

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, 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,14,15,16,16 atetradecahydrocyclopropa[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-tertbutylphenyl) pyrrolidine-2,5-[diyl]bis{benzene-4,1-diyl}carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]])biscarbamate hydrate	Page:	
Title of Study: A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 with Ritonavir (ABT-450/r) and ABT-267 in Adults with Chronic Hepatitis C Virus Infection (PEARL-I)		
Investigator: Pr. Christophe Hezode		
Study Sites: 46 investigative sites enrolled subjects in the United States (US), Puerto Rico, France, Hungary, Italy, Poland, Romania, Spain and Turkey		
Publications: 5 abstracts and 1 manuscript		

<p>Studied Period (Years): First Subject First Visit: 14 August 2012 Last Subject Last Visit: 17 February 2015</p>	<p>Phase of Development: 2</p>
<p>Objectives: The primary objective of Study M13-393 was to assess the safety and efficacy (the percentage of subjects with hepatitis C virus [HCV] ribonucleic acid [RNA] < lower limit of quantitation [LLOQ] 12 weeks after the last actual dose of study drug [sustained virologic response 12 weeks after the last actual dose of study drug {SVR₁₂}] of</p> <ul style="list-style-type: none"> • the combination of ABT-450 plus ritonavir plus ABT-267 (i.e., 2-DAA regimen) <ul style="list-style-type: none"> ○ among treatment-naïve and prior pegylated-interferon (pegIFN)/ribavirin (RBV) null responder HCV genotype (GT) 1b-infected subjects without cirrhosis and ○ among treatment-naïve and pegIFN/RBV treatment-experienced HCV GT1b-infected subjects with compensated cirrhosis • the 2-DAA regimen administered with or without RBV <ul style="list-style-type: none"> ○ among treatment-naïve and pegIFN/RBV treatment-experienced HCV GT4-infected subjects. <p>The secondary objectives of this study were to assess the rates of HCV RNA < LLOQ 24 weeks after the last actual dose of study drug (SVR₂₄) on-treatment virologic failure, and post-treatment relapse among all treated subjects.</p>	
<p>Methodology: Study M13-393 was a Phase 2, randomized, open-label, combination treatment study of the 2-DAA regimen (ABT-450 150 mg QD + ritonavir 100 mg QD + ABT-267 25 mg QD) in adult HCV GT1b-infected treatment-naïve and pegIFN/RBV treatment-experienced subjects with and without compensated cirrhosis. In addition, this was a combination treatment study of the 2-DAA regimen with or without RBV in adult HCV GT4-infected treatment-naïve and pegIFN/RBV treatment-experienced subjects.</p> <p>This study consisted of:</p> <ul style="list-style-type: none"> • Treatment Period: GT1b subjects in Groups 2 and 3 received 12 weeks of 2-DAA and GT4 subjects in Groups 1, 4, and 6 received 12 weeks of the 2-DAA regimen with or without RBV. GT1b subjects in Groups 7 and 8 received 24 weeks of the 2-DAA regimen. • Post-Treatment Period: Subjects who completed or prematurely discontinued the Treatment Period were followed for 48 weeks to monitor HCV RNA and the emergence and persistence of resistant viral variants. <p>The study was planned for approximately 320 subjects, with approximately 40 subjects in each of the 8 planned treatment groups. This study was divided into 2 separate substudies:</p>	

Methodology (Continued):

Substudy 1 (Non-Cirrhotic Subjects)

Groups 2 and 3 were enrolled in parallel, followed by Groups 1 and 4. During the treatment period, HCV GT1b-infected treatment-naïve and null responder subjects were enrolled to Groups 2 and 3 and HCV GT4-infected treatment-naïve subjects were randomized in a 1:1 ratio to Groups 1 and 4. Based upon review and assessment of available data from this study that indicated higher SVR rates with the addition of RBV, Group 6 was enrolled, and Group 5 was not enrolled.

- Group 1 (GT4 treatment-naïve): 2-DAA regimen for 12 weeks
- Group 2 (GT1b treatment-naïve): 2-DAA regimen for 12 weeks
- Group 3 (GT1b null-responder): 2-DAA regimen for 12 weeks
- Group 4 (GT4 treatment-naïve): 2-DAA regimen + RBV* BID for 12 weeks
- Group 5 (GT4 treatment-experienced): 2-DAA regimen for 12 weeks (not enrolled)
- Group 6 (GT4 treatment-experienced): 2-DAA regimen + RBV* BID for 12 weeks

* RBV was administered weight-based 1000 or 1200 mg divided twice daily (BID)

Substudy 2 (Subjects with Compensated Cirrhosis)

Groups 7 and 8 were opened for enrollment based upon review and assessment of available data from this study and other on-going studies. During the substudy 2 treatment period, treatment-naïve and treatment-experienced HCV GT1b-infected subjects with compensated cirrhosis enrolled into Groups 7 and 8:

