

Randomized Phase 3 Trial of Ombitasvir/Paritaprevir/Ritonavir for HCV Genotype 1b-infected Japanese Patients With or Without Cirrhosis

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List of abbreviations:

HCV, hepatitis C virus; GT, genotype; SVR, sustained virologic response; pegIFN, peginterferon; RBV, ribavirin; DAA, direct-acting antiviral agent; OBV, ombitasvir; NS, nonstructural; PTV, paritaprevir; r, ritonavir; ICH, International Conference on Harmonization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PCR, polymerase chain reaction; LLOQ, lower limit of quantitation; OTVF, on-treatment virologic failure; ULN, upper limit of normal; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse events; RAV, resistance-associated variant; ITT, intent-to-treat; CI, confidence interval; PT-INR, international normalized ratio; TEAE, treatment-emergent adverse event; CCB, calcium channel blocker.

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ABSTRACT

GIFT-I is a phase 3 trial evaluating efficacy and safety of a 12-week regimen of co-formulated ombitasvir(OBV)/paritaprevir(PTV)/ritonavir(r) for treatment of Japanese HCV genotype(GT) 1b-infected patients. GIFT-I consists of a double-blind, placebo-controlled substudy of patients without cirrhosis and an open-label substudy of patients with compensated cirrhosis. Patients without cirrhosis were randomized 2:1 to once daily OBV/PTV/r(25mg/150mg/100mg; Group A) or placebo(Group B). Patients with cirrhosis received open-label OBV/PTV/r(Group C). The primary efficacy endpoint was the rate of sustained virologic response 12 weeks post-treatment(SVR12) in interferon-eligible, treatment-naïve patients without cirrhosis and HCV RNA $\geq 100,000$ IU/ml in Group A. A total of 321 patients without cirrhosis were randomized and dosed with double-blind study drug(106 received double-blind placebo and later received open-label OBV/PTV/r) and 42 patients with cirrhosis were enrolled and dosed with open-label OBV/PTV/r. In the primary efficacy population, the SVR12 rate was 94.6%(106/112; 95% confidence interval 90.5-98.8). SVR12 rates were 94.9%(204/215) in Group A, 98.1%(104/106) in Group B(open-label), and 90.5%(38/42) in Group C. Overall, virologic failure occurred in 3.0%(11/363) of patients who received OBV/PTV/r. The rate of discontinuation due to adverse events was 0-2.4% in the three patient groups receiving OBV/PTV/r. The most frequent adverse event in patients in any group was nasopharyngitis.

Conclusion: In this broad HCV GT1b-infected Japanese patient population with or without cirrhosis, treatment with OBV/PTV/r for 12 weeks was highly effective and demonstrated a favorable safety profile.

In Japan, it is estimated that 2 million people are infected with hepatitis C virus(HCV)(1).

Prevalence of HCV infection increases with age in the Japanese population(2). While HCV genotype(GT) 1a infection is common in North America and Western Europe, in Japan approximately 99% of HCV GT1-infected patients have GT1b(3).

In HCV GT1-infected Japanese patients without cirrhosis, 12-week regimens of simeprevir with pegylated interferon(pegIFN) and ribavirin(RBV) plus 12-36 additional weeks of pegIFN/RBV increased sustained virologic response(SVR) rates compared to pegIFN/RBV alone(4-6).

However, these regimens result in SVR rates of only 36-53% in prior nonresponders, emphasizing the need for more efficacious therapies for this population(5). Simeprevir plus pegIFN/RBV therapy is also subject to treatment-limiting toxicity associated with pegIFN and RBV, including hematologic abnormalities resulting from pegIFN-mediated bone marrow suppression and inhibition of compensatory red blood cell reticulocytosis(7). An IFN/RBV-free regimen of the direct-acting antiviral agents(DAAs) daclatasvir and asunaprevir, which is administered twice daily, has recently been approved in Japan for the treatment of HCV GT1(8, 9). The daclatasvir and asunaprevir regimen eliminates pegIFN-related toxicity and achieves an SVR rate of 80.5% in previous nonresponders, but it has reduced efficacy to 40.5% in patients with baseline Y93 or L31 variants in NS5A and requires 24 weeks of treatment(10). New IFN/RBV-free treatment regimens for Japanese patients with durations as low as 12 weeks are emerging(11, 12).

A phase 2, randomized, open-label trial recently reported the efficacy and safety of the DAAs ombitasvir(OBV, an NS5A inhibitor) and paritaprevir(PTV, a NS3/4A protease inhibitor identified by AbbVie and Enanta that is administered with low-dose ritonavir to increase PTV's peak, trough, and overall drug exposure[PTV/r]) for treatment of HCV GT1b infection in Japanese patients(11). Prior pegIFN/RBV treatment-experienced HCV GT1b-infected Japanese patients without cirrhosis received 100/100mg or 150/100mg PTV/r plus 25mg OBV once daily for 12 or

24 weeks. High SVR12 and SVR24 rates (with a concordance of 100%) and a low rate of discontinuation due to adverse events were observed in HCV GT1b-infected patients regardless of treatment duration or PTV/r dose (11). A regimen of OBV/PTV/r plus the NS5B polymerase inhibitor dasabuvir is approved for treatment of HCV GT1b-infected patients in the United States and Europe. The 2-DAA regimen of OBV/PTV/r is being explored in Japanese patients due to the high prevalence of HCV GT1b and GT2 in Japan, combined with the broad antiviral activity of OBV and PTV and dasabuvir's lack of activity against GT2 (13-15), and the modestly increased PTV exposures observed in Japanese compared to Western patients (16).

