

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: ombitasvir, paritaprevir (ABT-450), ritonavir, dasabuvir, sofosbuvir, ribavirin	Volume:	
<p>Name of Active Ingredient:</p> <p>ombitasvir (ABT-267): Dimethyl [(2S,5S)-1-(4-<i>tert</i>-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</p> <p>paritaprevir (ABT-450): (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-[[5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-<i>a</i>][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate</p> <p>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</p> <p>dasabuvir (ABT-333): Sodium 3-(3-<i>tert</i>-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>	Page:	

<p>Name of Active Ingredient (Continued): sofosbuvir: (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. ribavirin: 1-β-D-ribofuranosyl-1<i>H</i>-1,2,4-triazole-3-carboxamide</p>		
<p>Title of Study: An Open-Label Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) and Dasabuvir Co-administered With or Without Sofosbuvir (SOF) and Ribavirin (RBV) in Direct-Acting Antiviral Agent (DAA) Treatment-Experienced Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection</p>		
<p>Coordinating Investigator: ██████████</p>		
<p>Study Sites: 10 sites in the United States</p>		
<p>Publications: 1 (abstract)</p>		
<p>Studied Period (Years): First Subject First Visit: 03 February 2015 Last Subject Last Visit: 07 July 2017</p>	<p>Phase of Development: 2</p>	
<p>Objectives: The primary objectives of this study were to assess the safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response ([SVR₁₂] [HCV RNA < lower limit of quantification (LLOQ) 12 weeks following treatment]) of co-formulated ombitasvir with paritaprevir and ritonavir (ombitasvir/paritaprevir/ritonavir) and dasabuvir co-administered with SOF, with or without RBV, in adults with genotype (GT) 1 HCV and prior failure of a DAA-containing treatment regimen. The secondary objectives were to assess the safety and the percentage of subjects achieving SVR₁₂ of co-formulated ombitasvir/paritaprevir/ritonavir and dasabuvir with RBV in chronic HCV GT1-infected adults who were SOF/ledipasvir treatment-experienced and treatment-naïve to all other anti-HCV therapies, the percentage of subjects with virologic failure during treatment and the percentage of subjects with virologic relapse post-treatment (PT) and to characterize the pharmacokinetics of DAAs including ritonavir, SOF (if applicable), GS-331007 (predominant circulating metabolite of SOF; if applicable), and RBV (if applicable) in adults with GT1 HCV and prior failure of a DAA treatment regimen.</p>		

Methodology:

This was a Phase 2, open-label, multicenter study evaluating the safety and efficacy of co-formulated ombitasvir/paritaprevir/ritonavir and dasabuvir co-administered with or without SOF and RBV for 12 or 24 weeks in adults with GT1 HCV who had experienced prior failure of a DAA-containing regimen (i.e., either on-treatment failure or PT relapse). The study comprised 2 parts.

In Part 1, approximately 20 HCV GT1-infected, DAA treatment-experienced subjects, including up to 6 subjects with compensated cirrhosis, were to be enrolled at approximately 10 sites in the US. At least 10 of the 20 subjects were to have experienced treatment failure after being treated with ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without RBV. Part 1 subjects received study treatment as follows:

- subtype 1 non-b, non-cirrhotic (Cohort 1): ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg once daily (QD) with dasabuvir 250 mg twice daily (BID) (hereafter, 3-DAA) and SOF 400 mg QD with RBV (weight-based dosing 1000 or 1200 mg divided BID or renally adjusted for subjects with creatinine clearance (CrCl) < 50 mL/min) for 12 weeks.
- subtype 1b (Cohort 2): 3-DAA and SOF 400 mg QD for 12 weeks.
- subtype 1 non-b, cirrhotic (Cohort 3): 3-DAA, SOF 400 mg QD, and RBV (weight-based dosing 1000 or 1200 mg divided BID or renally adjusted for subjects with CrCl < 50 mL/min) for 24 weeks.