- Group 7 (GT1b treatment-naïve): 2-DAA regimen for 24 weeks
- Group 8 (GT1b treatment-experienced): 2-DAA regimen for 24 weeks

Number of Subjects (Planned and Analyzed):

Planned: Approximately 320 subjects (40 per treatment group)

Analyzed: 316 subjects enrolled and received at least 1 dose of study drug (44, 42, 40, 42, 0, 49, 47, and 52 subjects in Groups 1, 2, 3, 4, 5, 6, 7, and 8, respectively)

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria for All Subjects: Male or female 18 to 70 years of age (inclusive); body mass index (BMI) was 18 to < 38 kg/m²; chronic HCV GT1b or 4-infection for 6 months; plasma HCV RNA level > 10,000 IU/mL; and subjects had to meet one of the following:

- **Treatment-naïve:** never received antiviral treatment for HCV infection (subjects with HCV GT1b infection with or without cirrhosis or HCV GT4 infection [Groups 1, 2, 4, and 7])

OR

- **Prior null responders:** previously received pegIFN/RBV for at least 10 weeks and failed to achieve a 2 log₁₀ IU/mL HCV RNA decrease at Week 12 (Weeks 10 – 16) (subjects with HCV GT1b infection with or without compensated cirrhosis or HCV GT4 infection [Groups 3, 5, 6, and 8])

OR

- **Partial responder:** Received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved 2 log₁₀ reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment (Subjects with HCV GT1b infection and compensated cirrhosis or HCV GT4 infection [Groups 5, 6, and 8])

Diagnosis and Main Criteria for Inclusion (Continued):

OR

- **Relapser:** Received at least 36 weeks of pegIFN/RBV for the treatment of HCV and HCV RNA was undetectable at the end of treatment, but was detectable within 52 weeks of follow-up (Subjects with HCV GT1b infection and compensated cirrhosis or HCV GT4 infection [Groups 5, 6, and 8]).

Additional Main Inclusion Criteria for Substudy 1: Liver biopsy demonstrating the absence of cirrhosis. In the absence of a biopsy within the 24 months prior to screening or during screening, the subject was required to have a screening FibroTest score of ≤ 0.72 and aspartate aminotransferase to platelet ratio index (APRI) ≤ 2 ; or a screening FibroScan[®] result of < 9.6 kPa.

Main Inclusion for Substudy 2: Child-Pugh score of ≤ 6 and documentation of cirrhosis by one of the following methods: Previous histologic diagnosis on liver biopsy (e.g., Metavir Score of > 3 [including 3/4 or 3 – 4], Ishak score of > 4), or FibroScan score ≤ 14.6 kPa within 6 months of Screening or during the Screening Period.

Main Exclusion Criteria for All Subjects: History of severe, life-threatening or other significant sensitivity to any drug; females who were pregnant or breastfeeding; recent history of drug or alcohol abuse that could have precluded adherence to the protocol; and positive test result for hepatitis B surface antigen or anti-HIV antibodies.

Main Exclusion for Substudy 1: Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis.

Main Exclusion for Substudy 2: Any current or past clinical evidence of Child-Pugh B or C Classification or clinical history of liver decompensation such as ascites, variceal bleeding or hepatic encephalopathy.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
ABT-450	AbbVie ^a	50 mg tablet/Oral	11-000782, 12-005949
Ritonavir	AbbVie ^a	100 mg soft gelatin capsule/Oral	12-001928, 12-004432, 12-006185, 12-001426, 13-001828
ABT-267	AbbVie ^a	25 mg tablet/Oral	11-002034, 11-002815
Ribavirin	Roche	200 mg tablet/Oral	12-006117, 12-006919
	Kadmon Pharmaceuticals, LLC	200 mg tablet/Oral	12-005991

a. Formerly Abbott Laboratories at the time of production.

Duration of Treatment: Subjects received 2-DAA regimen with or without RBV for 12 weeks in Groups 1, 2, 3, 4, and 6; and for 24 weeks in Groups 7 and 8.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

HCV RNA in IU/mL was assessed at all study visits during the Treatment Period and Post-Treatment Period.

Resistance:

Resistance analyses included baseline sequences from all available subjects as well as post-baseline from all virologic failures. For subjects who did not achieve SVR and who had HCV RNA ≥ 1000 IU/mL, the variants at each signature resistance-associated amino acid position by population nucleotide sequencing at baseline compared with the appropriate prototypic reference sequence, and the variants at each amino acid position by population and/or clonal nucleotide sequencing at available postbaseline time points compared with baseline and the appropriate prototypic reference sequences were tabulated and summarized.