Here, we report the efficacy and safety results from the phase 3 GIFT-I study, which examined the IFN- and RBV-free regimen of co-formulated OBV/PTV/r in Japanese treatment-naïve and treatment-experienced HCV GT1b-infected patients with and without cirrhosis.

Patients and Methods

Study Design

GIFT-1 is a phase 3 trial consisting of 2 substudies (1 double-blind and placebo-controlled, 1 open-label; Figure 1) conducted at 54 sites in Japan (ClinicalTrials.gov identifier NCT02023099). The study was approved by all institutional review boards and conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. All patients provided written informed consent before enrolling in the study.

Patient population

Patients were enrolled from December 2013–April 2014. Eligible patients were male or female, treatment-naïve or treatment-experienced (previously treated with an IFN-based therapy [IFN alpha, beta, or pegIFN, with or without RBV]), 18–75 years old, inclusive, with chronic HCV GT1b infection and HCV RNA level $>10,000$ IU/ml. Patients were excluded if they were co-infected with HBV or HIV, were previously treated with a DAA, or had any cause of liver disease other than chronic HCV infection. Substudy 1 enrolled patients with no past or current clinical evidence of cirrhosis. Substudy 2 enrolled patients with compensated cirrhosis (Child-Pugh score A), no clinical history of liver decompensation, serum alpha-fetoprotein ≤ 100 ng/mL, and no evidence of hepatocellular carcinoma on imaging. In each Substudy, presence or absence of cirrhosis was based on liver biopsy, FibroScan, Fibrotest/APRI, or Discriminant score test. Additional details of the eligibility criteria are in the Supplement.

Study Medication

In Substudy 1, patients without cirrhosis were randomized 2:1 to receive double-blind OBV/PTV/r 25mg/150mg/100mg(Group A) or double-blind placebo(Group B) once daily for 12 weeks(Figure 1). Following the double-blind period, patients in Group B received 12 weeks of open-label OBV/PTV/r 25mg/150mg/100mg once daily. The randomization was stratified according to prior IFN-based therapy(naïve versus experienced). Treatment-naïve patients were further stratified by HCV RNA level(<100,000 IU/ml versus ≥100,000 IU/ml, in accordance to definitions of low and high HCV RNA levels by the Japan Society of Hepatology(17)). Patients with HCV RNA ≥100,000 IU/ml were further stratified by eligibility for IFN-based therapy(eligible versus ineligible). Previously IFN-treated patients were further stratified by type of previous response to IFN-based therapy(relapse, nonresponder, or intolerant to IFN-based therapy). The randomization schedule was computer-generated by the sponsor. Sites utilized interactive response technology for randomization of patients to treatment.

The investigators, patients, and sponsor were unaware of the treatment assignment during the double-blind period. To prevent implicit unblinding, investigators, patients, and sponsor were also blinded to levels of HCV RNA, IP-10, alanine aminotransferase(ALT), aspartate aminotransferase(AST), bilirubin(indirect and total), and gamma-glutamyl transferase(GGT). In Substudy 2, patients with compensated cirrhosis were enrolled into Group C and received open-label OBV/PTV/r 25 mg/150 mg/100 mg once daily for 12 weeks.

Efficacy

Plasma HCV RNA levels were determined using COBAS TaqMan® real-time reverse transcriptase-PCR assay v2.0(Roche, Nutley, NJ; lower limit of quantitation[LLOQ], 25 IU/mL; lower limit of detection, 15 IU/mL). The primary efficacy endpoint was SVR12(HCV RNA < LLOQ 12 weeks after end of treatment) in the primary efficacy population(treatment-naïve patients without cirrhosis in Group A who were eligible for IFN-based therapy and had HCV RNA

≥100,000 IU/ml). Secondary efficacy endpoints were on-treatment virologic failure, relapse, and SVR12 rate in subpopulations (1-treatment-naïve patients without cirrhosis and HCV RNA < 100,000 IU/ml; 2-treatment-naïve IFN-ineligible patients without cirrhosis; 3-treatment-experienced patients without cirrhosis with relapse after a prior IFN-based therapy; 4-treatment-experienced patients without cirrhosis who were prior nonresponders to IFN-based therapy; 5-treatment-experienced IFN-intolerant patients without cirrhosis; and 6-patients with compensated cirrhosis). Additional analyses included normalization of ALT in patients without cirrhosis.

The primary analysis reported in this paper was conducted after all patients in Groups A and C reached post-treatment week 12 or prematurely discontinued the study. The primary analysis included efficacy data for Groups A and C, and safety data from double-blind treatment period for Groups A and B and open-label period for Group C. Additional analyses evaluated efficacy and safety data from open-label treatment for Group B after all patients in this group reached post-treatment week 12 or prematurely discontinued the study. The final data for the primary efficacy analysis was collected in October of 2014 and the final data for SVR12 analysis in Group B was collected in January of 2015.

On-treatment virologic failure (OTVF) was defined as confirmed HCV RNA ≥ LLOQ at any point during treatment after HCV RNA < LLOQ, confirmed increase of > 1 log₁₀ IU/ml from nadir in HCV RNA at any point during treatment, or failure to achieve HCV RNA < LLOQ with at least 6 weeks of treatment. Relapse was defined as HCV RNA < LLOQ at the end of treatment with a confirmed HCV RNA ≥ LLOQ between the final treatment visit and 12 weeks after the last dose of study drug, among patients with at least one post-treatment HCV RNA value who completed treatment (study drug duration ≥ 77 days). ALT normalization was defined as a final ALT level ≤ upper limit of normal (ULN) in the double-blind treatment period for patients with ALT > ULN at baseline.