In Part 2, approximately 10 HCV GT1-infected, SOF/ledipasvir treatment-experienced subjects (i.e., had previously received SOF/ledipasvir for at least 8 weeks) were to be enrolled at approximately 10 US sites. Eligible Part 2 subjects were treated as follows:

- subtype 1, SOF/ledipasvir treatment-experienced (Cohort 4): 3-DAA with RBV (weight-based dosing 1000 or 1200 mg divided BID or renally-adjusted for subjects with CrCl < 50 mL/min) for 24 weeks.

In the Treatment Period, subjects were assessed for antiviral response, patient-reported outcomes (by EuroQol 5 Dimensions 5 Levels Health State Instrument [EQ-5D-5L]), and safety and tolerability of study drug.

In the PT Period, all subjects who had been administered at least 1 dose of study drug were to be followed for 48 weeks to monitor for safety, HCV RNA, and the emergence and/or persistence of resistant viral variants.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 30 HCV GT1-infected subjects, including approximately 20 who were DAA treatment-experienced (up to 6 with compensated cirrhosis) in Part 1 and approximately 10 who were SOF/ledipasvir treatment-experienced in Part 2. At least 10 of the 20 subjects enrolled into Part 1 were to have experienced treatment failure after being treated with 3-DAA, with or without RBV.

Analyzed: 29 subjects: 22 subjects in Part 1 (6 with compensated cirrhosis) and 7 subjects in Part 2.

Diagnosis and Main Criteria for Inclusion:

Main Inclusion Criteria:

1. Male or female at least 18 years of age at screening.
2. A history of previous DAA-containing treatment for chronic HCV GT1 infection that resulted in either on-treatment virologic failure or PT relapse, defined as:
 - On-Treatment Failure: The subject was considered to have experienced on treatment failure of the prior DAA-containing treatment regimen if a) HCV RNA was quantifiable at the end of the DAA-containing therapy, or if b) the subject was documented to have met futility criteria as defined in the product label (e.g., for telaprevir or boceprevir); or
 - PT Relapse: The subject was considered to have experienced PT relapse if HCV RNA was < LLOQ at the end of the prior DAA-containing treatment regimen but was confirmed to be quantifiable during the 24 weeks after the end-of-treatment.
Treatment must have completed at least 1 month prior to the Screening Visit.
Part 2 only: prior on-treatment failure or PT relapse (as defined above) after receiving at least 8 weeks of SOF/ledipasvir. The subject must have been treatment naïve to all other anti-HCV therapies.
3. Screening laboratory result from the central clinical laboratory indicating HCV GT1 infection only.
4. Subjects were able to understand and adhere to the study visit schedule and all other protocol requirements and voluntarily signed and dated an informed consent.

Main Exclusion Criteria:

1. Positive test result for hepatitis B surface antigen (HBsAg) or human immunodeficiency virus (HIV) positive immunoassay.
2. Clinically significant abnormalities or co-morbidities, other than HCV infection, that made the subject an unsuitable candidate for this study or treatment with RBV (if applicable) in the opinion of the investigator.
3. Discontinuation of the prior DAA treatment regimen for reasons other than virologic failure (e.g., non-adherence and/or the occurrence of an adverse event).
4. History of solid organ transplant.
5. Screening laboratory analyses showing any of the following abnormal laboratory results.
 - calculated creatinine clearance < 30 mL/min as estimated by the Cockcroft-Gault method;
 - albumin < 2.8 g/dL;
 - hemoglobin < lower limit of normal (LLN);
 - platelets < 25×10^9 cells/L;
 - total bilirubin > 3.0 mg/dL.
6. Any current or past clinical evidence of Child-Pugh B or C classification (Child Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding, or hepatic encephalopathy.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:			
Investigational Product	Manufacturer	Dosage Form/Mode of Administration	Bulk Lot Number
Ombitasvir/ABT-450/ Ritonavir	AbbVie	12.5/75/50 mg tablet/oral	13-001960
Dasabuvir	AbbVie	250 mg tablet/oral	12-007842
Sofosbuvir	Gilead	400 mg tablet/oral	14-004864
RBV	generic manufacturer	200 mg tablet/oral	14-001215, 14-005989
Duration of Treatment:			
Subjects in Part 1 received 3-DAA and SOF, with or without RBV, for 12 or 24 weeks. Subjects in Part 2 received 3-DAA and RBV for 24 weeks.			
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:			
Not applicable.			
Criteria for Evaluation			
Efficacy:			
HCV RNA in international units (IU)/mL was assessed at various time points from Day 1 through 48 weeks after completion of treatment.			
Resistance:			
The following resistance information was provided for all subjects:			
<ul style="list-style-type: none"> the amino acid variants at baseline at signature resistance-associated positions identified by population and/or deep sequencing and comparison to the appropriate prototypic reference sequence. 			
The following resistance information was provided for subjects who experienced virologic failure or treatment discontinuation:			
<ul style="list-style-type: none"> the amino acid variants in available post-baseline samples identified by population and/or deep sequencing and comparison to the baseline sequence; the amino acid variants in available post-baseline samples at signature resistance-associated positions identified by population and/or deep sequencing and comparison to the appropriate prototypic reference sequence; the persistence of viral resistance-associated amino acid variants during the PT period. 			
Patient-Reported Outcomes:			
Patient reported outcomes were assessed using EQ-5D-5L at various visits throughout the study.			
Pharmacokinetics:			
Individual plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, SOF (if applicable), GS-331007 (if applicable), and RBV (if applicable) were determined at each visit through the end of the Treatment Period (Week 12 or Week 24).			
Safety:			
Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, and vital signs.			

Statistical Methods

Efficacy analyses were performed on the intent-to-treat (ITT) population, consisting of all subjects who received at least one dose of study drug. Demographics, baseline characteristics, medical history, previous/concomitant medications, subject disposition, exposure, and compliance were summarized for the safety population, which was the same as the ITT population for this study.

Efficacy:

Primary Endpoint

The primary efficacy endpoint was the percentage of subjects in Part 1 achieving SVR₁₂ (HCV RNA < LLOQ 12 weeks after the last actual dose of study drugs). The number and percentage of subjects achieving SVR₁₂ were calculated and a 2-sided 95% Wilson score confidence interval (CI) for a binomial proportion was computed.

Secondary Endpoints

The secondary efficacy endpoints were:

- The percentage of Part 2 subjects who achieved SVR₁₂;
- The percentage of subjects with virologic failure during the Treatment Period defined as confirmed HCV RNA \geq LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA (2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir) at any time point during treatment or failure to suppress during treatment (all on-treatment values of HCV RNA \geq LLOQ) with at least 6 weeks of treatment. Note that a single value \geq LLOQ or $> 1 \log_{10}$ IU/mL above nadir during treatment followed by lost to follow-up was considered a failure;
- The percentage of subjects with virologic relapse PT defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after the last actual dose of active study drug (up to and including the SVR₁₂ assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completed treatment. Completion of treatment was defined as a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment and ≥ 154 days for subjects assigned to 24 weeks of treatment.

The numbers and percentages of subjects with virologic failure during treatment and with virologic relapse PT were calculated separately for each study part. The corresponding 2-sided 95% Wilson score CIs for a binomial proportion were calculated for each of the secondary endpoints.

Resistance:

The following resistance information was analyzed for all baseline samples from subjects: 1) the prevalence of polymorphisms at signature amino acid positions at baseline, identified by next-generation sequencing (NGS), was compared to the appropriate subtype specific prototypic reference sequence; and, (2) a comparison of SVR₁₂ rates in subjects with or without baseline polymorphisms was conducted. (3) For subjects experiencing virologic failure, variants by NGS relative to baseline or subtype-specific prototypic reference sequence were identified.

Patient-Reported Outcomes:

Visit means along with summary statistics (n, mean, SD, median, minimum and maximum) for change from baseline to each post-baseline visit for the EQ-5D-5L health index and visual analog scale (VAS) scores were calculated separately for each part of the study.