Patient-Reported Outcomes:

The change in disease-specific function and wellbeing were assessed using the HCV Patient-Reported Outcomes (HCV-PRO) instrument. Health state utility was assessed using the EuroQol-5 Dimensions-5 Level (EQ-5D-5L) instrument. Satisfaction with therapy was assessed using the HCV Treatment Satisfaction (HCVTSat) instrument.

Pharmacokinetic:

Plasma concentrations for ABT-450, ritonavir, ABT-267, and RBV were determined in samples harvested at each study visit; the time of the last dose of study drug was also recorded.

Safety:

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

Statistical Methods

Efficacy:

The primary efficacy endpoint was the percentage of subjects with SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug). For each treatment group (i.e., Groups 1 – 4, 6 – 8), the number and percentage of subjects with SVR₁₂ were summarized along with exact 95% confidence intervals. Pairwise comparisons between Groups 1 and 4 and Groups 2 and 3 were performed using a logistic regression model with treatment group, baseline log₁₀ HCV RNA level, and interleukin 28B (IL28B) genotype (CC, non-CC) as predictors. Treatment differences (with 95% confidence intervals) for the specified comparisons were estimated using stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IL28B genotype (CC or non-CC).

The secondary efficacy endpoints were:

- The percentage of subjects with SVR₂₄ (HCV RNA < LLOQ 24 weeks after the last actual dose of study drug),
- The percentage of subjects with virologic failure during treatment (defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, confirmed increase from nadir in HCV RNA [2 consecutive HCV RNA measurements > 1 log₁₀ IU/mL above nadir] during treatment, or all measurements of HCV RNA ≥ LLOQ during treatment, with at least 6 weeks [– 36 days] of treatment),
- The percentage of subjects with post-treatment relapse (defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after the last dose of study drugs among subjects who completed treatment with HCV RNA < LLOQ at the end of treatment).

For each treatment group (i.e., Groups 1 – 4, 6 – 8), the number and percentage of subjects meeting each secondary efficacy endpoint were summarized along with exact 95% confidence intervals. For SVR₂₄, pairwise comparisons between Groups 1 and 4 and Groups 2 and 3 were performed using a logistic regression model with treatment group, baseline log₁₀ HCV RNA level, and IL28B genotype (CC, non-CC) as predictors. In addition, treatment differences (with 95% confidence intervals) for the specified comparisons were estimated using stratum-adjusted Mantel-Haenszel proportion and continuity-corrected variance, adjusting for IL28B genotype (CC or non-CC).

Resistance:

The following resistance information was analyzed for subjects receiving active drugs who did not achieve SVR and were in the primary virologic failure (PVF) population: 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 postbaseline time points identified by population and/or clonal nucleotide sequencing were compared to baseline and the appropriate prototypic reference sequences, 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 were summarized for all subjects not achieving SVR regardless of the reason, and 4) the persistence of viral resistance was summarized for all subjects not achieving SVR, regardless of the reason.

Statistical Methods (Continued)

Pharmacokinetic:

Plasma concentrations of ABT-450, ABT-267, ritonavir, and ribavirin were tabulated for each subject and group. Summary statistics were computed for each time and visit. Plasma trough concentrations (C_{trough}) in GT4- and GT1b-infected subjects were summarized by binning.

Safety:

The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment arm. Tabulations were also provided for the number and percentage of subjects with TEAEs by severity (mild, moderate, or severe) and relationship to study drug. Change from baseline in laboratory tests and vital sign measurements to each time point of collection was summarized by arm. The number and percentage of subjects with laboratory and vital sign values during the Treatment Period that were potentially clinically significant (PCS), according to predefined criteria were summarized.

Summary/Conclusions

HCV GT4 Response

All HCV GT4-infected noncirrhotic treatment-naïve subjects who received 2-DAA + RBV for 12 weeks achieved the primary efficacy endpoint of SVR₁₂. In comparison, 90.9% of the treatment-naïve subjects who received 2-DAA without RBV for 12 weeks achieved SVR₁₂, indicating that the addition of RBV to the treatment regimen contributes to maximizing SVR. Therefore, only the 2-DAA + RBV regimen was evaluated in GT4-infected treatment experienced subjects, and all subjects in this cohort achieved SVR₁₂.

The SVR₁₂ rates for each GT4-infected treatment group are listed as follows:

- 2-DAA for 12 Weeks
 - 90.9% (40/44) for treatment-naïve subjects (95% CI: 78.3, 97.5) (Group 1)
- 2-DAA + RBV for 12 Weeks
 - 100.0% (42/42) for treatment-naïve subjects (95% CI: 91.6, 100.0) (Group 4)
 - 100.0% (49/49) for treatment-experienced subjects (95% CI: 92.7, 100.0) (Group 6)

The unadjusted estimate of the difference in SVR₁₂ rates between the cohorts of HCV GT4-infected treatment-naïve subjects treated with 2-DAA alone (Groups 1) and those treated with 2-DAA + RBV (Group 4) was 9.09% (95% CI: 0.60, 17.59). The treatment group difference in SVR₁₂ rates was not statistically significant when the Mantel-Haenszel method was used to adjust for differences in the proportion of IL28B CC subjects (versus non-CC) (difference of 9.16% [95% CI: -1.29, 19.61], $P = 0.086$).