Safety

Adverse events were evaluated at all study visits. Data on all adverse events was collected from the start of study drug administration through 30 days after the last dose of study drug. Serious adverse events are recorded from the time a patient signed the informed consent form through the end of study participation. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0, and their severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse events, Version 4.0 (NCI CTCAE). Clinical laboratory testing was performed at visits during the treatment and post-treatment periods.

Resistance Analyses

Resistance testing was performed on all available patient samples at baseline, and for patients who did not achieve SVR on the first available sample after virologic failure (OTVF or relapse) that had an HCV RNA level ≥ 1000 IU/mL. Resistance-associated variants (RAVs) in NS3/4A (D168E) and NS5A (L28M, R30Q, L31F/M/V, Q54Y, P58S, A92E, Y93H/S) were identified by population sequencing.

Statistical Analysis

Demographic, efficacy, and safety analyses were performed on the intent-to treat (ITT) population, defined as all patients who received at least one dose of double-blind or open-label study drug. Data from Substudies 1 and 2 were analyzed separately. The primary efficacy analysis compared the SVR12 rate in the primary efficacy population to a predefined threshold of 63%, based on the historical SVR rate of 73% in the corresponding population of Japanese patients treated with telaprevir plus pegIFN/RBV (18). Due to the expected safety and tolerability benefits of the IFN-free OBV/PTV/r regimen in Japanese patients (11), a threshold 10% lower

than the historical SVR rate was considered acceptable. To establish superiority, the lower bound of the 95% confidence interval(CI) for the SVR12 rate in the primary efficacy population, calculated using the normal approximation to the binomial distribution, was to exceed 63%.

Based on the considerations for the primary efficacy end point, it was calculated that a sample size of 100 treatment-naïve Japanese patients without cirrhosis who were eligible for IFN-based therapy and had HCV RNA \geq 100,000 IU/ml in the active drug group(Group A) would provide >90% power to demonstrate superiority to the predefined threshold of 63%, assuming an expected SVR12 rate of 95% with the study drug. Additional details of planned sample sizes of subpopulations of interest are provided in Supplemental Table 1. No formal comparisons to an SVR threshold were performed within these subpopulation groups.

Secondary efficacy endpoints were analyzed in patients in Groups A and C who received active study drug. Percentage of patients with SVR12, OTVF, and relapse were also assessed in patients in Group B who received active study drug during the open-label period. Except for the primary analysis of the primary efficacy endpoint, 2-sided 95% CIs for the SVR12 rates were calculated using the Wilson score method.

Rates of ALT normalization, treatment-emergent adverse events and post-baseline grade 3 or 4 laboratory abnormalities during the double-blind treatment period were compared between patients in Groups A and B with a Fisher's exact test. Safety data for Group B and Group C during the open-label treatment period were summarized separately. SAS software version 9.3(SAS Institute, Inc. Cary, NC) for the UNIX operating system was used for all analyses. All statistical tests and CIs were 2-sided with a significance level of 0.05.

RESULTS

Baseline Patient Demographics and Characteristics

Of 467 patients screened, 321 patients without cirrhosis were randomized in Substudy 1 (215 to double-blind OBV/PTV/r [Group A], 106 to double-blind placebo [Group B]) and 42 patients with cirrhosis were enrolled in Substudy 2 (open-label OBV/PTV/r [Group C]) (Figure 1 and Supplemental Figure 1). All enrolled patients received at least one dose of study drug. The baseline characteristics of patients without cirrhosis in Groups A and B (Substudy 1) were generally similar (Table 1). Among patients with cirrhosis (Substudy 2), 78.6% were treatment-experienced, and mean (standard deviation) baseline platelet count, albumin, and international normalized ratio (PT-INR) were $114.2(47.4) \times 10^9$ cells/L, 38.2(3.9) g/L, and 1.060(0.091), respectively.

Virologic Response

Rapid virologic and end of treatment responses and SVR4 for the three patient groups are presented in Supplemental Table 2. SVR12 rates for patients with and without cirrhosis receiving OBV/PTV/r are displayed in Figure 2. In the primary efficacy population, the SVR12 rate was 94.6% (106/112, 95% CI 90.5-98.8). The lower bound of the 95% CI was 90.5%, establishing superiority of the OBV/PTV/r regimen to the predefined threshold (Figure 2). The overall SVR12 rate among patients without cirrhosis in Group A was 94.9% (204/215); the SVR12 rates in all treatment-naïve and treatment-experienced patients were 94.2% (131/139) and 96.1% (73/76) respectively.

The overall SVR12 rate in patients without cirrhosis receiving open-label OBV/PTV/r (Group B) was 98.1% (104/106); SVR12 rates in treatment-naïve and treatment-experienced patients were 98.5% (67/68) and 97.4% (37/38) respectively in this group. The overall SVR12 rate in patients with cirrhosis receiving open-label OBV/PTV/r (Group C) was 90.5% (38/42), including 100% (9/9)

and 87.9%(29/33) in treatment-naïve and treatment-experienced patients, respectively. SVR12 rates for all other predefined subpopulations were greater than 90%(Table 2).