Statistical Methods (Continued)

Pharmacokinetics:

Plasma concentrations of paritaprevir, ritonavir, ombitasvir, dasabuvir, dasabuvir M1 metabolite, SOF, GS-331007 (predominant circulating metabolite of SOF), and RBV were tabulated for each subject. Summary statistics were computed for each time point (for intensive pharmacokinetic data) or binned time interval (for sparse pharmacokinetic data).

For the intensive pharmacokinetic data from Week 4, values for the pharmacokinetic parameters of paritaprevir, ombitasvir, ritonavir, dasabuvir, and dasabuvir M1 metabolite, SOF (if applicable), GS-331007 (predominant circulating metabolite of SOF; if applicable) and RBV (if applicable) including the maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), C_{trough} , and area under the plasma concentration-time curve (AUC) were calculated and tabulated for each analyte.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]) (version 20.0). The number and percentage of subjects with treatment-emergent adverse events (TEAEs) were tabulated by primary System Organ Class (SOC) and preferred term. Tabulations were also provided in which the number of subjects with TEAEs was presented by severity rating and relationship to study drugs.

Changes from baseline in laboratory tests and vital sign measurements to each post-baseline visit were summarized descriptively. In addition, the number and percentage of subjects with post-baseline laboratory and vital sign values meeting prespecified criteria for potentially clinically significant (PCS) values, according to predefined criteria, during treatment were summarized. Hemoglobin and liver function tests were also categorized using Common Terminology Criteria for Adverse Events (CTCAE) grades, and the number and percentage of subjects with values within each CTCAE grade level during treatment were calculated.

Summary/Conclusions

Efficacy Results:

In Part 1, SVR₁₂ was achieved by 21 of 22 (95.5%) subjects, and SVR₂₄ was achieved by 20 of 22 (90.9%) subjects. One subject infected with subtype 1 non-b and treated with 3-DAA, SOF, and RBV for 12 weeks (Cohort 1) failed to achieve both SVR₁₂ and SVR₂₄, having relapsed by PT Week 12. One subject infected with subtype 1b and treated with 3-DAA and SOF (Cohort 2) failed to achieve SVR₂₄, having discontinued study drug prematurely.

In Part 2 (Cohort 4), SVR₁₂ and SVR₂₄ were achieved by 6 of 7 (85.7%) SOF/ledipasvir treatment-experienced subjects treated with 3-DAA and RBV. One subject who did not meet the eligibility criteria for enrollment into Cohort 4 experienced on treatment virologic failure (i.e., breakthrough) at the Week 4 visit.