The secondary efficacy endpoint of SVR₂₄ was achieved in 86.4% of subjects in the treatment-naïve group receiving 2-DAA alone (Group 1: 38/44, 95% CI: 72.6, 94.8) and 100% in the treatment-naïve and treatment-experienced groups receiving 2-DAA + RBV (Group 4: 42/42, 95% CI: 91.6, 100.0) (Group 6: 49/49, 95% CI: 92.7, 100.0). Since no new relapses were observed after Post-Treatment Week 12, the lower rates observed for SVR₂₄ compared with SVR₁₂ in Group 1 were due to missing SVR₂₄ data for 2 subjects who had achieved SVR₁₂.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

HCV GT4 Response (Continued)

In the HCV GT4 treatment groups treated with 2-DAA + RBV, no virologic failures occurred during the Treatment Period and no relapses were observed during the Post-Treatment Period. For treatment-naïve GT4-infected subjects who received 2-DAA without RBV (Group 1), 1 of the 44 subjects experienced on-treatment virologic failure and 2 subjects relapsed within 12 weeks post-treatment.

HCV GT1b Response

All cohorts of GT1b-infected subjects were treated with the 2-DAA regimen without concomitant administration of RBV. The primary efficacy endpoint of SVR₁₂ in HCV GT1b-infected subjects was achieved with 12 weeks of 2-DAA in 95.2% of treatment-naïve and 90% of the treatment-experienced null responder noncirrhotic subjects. High SVR₁₂ rates of 97.9% and 98.1% were also achieved with 2-DAA administered for 24 weeks in treatment-naïve and treatment-experienced subjects with compensated cirrhosis, respectively. The SVR₁₂ rates for each GT1b-infected treatment group are listed as follows:

- Noncirrhotic Subjects Treated with 2-DAA for 12 Weeks
 - 95.2% (40/42) for treatment-naïve subjects (95% CI: 83.8, 99.4) (Group 2)
 - 90.0% (36/40) for treatment-experienced null responders (95% CI: 76.3, 97.2) (Group 3)
- Subjects with Compensated Cirrhosis Treated with 2-DAA for 24 Weeks
 - 97.9% (46/47) for treatment-naïve subjects (95% CI: 88.7, 99.9) (Group 7)
 - 98.1% (51/52) for treatment-experienced subjects (95% CI: 89.7, 100.0) (Group 8)

The difference in SVR₁₂ between the cohorts of noncirrhotic treatment-naïve and treatment-experienced subjects was not statistically significant based on a logistic regression model using HCV RNA level and IL28B genotype as predictive ($P = 0.381$); however, the study sample size was based on having sufficient power to detect a treatment group difference of at least 25%. The unadjusted SVR₁₂ rate in Group 2 was higher than the SVR₁₂ rate in Group 3 by 5.12% (95% CI: -6.28, 16.52). When the Mantel-Haenszel method was used to adjust the comparison for differences in the proportion of IL28B CC subjects (versus non-CC), the estimate of the treatment group difference in SVR₁₂ rates increased slightly to 5.53% (95% CI: -8.48, 19.55) and was not statistically significant ($P = 0.439$).

The secondary efficacy endpoint of SVR₂₄ was achieved in at least 90% of subjects in each noncirrhotic treatment group with a similar rate for both treatment-naïve (92.9% [39/42]; 95% CI: 80.5, 98.5) and treatment-experienced null responders (90.0% [36/40]; 95% CI: 76.3, 97.2). Since no new relapses were observed after Post-Treatment Week 12, the lower rate observed for SVR₂₄ compared with SVR₁₂ for treatment-naïve subjects was due to missing SVR₂₄ data for 1 subject who had achieved SVR₁₂.

In the cirrhotic HCV GT1b groups treated with 2-DAA for 24 weeks, SVR₂₄ was achieved in all subjects who had achieved SVR₁₂; 97.9% of treatment naïve subjects (46/47; 95% CI: 88.7, 99.9) and 98.1% of treatment-experienced subjects (51/52; 95% CI: 89.7, 100.0).