ALT Normalization

In patients without cirrhosis with ALT levels>ULN at baseline, ALT normalized at the end of the double-blind treatment period in a significantly greater proportion in patients receiving OBV/PTV/r versus placebo(94.3%[116/123] versus 18.9%[10/53]; $P<0.001$).

Virologic Failure

Virologic failure(OTVF or relapse) occurred in 3.0%(11/363) of patients who received OBV/PTV/r(double-blind and open-label periods). Virologic failure occurred in 2.8%(6/215), 1.9%(2/106), and 7.1%(3/42) of patients in Groups A, B, and C, respectively. OTVF occurred in 0.5%(1/215), 0.9%(1/106), and 2.4%(1/42) of patients in Groups A, B, and C, respectively. Relapse occurred in 2.4%(5/209), 1.0%(1/105), and 5.0%(2/40) of patients in Groups A, B, and C, respectively. Additional information on patients who experienced virologic failure is in Supplemental Table 3.

Resistance Associated Variants

RAVs in NS3/4 and NS5A were detected in 1% and 38% of patients at baseline, respectively. The most commonly detected NS3A and NS5A RAVs in baseline samples were D168E(4/351, 1%) and Y93H(49/357, 14%), respectively. RAVs were observed in both NS3 and NS5A at the time of virologic failure in 10 of the 11 patients who experienced OTVF or relapse. In NS3, D168V alone or in combination with Y56H was observed in 73%(8/11) of patients, D168A in combination with Y56H was observed in 2 patients, and 1 patient did not have any treatment emergent RAVs in NS3. In NS5A, Y93H was pre-existing in 8 patients and at the time of failure; Y93H alone or in combination with L28M, R30Q, L31M, L31V, and/or P58S was observed in 91%(10/11) of patients; L31F was observed in 1 patient.

Safety

Rates of treatment-emergent adverse events (TEAEs) in the three patient groups are in Table 3.

During the double-blind period, a greater percentage of patients without cirrhosis receiving OBV/PTV/r than placebo experienced TEAEs (68.8% [148 of 215 patients] versus 56.6% [60 of 106 patients], $P < 0.05$) (Table 3). TEAEs were predominantly Grade 1 or 2 in severity. TEAEs occurring with a frequency greater than 5% among patients without cirrhosis during the double-blind period in either treatment group were nasopharyngitis (16.7% [36 patients], OBV/PTV/r; 13.2% [14 patients], placebo), headache (8.8% [19 patients], OBV/PTV/r; 9.4% [10 patients], placebo), and peripheral edema (5.1% [11 patients], OBV/PTV/r; 0%, placebo). The only TEAE significantly more frequent with OBV/PTV/r versus placebo during the double-blind period was peripheral edema. The proportions of serious TEAEs and TEAEs leading to study drug discontinuation were not significantly different in patients receiving OBV/PTV/r versus placebo (3.3% [7 patients] versus 1.9% [2 patients], $P > 0.05$; and 0.9% [2 patients] versus 0%, $P > 0.05$, respectively). TEAEs leading to study drug discontinuation in patients receiving OBV/PTV/r were anuria and hypotension in one patient each.

The TEAE profile in patients without cirrhosis receiving open-label OBV/PTV/r was comparable to that of patients without cirrhosis receiving double-blind OBV/PTV/r (Table 3). TEAEs were predominantly Grade 1 or 2. TEAEs occurring with a frequency greater than 5% in this group were nasopharyngitis (7.5% [8 patients]) and headache (6.6% [7 patients]). Peripheral edema occurred in 3.8% (4 patients) of patients. Serious TEAEs occurred in 2.8% (3 patients) of patients in this group, and no patient discontinued treatment due to TEAEs.

Among patients with cirrhosis receiving open-label OBV/PTV/r, 73.8% (31 of 42 patients) experienced at least 1 TEAE (Table 3). TEAEs were predominantly Grade 1 or 2 in severity. TEAEs occurring with a frequency greater than 5% were nasopharyngitis (14.3% [6 patients]), pyrexia (9.5% [4 patients]), nausea (7.1% [3 patients]), peripheral edema (7.1% [3 patients]),

decreased platelet count(7.1%[3 patients]), and headache(7.1%[3 patients]). Serious TEAEs occurred in 4.8%(2 patients) of patients with cirrhosis. One patient(2.4%) had a serious TEAE(pulmonary edema) that led to study drug discontinuation.

All patients in the study who experienced a TEAE of peripheral edema were using concomitant calcium channel blockers(CCBs). Additional analyses indicated that the incidence of any edema-related TEAEs(defined as peripheral edema, edema, face edema, or pulmonary edema) was related to the use and dose of CCBs(Supplemental Tables 4 and 5).

There were no deaths due to a TEAE in any patient group; however, two deaths occurred more than 30 days after the end of treatment. One patient was a 71-year-old female with compensated cirrhosis who experienced a fatal non-related, non-treatment emergent adverse event of lymphangiosis carcinomatosa on post-treatment Day 76. HCV RNA levels were<LLOQ at all measurements from open-label treatment Day 11 until post-treatment Day 54, the last timepoint measured. The other patient was a 65-year-old female with compensated cirrhosis who achieved SVR12 and experienced a non-related, non-treatment emergent adverse event of hepatocellular carcinoma on Post-treatment Day 84 and died on post-treatment day 253.