Summary/Conclusions (Continued)				
Efficacy Results (Continued):				
Virologic Response (SVR₁₂, SVR₂₄) for DAA Treatment-Experienced Subjects in Part 1 and SOF/Ledipasvir Treatment-Experienced Subjects in Part 2 (ITT Population)				
Virologic Finding	Part 1 3-DAA + SOF ± RBV		Part 2 3-DAA + RBV	
	SVR₁₂	SVR₂₄	SVR₁₂	SVR₂₄
SVR, n/N (%)	21/22 (95.5)	20/22 (90.9)	6/7 (85.7)	6/7 (85.7)
95% CI ^a (%)	78.2, 99.2	72.2, 97.5	48.7, 97.4	48.7, 97.4
Nonresponders, n/N (%)	1/22 (4.5)	2/22 (9.1)	1/7 (14.3)	1/7 (14.3)
Reason for nonresponse, n/N (%)				
On-treatment virologic failure	0/22	0/22	1/7 (14.3)	1/7 (14.3)
Breakthrough	0/22	0/22	1/7 (14.3)	1/7 (14.3)
Fail to suppress	0/22	0/22	0/7	0/7
Relapse by PT Week 12	1/21 ^b (4.8)	1/21 ^b (4.8)	0/6 ^c	0/6 ^c
Relapse by PT Week 24	NA	0/20 ^d	NA	0/6 ^e
Premature study drug discontinuation	0/22	1/22 (4.5)	0/7	0/7
Missing SVR ₁₂ /SVR ₂₄ data	0/22	0/22	0/7	0/7
Other	0/22	0/22	0/7	0/7
<p>BID = twice daily; CI = confidence interval; DAA = direct-acting antiviral agent; 3-DAA = ombitasvir/paritaprevir/ritonavir 25 mg/150 mg/100 mg QD and dasabuvir 250 mg BID; PT = Post-Treatment; QD = once daily; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; SVR₁₂ = sustained virologic response at 12 weeks postdosing; SVR₂₄ = sustained virologic response at 24 weeks postdosing</p> <p>a. Calculated using the Wilson score method.</p> <p>b. One subject was excluded from the denominator in the calculation of Relapse₁₂ due to premature discontinuation from treatment.</p> <p>c. One subject was excluded from the denominator in the calculation of Relapse₁₂ because the subject did not have HCV RNA < LLOQ at final treatment visit and prematurely discontinued from treatment.</p> <p>d. Two subjects were excluded from the denominator in the calculation of Relapse₂₄, 1 due to missing HCV RNA data in the SVR₂₄ assessment window and 1 for not achieving SVR₁₂.</p> <p>e. One subject was excluded from the denominator in the calculation of Relapse₂₄ due to not achieving SVR₁₂.</p> <p>Part 1: DAA treatment-experienced subjects infected with subtype 1 non-b, without cirrhosis (Cohort 1) and with compensated cirrhosis (Cohort 3) were treated with 3-DAA, SOF 400 mg QD, and RBV for 12 (Cohort 1) or 24 weeks (Cohort 3). DAA treatment-experienced subjects infected with subtype 1b (Cohort 2) were treated with 3-DAA and SOF 400 mg QD for 12 weeks.</p> <p>Part 2: SOF/ledipasvir treatment-experienced subjects infected with subtype 1 (Cohort 4) were treated with 3-DAA and RBV for 24 weeks.</p>				

Summary/Conclusions (Continued)

Resistance Results (Continued):

Resistance analyses included evaluation of prevalence of baseline polymorphisms at amino acid positions important for the NS3/4A protease, NS5A, and NS5B inhibitor classes. At 15% detection threshold, among subjects experienced to PI, PI + NS5A inhibitor, PI + NS5A inhibitor + non-nucleoside NS5B inhibitor, or PI + nucleotide NS5B inhibitor, 88.9% (16/18) of GT1a-infected subjects had baseline polymorphisms V55A, Q80K/L, or D168E/V in NS3, and 50.0% (1/2) of GT1b-infected subjects had V132I in NS3 at baseline. Among subjects experienced to PI + NS5A inhibitor, PI + NS5A inhibitor + non-nucleoside NS5B inhibitor, or nucleotide NS5B inhibitor + NS5A inhibitor, 82.6% (19/23) of GT1a-infected subjects had baseline polymorphisms K24R, M28T/V, Q30E/H/R/T, H58D/P, E62D, Y93C/F/N in NS5A, and the single GT1b-infected subject had L31M, Q54H, and Y93H in NS5A at baseline. Among GT1a-infected subjects experienced to PI + NS5A inhibitor + non-nucleoside NS5B inhibitor, L314H, M414I/T, or S556G in NS5B were detected in 64.3% (9/14) of subjects at baseline. None of the subjects had polymorphisms at position 282 that is associated with resistance to nucleotide NS5B inhibitors. Baseline polymorphisms in NS3, NS5A, or NS5B had no impact on treatment outcome.