Summary/Conclusions

Efficacy Results (Continued):

HCV GT1b Response (Continued)

In the HCV GT1b noncirrhotic treatment groups, none of the 42 treatment-naïve subjects (Group 2) experienced virologic failure during the Treatment Period and no relapses were observed during the 48-week Post-Treatment Period. Of the 40 treatment-experienced null responders (Group 3), 1 subject had a virologic failure at Week 8, and 3 subjects relapsed within 12 weeks post-treatment.

In the HCV GT1b treatment groups with compensated cirrhosis, none of the 99 subjects experienced virologic failure during the Treatment Period. One of the 52 treatment-experienced subjects (Group 8) experienced a relapse within 12 weeks post-treatment.

Resistance Results:

Resistance analyses included all GT1b and GT4 virologic failures as well as baseline sequences from all subjects with an available baseline sample. In GT1b, there was no apparent association between the presence of variants at resistance-associated amino acid positions at baseline within NS3 and treatment outcome, while variant Y93H in nonstructural protein 5A (NS5A) in GT1b-infected subjects was more prevalent among subjects not achieving SVR₁₂. The predominant resistance associated treatment-emergent variants observed in GT1b-infected subjects not achieving SVR₁₂ were D168V in NS3 and Y93H in NS5A. Treatment-emergent variants in NS3 in genotype 1b-infected subjects declined through Post-Treatment Week 24 (2/4, 50%) and Post-Treatment Week 48 (0/4, 0%). Treatment-emergent resistance-associated variants in NS5A in genotype 1b-infected subjects remained detectable in 2 of 3 (67%) subjects at Post-Treatment Week 24 and Post-Treatment Week 48.

A phylogenetic analysis on sequences from the baseline sample of GT4-infected subjects indicated that most subjects were infected with either subtype 4a or 4d. All HCV GT4-infected subjects who did not achieve SVR₁₂ due to virologic failure were infected with subtype 4d. There was no apparent association between the presence of variants at resistance-associated amino acid positions at baseline in NS3 or NS5A and treatment outcome in the GT4-infected subjects. The predominant resistance-associated treatment-emergent variants at the time of failure in the 3 GT4d-infected subjects not achieving SVR₁₂ were D168V in NS3, and L28S and L28V in NS5A.

Treatment-emergent variants in NS3 in genotype 4d-infected subjects declined through Post-Treatment Week 24 (2/3, 67%) and Post-Treatment Week 48 (0/3, 0%). Treatment-emergent resistance associated variants in NS5A in genotype 4d-infected subjects remained detectable in 3 of 3 (100%) subjects at Post-Treatment Week 24 and in 2 of 3 (67%) of the subjects through Post-Treatment Week 48.

Patient Reported Outcomes Results:

Improvements in the HCV-PRO total score from baseline to the Final Treatment Visit and Post-Treatment Week 24 were observed in each treatment group, with mean increases ranging from 1.48 to 14.23 (scale of 0 to 100) across GT4 treatment groups and 7.07 to 12.41 across GT1b treatment groups. Overall, the differences between treatment groups were not statistically significant. Similarly, improvements in mean changes from baseline in the EQ-5D-5L Health Index score and EQ-5D-5L Visual Analog Scale (VAS) score were also observed after treatment, and the differences between treatment groups were not statistically significant within genotype. The mean overall scores for HCVTSat were > 9 for each treatment group (scale from 1 [not satisfied at all] to 10 [extremely satisfied]). The mean Composite Index score, which assessed how items may have influenced the subjects' perception of treatment satisfaction, was > 3.5 for each treatment group (scale from 1 [not influential at all] to 5 [extremely influential]).

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Plasma concentrations at 4 hours poststudy drug dosing on Day 1 for ABT-450, ritonavir, and ABT-267 in GT1b-infected noncirrhotic subjects were 459 – 601 ng/mL, 608 – 755 ng/mL, and 89 – 99 ng/mL, respectively; and in GT4-infected noncirrhotic subjects were 185 – 417 ng/mL, 500 – 544 ng/mL, and 73 – 88 ng/mL, respectively. In GT4-infected subjects, the RBV concentration at 4 hours postdosing on Day 1 was 397 – 442 ng/mL.

These results indicated that exposures of ABT-450, ritonavir, and ABT-267 were lower in GT4-infected noncirrhotic subjects compared to GT1b-infected noncirrhotic subjects. Similar results were also observed for binned concentrations representing C_{trough} values

In GT1b-infected cirrhotic subjects, the 4-hour concentration for ABT-450 was higher (465 – 1220 ng/mL) whereas concentrations of ritonavir (424 – 590 ng/mL) and ABT-267 (49 – 84 ng/mL) were lower compared with GT1b-infected non-cirrhotic subjects.