Post-baseline laboratory values of grade 3 or higher are presented in Table 3. There were no grade 4 values for any laboratory parameter. One diabetic patient without cirrhosis receiving double-blind OBV/PTV/r had an asymptomatic ALT value>5X ULN, concurrent with acute worsening of glycemia during betamethasone use. ALT peaked at treatment day 57(556 IU/mL) and resolved while continuing DAA treatment. In this patient, discontinuation of betamethasone was followed by decrease of blood glucose levels and ALT declines. This patient completed study drug and achieved SVR12. Another patient without cirrhosis receiving double-blind placebo had elevations in ALT and AST>5X ULN. There were no grade 3 or higher elevations in total bilirubin in patients without cirrhosis. One patient with cirrhosis receiving open-label

OBV/PTV/r had a total bilirubin elevation >3X ULN. This patient was diagnosed with hepatocellular carcinoma on Post-treatment Day 84 and died on post-treatment day 253. No patient met biochemical criteria for Hy's law.

There were no hemoglobin decreases <8 g/dL. No patient received erythropoietin or blood transfusions during the study. No patient had a decrease in platelet count below $50 \times 10^9/L$.

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DISCUSSION

The results from this phase 3 trial in Japanese patients with HCV GT1b infection with or without cirrhosis demonstrated that high SVR rates can be achieved with 12 weeks of the IFN-free and RBV-free regimen of OBV/PTV/r. These high SVR12 rates are comparable with or higher than those reported for other 2-DAA and 3-DAA IFN-free regimens that have been evaluated in Japan, Europe, and the United States(10, 12, 19-28).

A 24-week regimen of daclatasvir once daily and asunaprevir twice daily achieved SVR24 rates of 84.0%(168/200) and 90.9%(20/22) in Japanese HCV GT1b-infected patients without and with cirrhosis, respectively(10). A recent report on 12-week regimens of ledipasvir and sofosbuvir with or without RBV indicated SVR12 rates of 100%(171/171) for the RBV-free and 98%(167/170) for the RBV-containing regimen in Japanese patients(12). In the current study, high SVR12 rates were demonstrated in a broad HCV GT1b-infected Japanese patient population receiving a 12 week regimen of once daily OBV/PTV/r. The rates of discontinuation due to adverse events were comparably low for OBV/PTV/r and other regimens(10, 12).

A low rate of virologic failure(3%, 11/363) was observed in this study; RAVs were observed in both NS3 and NS5A in 10 of 11 patients who experienced virologic failure, including 8 patients who had pre-existing NS5A RAV Y93H. In Japan, it has been reported that the NS5A variant Y93H is present in 8.2%-25% of Japanese HCV GT1b-infected patients(29). The NS5A variant Y93H in GT1b decreased activity of the NS5A inhibitor daclastavir in Japanese patients(10). In an analysis of patients who received ledipasvir and sofosbuvir in phase 3 trials in the United States and Europe, 37 patients(29 GT1a, 8 GT1b) experienced virologic failure(30). Among the 8 GT1b virologic failures, 88%(7/8) had virus with NS5A variants L31I/M/V or Y93H in samples at the time of virologic failure. Three of these 7(43%) HCV GT1b infected-patients were reported to have had baseline NS5A RAVs. Interestingly, the patient who experienced relapse in the study evaluating the efficacy of ledipasvir and sofosbuvir in Japanese patients had HCV GT1b

with NS5A variant Y93H at baseline and at the time of relapse(12). Unfortunately, the study did not provide the frequency of specific NS5A RAVs detected at baseline; thus no assessment can be made about the impact of pre-existing NS5A RAVs to ledipasvir in Japanese patients.

However, the data from the United States and Europe studies suggest a potential impact of NS5A RAVs on the activity of ledipasvir. In our study the frequency of pre-existing Y93H was 14%, and 83% of patients harboring that NS5A RAV achieved SVR12.

In the current trial, 90.5%(38/42) of patients with cirrhosis achieved SVR12. Notably, the 7.1% rate of virologic failure observed in cirrhotic patients in the current study results from only 3 patients experiencing virologic failure. It is unknown whether extending treatment duration or co-administration of RBV would result in increased efficacy in this population or in populations such as patients with baseline RAVs.

The double-blind, placebo-controlled design of Substudy 1 allowed a robust analysis of safety in this trial through a direct comparison between non-cirrhotic patients receiving OBV/PTV/r versus placebo. TEAEs experienced by patients receiving either OBV/PTV/r or placebo during the double-blind period were predominantly Grade 1 or 2 in severity. There was no significant difference between groups in the rate of serious TEAEs or TEAEs leading to discontinuation. Among TEAEs occurring in >5% of patients, only peripheral edema occurred significantly more frequently in patients receiving OBV/PTV/r versus placebo. All patients in this study who experienced peripheral edema were also taking concurrent CCBs. Peripheral edema is known to be associated with CCBs(31). Concomitant administration of OBV/PTV/r with CCBs may result in increased plasma levels of CCBs due to a known drug-drug interaction with ritonavir(32). Post-hoc analyses indicated that frequency of edema-related adverse events in this study was related to dose of CCBs, with patients on the lowest dose of CCBs experiencing a numerically lower frequency of edema-related events. These data suggest that either lowering

the dose of CCBs or substituting with a drug of a different class should be considered during OBV/PTV/r treatment.

