinuation of study treatment. The safety profiles observed in this study were consistent with those observed for the combination of 3 DAAs with and without RBV in previous studies. Consistent with the reported safety profile of TPV/PR in the TPV SmPC, the TPV/PR regimen was not as well tolerated, with 12.0% and 8.0% of subjects experiencing serious adverse events and discontinuing study treatment due to adverse events, respectively. In addition, the lower tolerability of TPV/PR treatment likely reduced the treatment success since 4 of the 6 subjects who prematurely discontinued TPV/PR treatment due to adverse events failed to achieve SVR_{12}. The RBV-associated toxicities, such as anemia, occurred at much lower frequency and with less severity in combination with DAA treatment than in combination with pegIFN treatment.