Safety Results:

Noncirrhotic Subjects

Treatment-emergent adverse events (AEs) were reported for 77.0% (97/126) of noncirrhotic subjects treated with 2-DAA for up to 12 weeks, with a similar incidence across the HCV populations enrolled (i.e., treatment-naïve GT4, treatment-naïve GT1b, and treatment-experienced GT1b null responders). In noncirrhotic subjects treated with 2-DAA + RBV for up to 12 weeks, TEAEs were reported for 86.8% (79/91) of subjects, with a similar incidence between the HCV populations enrolled (i.e., treatment-naïve GT4 and treatment-experienced GT4).

Treatment-emergent AEs reported in 10% of noncirrhotic subjects treated with 2-DAA or 2-DAA + RBV were headache (29.4% 2-DAA, 30.8% 2-DAA + RBV), asthenia (12.7% 2-DAA, 28.6% 2-DAA + RBV), fatigue (7.1% 2-DAA, 15.4% 2-DAA + RBV), nausea (9.5% 2-DAA, 14.3% 2-DAA + RBV), and insomnia (2.4% 2-DAA, 13.2% 2-DAA + RBV). Treatment-emergent AEs that were considered at least possibly related to DAA study drug by the investigator and reported in 10% of noncirrhotic subjects treated with 2-DAA or 2-DAA + RBV were headache (20.6% for 2-DAA, 20.9% for 2-DAA + RBV), asthenia (11.9% for 2-DAA, 23.1% for 2-DAA + RBV), and fatigue (4.8% for 2-DAA, 12.1% for 2-DAA + RBV). Treatment-emergent AEs that were considered at least possibly related to RBV study drug in 10% of subjects treated with 2-DAA + RBV were asthenia (25.3%), headache (19.8%), fatigue (13.2%), and nausea (12.1%).

The majority of all AEs were mild. Few severe AEs were reported, occurring in only 5 of the 217 noncirrhotic subjects. No preferred term was reported as severe for more than 1 subject.

No subjects discontinued study drug due to a TEAE and the incidence of serious adverse events (SAEs) was low, reported for 4 subjects treated with 2-DAA (atrial fibrillation for 1 subject, contusion and road traffic accident for 1 subject, chronic obstructive pulmonary disease exacerbation for 1 subject, and device extrusion [malleable penile prosthesis] for 1 subject). All SAEs resolved, and 3 of the 4 serious adverse events were considered not related to study drug. The atrial fibrillation for the remaining subject was considered probably related to study drug by the investigator. None of the SAEs resulted in discontinuation or interruption of study drug. No SAEs were reported for subjects treated with 2-DAA + RBV. No TEAEs resulted in death or study drug discontinuation for any noncirrhotic subject.

Summary/Conclusions (Continued)

Safety Results (Continued):

Noncirrhotic Subjects (Continued)

No hepatotoxicity-related TEAEs of interest were reported in noncirrhotic subjects, and no other TEAEs of interest (i.e., bilirubin-related, anemia-related, or drug-induced rash) were serious or required study drug interruption or discontinuation. Bilirubin-related TEAEs of hyperbilirubinemia were reported for 2.2% (2/91) of subjects treated with 2-DAA + RBV and no subjects (0/126) treated with 2-DAA without RBV. Anemia TEAEs of interest were identified in 5.5% (5/91) of subjects treated with 2-DAA + RBV and no subjects (0/126) treated with 2-DAA without RBV. Rash events of special interest were reported for 10.3% (13/126) of subjects treated with 2-DAA without RBV and 12.1% (11/91) of subjects treated with 2-DAA + RBV, with pruritus being the most commonly reported preferred term (6.3% for 2-DAA without RBV; 6.6% for 2-DAA + RBV).

Of the 91 subjects treated with 2-DAA + RBV, 4 subjects required RBV dose modifications because of hemoglobin decreased, hemolytic anemia, or anemia. Two additional subjects required RBV dose modifications for other reasons (anxiety, insomnia, and heart palpitation for 1 subject, and erythema for the other subject).

No hemoglobin decreases required RBV dose interruption or discontinuation.

Hematology results showed small mean decreases in hemoglobin that were greater for 2-DAA + RBV treatment (-20.6 g/L at Final Treatment Visit) than for 2-DAA treatment (-5.3 g/L Final Treatment Visit). The mean decreases were observed within the first 4 weeks of treatment, were not progressive over time, and the values for 2-DAA + RBV treatment returned to near baseline levels within 4 weeks after the end of treatment. Only 1 subject (2-DAA + RBV) had a single common toxicity criteria for adverse events (CTCAE) grade 3 low hemoglobin value that was isolated and returned to normal at the next assessment time. Three additional subjects (1 treated with 2-DAA, 2 treated with 2-DAA + RBV) had grade 2 low hemoglobin values. None of the grade 2 or 3 hemoglobin values were reported as AEs, and none were associated with AEs that were severe, serious, or resulted in discontinuation of study drug or RBV dosage modification.