An elevation in ALT to >5X ULN occurred in a patient in this study who was receiving concomitant betamethasone. A pharmacodynamic interaction has been observed between ethinyl estradiol and the OBV/PTV/r plus dasabuvir regimen(33), suggesting that this elevation may have been related to steroid use. However, the pattern of increase and resolution of ALT levels in this patient was unlike that previously observed in patients receiving concomitant ethinyl estradiol; therefore, the ALT elevation in this patient was not believed to be related to betamethasone use. Furthermore, reports suggest a relationship between elevated glucose levels and elevated ALT(34, 35), and this ALT elevation occurred in a diabetic patient concurrent with acute worsening of glycemia.

This trial included a double-blind, placebo-controlled substudy, which facilitated a robust comparison of adverse events in patients receiving active regimen versus placebo. However, in groups that received open-label treatment, the open-label design may have impacted reporting of adverse events. Additional limitations are the small number of patients included in some subpopulations, and the exclusion of patients who previously received HCV therapy that included a DAA.

In conclusion, high SVR12 rates were achieved with the IFN- and RBV-free OBV/PTV/r regimen in HCV GT1b-infected Japanese patients. This 2-DAA regimen was well-tolerated with low rates of discontinuation due to TEAEs. Together these results suggest that the OBV/PTV/r regimen is a promising therapeutic option for HCV GT1b-infected patients in Japan.

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Author names in bold designate shared co-first authorship.

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Figure Legends.

Figure 1. GIFT-I Study Design.

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; SVR12, sustained virologic response 12 weeks post-treatment.

*Randomization was 2:1 to Groups A and B.

Figure 2. SVR12 Rates.

SVR12, sustained virologic response 12 weeks post-treatment; DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir.

Error bars represent 95% confidence intervals calculated by normal approximation to the binomial for the primary efficacy population and by Wilson score method for all others. The threshold of 63% (based on the historical telaprevir-based SVR rate) to which the SVR12 rate for the primary efficacy population was compared is marked with a horizontal line on the first column. The primary efficacy population was composed of patients randomized to Group A who received study drug and who were treatment-naïve without cirrhosis, IFN-eligible, and had HCV RNA $\geq 100,000$ IU/ml.

Table 1. Baseline Demographics and Patient Characteristics.

	Substudy 1 Patients without cirrhosis		Substudy 2 Patients with cirrhosis
	Group A DB OBV/PTV/r N=215	Group B DB Placebo N=106	Group C OL OBV/PTV/r N=42
Sex, female; n(%)	135(62.8)	59(55.7)	22(52.4)
Age, yr			
mean(SD)	61.1(9.6)	61.5(9.3)	61.8(8.3)
≥ 65, n(%)	86(40.0)	47(44.3)	21(50.0)
BMI, kg/m ²			
mean(SD)	22.4(3.1)	22.3(2.7)	23.6(3.6)
≥25, n(%)	45 (20.9)*	14(13.2)	13(31.0)
IL28B CC genotype; n(%)	120 (55.8)	54 (50.9)	27(64.3)
HCV RNA level			
log ₁₀ IU/ml, mean(SD)	6.74(0.58)	6.68(0.61)	6.64(0.71)
≥100,000 IU/ml, n(%)	211(98.1)	103(97.2)	41(97.6)
Prior therapy (IFN-status)			
Treatment-naïve, n(%)	139(64.7)	68(64.2)	9(21.4)
IFN-eligible, n/N(%)	116/139(83.5)	58/68(85.3)	NA
IFN-ineligible, n/N(%)	23/139(16.5)	10/68(14.7)	NA
Treatment-experienced [†] , n(%)	76(35.3)	38(35.8)	33(78.6)
Relapser, n/N(%)	22/76(28.9)	11/38(28.9)	8/33(24.2)
Nonresponder, n/N(%)	28/76(36.8)	14/38(36.8)	19/33(57.6)
IFN-intolerant, n/N(%)	26/76(34.2)	13/38(34.2)	5/33(15.2)
Baseline fibrosis stage			
F0-F1, n/N(%)	49/82(59.8)	23/31(74.2)	0
F2, n/N(%)	17/82(20.7)	1/31(3.2)	0
F3, n/N(%)	16/82(19.5)	7/31(22.6)	1(2.4) [‡]
F4, n/N(%)	0	0	41(97.6)
Missing data [§] , n	133	75	0

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; SD, standard deviation; BMI, body-mass index; IFN, interferon; NA, not available.

*Statistically significant difference between Group A and Group B(placebo) using chi-square test at $P=0.05$ level.

[†]One treatment-experienced patient with cirrhosis had a missing response type.

[‡]Discriminant score at Screening indicated presence of cirrhosis, but FibroTest at baseline indicated Stage F3.

[§]Values were missing for a total of 208 patients whose cirrhosis status(yes/no) was determined by serum discriminant score, which does not differentiate between Metavir scores F0 to F3.

Table 2. SVR12 Rates in Subpopulations of Patients Without Cirrhosis.

	Group A DB OBV/PTV/r N=215		Group B OL OBV/PTV/r N=106	
	n/N	% (95% CI)	n/N	% (95% CI)
All patients without cirrhosis	204/215	94.9 (91.1-97.1)	104/106	98.1 (93.4-99.5)
Treatment-naïve	131/139	94.2 (89.1-97.1)	67/68	98.5 (92.1-99.7)
HCV RNA< 100,000 IU/mL	6/6	100 (61.0-100)	2/2	100 (34.2-100)
IFN ineligible	21/23	91.3 (73.2-97.6)	9/10	90.0 (59.6-98.2)
Treatment-experienced	73/76	96.1 (89.0-98.6)	37/38	97.4 (86.5-99.5)
Relapser	21/22	95.5 (78.2-99.2)	10/11	90.9 (62.3-98.4)
Nonresponder	28/28	100 (87.9-100)	14/14	100 (78.5-100)
IFN Intolerant	24/26	92.3 (75.9-97.9)	13/13	100 (77.2-100)

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; IFN, interferon.