One out of 2 GT1a-infected subjects in Cohort 1 experienced to NS3/4A protease inhibitor (PI), and 1 out of 7 GT1a infected subjects in Cohort 4 experienced to nucleotide NS5B inhibitor + NS5A inhibitor experienced virologic failure. The GT1a-infected virologic failure subject experienced to PI had Q80K in NS3 at baseline, but had no treatment-emergent substitutions in NS3; baseline or treatment-emergent substitutions were not detected in NS5A or NS5B at signature amino acid positions. The GT1a-infected virologic failure subject experienced to nucleotide NS5B inhibitor + NS5A inhibitor had Q80K in NS3 and Y93N in NS5A at baseline; treatment-emergent substitutions Y56H + D168A/V in NS3 and M414V, E446K, A553T, and D559G in NS5B were detected at the time of failure.

Patient-Reported Outcomes Results:

Small mean increases (improvements) or no change from baseline were observed for EQ 5D-5L VAS score and EQ-5D-5L health index score at the Final Treatment and Final PT visits among DAA treatment-experienced subjects treated with 3-DAA and SOF, with or without RBV, in Part 1. Small mean decreases from baseline were observed for EQ-5D-5L VAS score and small mean increases from baseline were observed for EQ 5D-5L health index score at the Final Treatment and Final PT visits among SOF/ledipasvir treatment-experienced subjects treated with 3-DAA and RBV in Part 2.

Pharmacokinetic Results:

In DAA-treatment-experienced adults with GT1 HCV infection, subjects without cirrhosis and with compensated cirrhosis have generally overlapping ranges of exposures for each component of the 3-DAA regimen, SOF, and RBV.

Summary/Conclusions (Continued)

Safety Results:

Treatment-emergent adverse events were mild or moderate in severity with the exception of events reported for 2 subjects in Part 1 and 1 subject in Part 2 who experienced severe TEAEs (headache, impaired glucose tolerance, pneumonia).

The most common ($\geq 10.0\%$ of subjects) TEAEs in Part 1 were fatigue, headache, diarrhea, insomnia, dizziness, and nausea. These events were generally assessed as mild in severity and having a reasonable possibility of being related to DAA treatment. In Part 2, fatigue (3 of 7 subjects, 42.9%) was the only TEAE reported for more than 1 subject. The fatigue events were generally assessed as mild in severity and having a reasonable possibility of being related to DAA treatment.

Two (9.1%) subjects in Part 1 (serious adverse events [SAEs] of pneumonia and cellulitis) and none in Part 2 experienced treatment-emergent SAEs. No commonality was evident among the reported serious events (pneumonia and cellulitis for 1 subject each). Neither of these events was assessed by the investigator as having a reasonable possibility of being related to DAA treatment or the RBV.

One subject in Part 1 (due to the SAE of pneumonia) and none in Part 2 discontinued study drug due to a TEAE.

No subject experienced a TEAE that met the criteria for adverse event of special interest, including severe cutaneous reactions (Standardized MedDRA query narrow search) or hepatic decompensation (Product MedDRA query).

One subject in Cohort 1 and 1 subject in Cohort 4 experienced a grade 3 or higher alanine aminotransferase elevation during the Treatment Period, which decreased to grade 1 and the normal reference range, respectively, by the end of treatment. None of the subjects experienced a grade 3 or higher total bilirubin elevation. There was no Hy's law case.

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

Conclusions:

- In Part 1, SVR₁₂ was achieved by 95.5% (21/22) of DAA treatment-experienced subjects infected with HCV GT1b or GT1 non-b who were treated with 3-DAA and SOF, with or without RBV, for 12 weeks or 24 weeks, with a 95% CI of (78.2%, 99.2%).
- In Part 2, SVR₁₂ was achieved by 85.7% (6/7) of SOF/ledipasvir treatment-experienced subjects infected with HCV GT1 who were treated with 3-DAA and RBV for 24 weeks, with a 95% CI of (48.7%, 97.4%).
- In DAA treatment-experienced adults with GT1 HCV infection, subjects without cirrhosis and with compensated cirrhosis had generally overlapping ranges of exposures for each component of the 3-DAA regimen, SOF, and RBV.
- The regimen of 3-DAA, co-administered with or without SOF and RBV, was generally well tolerated, with a pattern of adverse events that was predominantly mild, infrequently serious, and resulted in few discontinuations.