Small mean decreases in total bilirubin were observed at most visits for subjects treated with 2-DAA. Small mean increases in bilirubin were observed with 2-DAA + RBV treatment, with maximum increases at Week 2 (5.6 µmol/L), followed by a reversal towards the baseline mean and small mean decreases after the end of treatment. Individual bilirubin results that were grade 2 or higher were observed for a higher percentage of subjects treated with 2-DAA + RBV versus subjects treated with 2-DAA alone (15.4% versus 6.4%). Bilirubin values that were grade 3 or higher were reported in 3 subjects (3.3%) treated with 2-DAA + RBV and no subjects treated with 2-DAA alone. Other liver function test results that were grade 2 or higher were reported in less than 5% of subjects for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and no subjects for alkaline phosphatase. Grade 3 or higher ALT or AST values were observed in 3 subjects treated with 2-DAA and no subjects treated with 2-DAA + RBV. The grade 3 liver function test elevations resulted in interruption of study drug for 1 subject treated with 2-DAA alone, and the subject resumed study drug administration without recurrence. No liver function test results led to discontinuation of study drug. No subject was assessed by the independent expert hepatic panel as meeting criteria for Hy's law. Two subjects had ALT and total bilirubin values in Hy's law quadrant, and both cases were assessed and categorized by the expert hepatic panel as not potential Hy's law cases, unequivocally.

Summary/Conclusions (Continued)

Safety Results (Continued):

Noncirrhotic Subjects (Continued)

No other clinically meaningful observations for noncirrhotic subjects treated with 2-DAA or 2-DAA + RBV were noted for hematology, clinical chemistry, urinalysis, vital signs, or ECG assessments.

Subgroup analyses based on sex, age, and race did not identify any safety concerns specific to any subgroup, however, the sample size within some subgroups for some regimens was small and definitive conclusions could not be made.

Cirrhotic Subjects

Treatment-emergent AEs were reported for 77.8% (77/99) of cirrhotic GT1b-infected subjects treated with 2-DAA for up to 24 weeks, with a similar incidence in the HCV populations enrolled (i.e., treatment-naïve and treatment-experienced). Treatment-emergent AEs reported in 10% of cirrhotic subjects were headache (19.2%), asthenia (17.2%), pruritus (17.2%), diarrhea (14.1%), back pain (11.1%), fatigue (10.1%), and nausea (10.1%). The only TEAE considered at least possibly related to DAA study drug by the investigator and reported in 10% of cirrhotic subjects was pruritus (16.2%).

The majority of all AEs were mild. Few severe AEs were reported, occurring in 4 of the 99 cirrhotic subjects. No preferred term was reported as severe for more than 1 subject.

The incidence of SAEs was low (5.1%, (5/99) and included hepatic neoplasm for 1 subject, esophageal varices hemorrhage for 1 subject with pre-existing esophageal varices and distant history of gastroesophageal bleeding, ALT and AST increased (grade 4) for 1 subject, artery aneurysm of the common iliac for 1 subject, and humerus fracture and focal epilepsy for 1 subject. The SAEs resulted in no change in study drug administration for 4 subjects, and discontinuation of study drug for the subject with esophageal varices hemorrhage. All SAEs resolved with the exception of focal epilepsy that was not related to study drug. No TEAEs resulted in death. Two non-TEAEs resulted in death including gastrointestinal hemorrhage, which occurred 92 days after the last dose of study drug for the subject who had discontinued because of esophageal varices hemorrhage, and multiple organ failure, which occurred 355 days after the last dose of study drug after a previous SAE of hepatic neoplasm, study drug discontinuation due to ascites, and multiple hospitalizations for management of HCC, hemorrhagic esophageal varices, and liver transplant rejection.

Treatment-emergent AEs resulted in discontinuation of study drug for 3 of the 99 (3.0%) cirrhotic subjects. The events resolved for all 3 subjects. The investigator assessed these events as probably related to study drug for 1 subject who developed isolated edema peripheral concurrent with calcium channel blocker treatment; not related to study drug for the subject who discontinued because of an SAE of esophageal varices hemorrhage (subject had pre-existing esophageal varices, as noted above); and probably not related to study drug for 1 subject who discontinued because of ascites that developed subsequent to an SAE of hepatic neoplasm, as noted above.

Hepatotoxicity-related TEAEs of interest were identified for 4 cirrhotic subjects and all events were assessed by the investigator as not related or probably not related to study drug. Two subjects had events that were serious and/or resulted in discontinuation of study drug, as noted above (serious hepatic neoplasm followed by discontinuation due to ascites for 1 subject, and serious esophageal varices hemorrhage that also resulted in discontinuation for 1 subject).