HCV RNA<100,000 IU/ml and IFN ineligible were not mutually exclusive. 95% CIs were calculated using Wilson score method.

Table 3. Overview of Treatment-Emergent Adverse Events and Laboratory Value Abnormalities in Patients With and Without Cirrhosis.

	Substudy 1 Patients without cirrhosis			Substudy 2 Patients with cirrhosis
	Group A DB OBV/PTV/r N=215	Group B DB Placebo N=106	Group B OL OBV/PTV/r N=106	Group C OL OBV/PTV/r N=42
Any treatment-emergent adverse event (TEAE), n(%)	148(68.8)*	60(56.6)	68(64.2)	31(73.8)
TEAE leading to discontinuation, n(%)	2(0.9)	0	0	1(2.4)
Serious TEAE [†] , n(%)	7(3.3)	2(1.9)	3(2.8)	2(4.8)
Common TEAEs [‡] , n(%)				
Nasopharyngitis	36(16.7)	14(13.2)	8(7.5)	6(14.3)

Headache	19(8.8)	10(9.4)	7(6.6)	3(7.1)
Peripheral edema	11(5.1)*	0	4(3.8)	3(7.1)
Nausea	9(4.2)	4(3.8)	1(0.9)	3(7.1)
Pyrexia	4(1.9)	1(0.9)	1(0.9)	4(9.5)
Decreased platelet count	0	0	0	3(7.1)
Post-baseline abnormalities in laboratory values (Grade 3 or higher), n/N(%)				
ALT, >5X ULN	1/213(0.5)	1/106(0.9)	0	0
AST, >5X ULN	0	1/106(0.9)	0	0
Total bilirubin, >3X ULN	0	0	0	1/42(2.4)
Hemoglobin, <8 g/dL	0	0	0	0

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir ; ALT, alanine

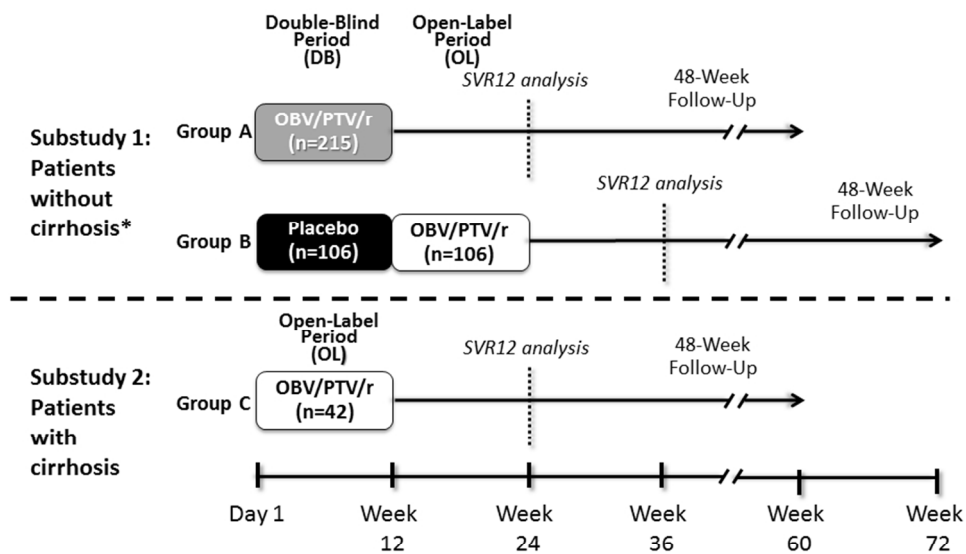
aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal. The only statistical

comparisons of safety data performed were between Groups A and B during the double-blind period.

* $P < 0.05$ Fisher's exact test (A versus B during the double-blind period).

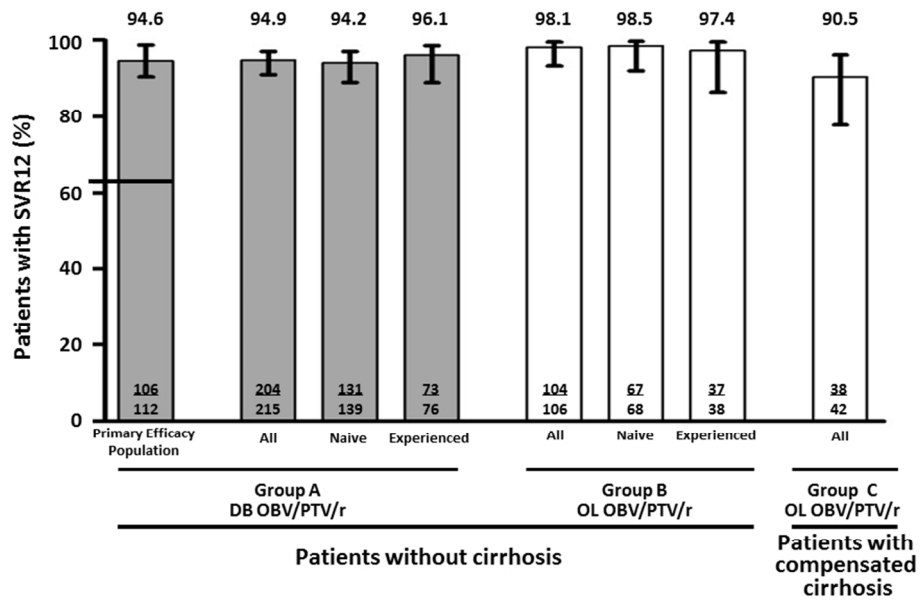
†Definition in Supplement.