Summary/Conclusions (Continued)

Safety Results (Continued):

Cirrhotic Subjects

No other TEAEs of interest (i.e., bilirubin-related, anemia-related, or drug-induced rash) were serious or required study drug interruption or discontinuation. Bilirubin-related TEAEs of hyperbilirubinemia were reported in 1.0% (1/99) of cirrhotic subjects, and anemia TEAEs of interest were reported in 2.0% (2/99) of cirrhotic subjects. Rash events of special interest were reported in 22.2% (22/99) of cirrhotic subjects, with the most commonly reported preferred term being pruritus (17.2%). All events were mild or moderate except for 1 severe event of pruritus that resolved with medication.

Hemoglobin changes over time were minimal, with a mean decrease of 3.6 g/L at the Final Treatment Visit. Only 2 subjects had a grade 2 hemoglobin value during the Treatment Period, and no subjects had > grade 2 values.

Individual liver function test results that were grade 2 or higher were observed in 14.1% of subjects for bilirubin, 7.1% of subjects for ALT, 4.0% of subjects for AST, and no subjects for alkaline phosphatase. The percentage of subjects with grade 3 or 4 values was much lower (3.0% for bilirubin, 3.0% for ALT, and 2.0% for AST), and reported for a total of 5 subjects. One subject had grade 4 ALT and AST values that were reported as SAEs considered possibly related to 2-DAA study drug; the values returned to normal levels by the Final Treatment Visit. This subject had ALT and total bilirubin values in Hy's law quadrant. The subject was assessed by the independent expert hepatic panel and categorized by the panel as a potential Hy's law case possibly related to study drug; they further commented that it was a case of atypical Hy's law with adaptation because Hy's law was not intended for application in scenarios with underlying hepatic compromise. Furthermore, bilirubin started increasing before ALT peaked suggesting that the trajectory of the bilirubin elevation was unrelated to ALT elevation, and the international normalized ratio (INR) did not increase significantly as would be expected in global hepatic synthetic dysfunction. The subject remained asymptomatic, and values for ALT, AST, and bilirubin decreased with continued DAA dosing. No subject discontinued from the study or had study drug interrupted because of liver function test results.

No other clinically meaningful observations for cirrhotic subjects treated with 2-DAA were noted for hematology, clinical chemistry, urinalysis, vital signs, or ECG assessments. Subgroup analyses based on sex and age did not identify any safety concerns specific to any subgroup, however, the sample size within some subgroups for some regimens was small and definitive conclusions could not be made.

Summary/Conclusions (Continued)

Conclusions:

Treatment with the 2-DAA regimen for 12 weeks demonstrated efficacy in noncirrhotic GT4- and GT1b-infected subjects and in GT1b-infected cirrhotic subjects when administered for 24 weeks.

All HCV GT4-infected noncirrhotic treatment-naïve subjects who received the 2-DAA regimen with concomitant RBV for 12 weeks achieved the primary efficacy endpoint of SVR₁₂. In comparison, 90.9% for treatment-naïve subjects who received 2-DAA without RBV for 12 weeks achieved SVR₁₂, indicating that the addition of RBV to the treatment regimen contributes to maximizing SVR. However, given the high SVR₁₂ observed in the cohort of treatment-naïve subjects and the limited availability of IFN-free therapeutic options, the 2-DAA regimen without RBV may provide benefit to HCV GT4-infected patients with a history of intolerance to RBV or who are ineligible for RBV treatment. Among the 129 HCV GT4-infected subjects who achieved SVR₁₂ and had virologic response data at Post-Treatment Week 24, all subjects maintained their response through 24 weeks post treatment (achieved SVR₂₄).

High SVR₁₂ rates were also observed after treatment with the 2-DAA regimen for 12 weeks in noncirrhotic subjects infected with HCV GT1b when administered without RBV in treatment-naïve subjects (SVR₁₂: 95.2%) and in treatment-experienced subjects who were previously null responders to pegIFN/RBV treatment (SVR₁₂: 90.0%). A 24-week treatment period with the 2-DAA regimen demonstrated efficacy in subjects with compensated cirrhosis in both treatment-naïve (SVR₁₂: 97.9%) and in treatment-experienced subjects (SVR₁₂: 98.1%). Among the 172 HCV GT1b-infected subjects who achieved SVR₁₂ and had virologic response data at Post-Treatment Week 24, all subjects maintained their response through 24 weeks post-treatment (achieved SVR₂₄).

Treatment-emergent, resistance-associated variants in NS3 and NS5A were detected in GT4d- and GT1b-infected subjects who experienced virologic failure. While treatment-emergent, resistance-associated variants in NS3 declined through Post Treatment Weeks 24 and 48, variants in NS5A remained detectable through Post-Treatment Week 48 in both GT4d- and GT1b-infected virologic failures.

The 2-DAA regimens with and without RBV were generally well tolerated in subjects both with and without compensated cirrhosis.