‡Occurring in more than 5% of patients in any group.



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Diagnosis and Main Criteria for Inclusion/Exclusion:**Main Inclusion:**

- Japanese male or female and age is between 18 and 75 years, inclusive, at time of screening.
- Chronic HCV infection at prior to study enrollment. Chronic HCV infection is defined as one of the following:
 - Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCVAb at the time of Screening; or
 - Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection at or prior to Screening.
- Patient has plasma HCV RNA level > 10,000 IU/mL at Screening.
- Patient must be:
 - Non-cirrhotic naïve patient, as defined as a patient who has never received any HCV treatment and meet one of the following categories;
 - Naïve eligible patient will be defined as naïve patient who is considered by the investigator to be a good candidate to receive an IFN-based therapy [IFN (alpha, beta or pegIFN) with or without RBV]; or
 - Naïve ineligible patient will be defined as naïve patient who is considered by the investigator to be a poor candidate to receive an IFN-based therapy [IFN (alpha, beta or pegIFN) with or without RBV], due to medical reasons, such as, but not limited to, advanced age, depression, myelosuppression, diabetes, autoimmune disease, retinopathy or cardiovascular or renal dysfunction;

OR

Non-cirrhotic experienced patient, as defined as a patient who has documentation of prior IFN-based therapy [IFN (alpha, beta or pegIFN) with or without RBV] and meet one of the following categories:

- Nonresponder: received at least 12 weeks of IFN-based therapy for the treatment of HCV and failed to achieve undetectable HCV RNA (HCV RNA < LLOD) at the end of treatment; or
- Relapser: received IFN-based therapy for the treatment of HCV and was undetectable at or after the end of treatment, but subsequently had detectable HCV RNA within 52 weeks of treatment follow-up; or
- IFN Intolerant: treatment of HCV was discontinued during the treatment period due to intolerance to any of the components of the IFN-based therapy.

OR

Cirrhotic naïve patient, as defined as a patient who has never received any HCV treatment,

OR

Cirrhotic experienced patient, as defined as a patient who has documentation of prior IFN-based therapy [IFN (alpha, beta or pegIFN) with or without RBV].

- Screening laboratory result from central clinical laboratory indicating HCV subgenotype 1b-infection without co-infection with any other genotype/subgenotype.
- Patients randomized in Substudy 1 will be non-cirrhotic, defined by the results of one of the following, performed according to local standard practice:
 - A liver biopsy during or within 24 months prior to screening demonstrating the absence of cirrhosis, e.g., a Metavir or New Inuyama Score ≤ 3 , or an Ishak score ≤ 4 ; or
 - In the absence of a biopsy within the 24 months prior to screening or performed during the screening period:
 - A screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2 ; or
 - A screening transient elastography (e.g., FibroScan) result of < 12.5 kPa; or

- A screening Discriminant Score (z) less than zero, according to the following formula: $z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate } (\mu\text{g}\times\text{l-1})] - 0.075 \times [\text{platelet } (\times 10^4 \text{ cells/mm}^3)] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$

Patients with a FibroScan result that is ≥ 12.5 kPa and < 14.6 KPa; or a FibroTest result that is ≤ 0.72 and an APRI > 2 ; **or** a FibroTest result that is ≥ 0.73 and an APRI ≤ 2 ; **or** a Discriminant Score = 0, must have a liver biopsy performed within 24 months prior to screening showing no evidence of cirrhosis, or in the absence of an available biopsy result within 24 months prior to screening, may undergo a liver biopsy during screening to rule out cirrhosis. The result of the liver biopsy will be considered the decisive result for study eligibility and patients may be enrolled only if the biopsy performed within the previous 24 months or during the Screening period shows no evidence of cirrhosis.

- Patients enrolled in Substudy 2 will have cirrhosis, defined by the results of one of the following, performed according to local standard practice:
 - Liver biopsy within the 24 months prior to screening or performed during the screening period demonstrating the presence of cirrhosis [e.g., Metavir Score or New Inuyama Score > 3 (including 3-4 or 3/4) or an Ishak score > 4]; or
 - In the absence of a biopsy within the 24 months prior to screening or performed during the screening period, patients could have one of the following performed and must have demonstrated the qualifying result, as follows
 - A screening FibroTest ≥ 0.73 and APRI > 2 ; or
 - A FibroScan score ≥ 14.6 kPa within 6 months of screening or during the screening period; or
 - A screening Discriminant Score (z) greater than zero, according to the following formula: $z = 0.124 \times [\text{gamma-globulin (\%)}] + 0.001 \times [\text{hyaluronate } (\mu\text{g}\times\text{l-1})] - 0.075 \times [\text{platelet } (\times 10^4 \text{ cells/mm}^3)] - 0.413 \times \text{gender (male, 1; female, 2)} - 2.005$

Patients with a FibroScan result that is ≥ 12.5 kPa and < 14.6 KPa; or a FibroTest result that is ≤ 0.72 and an APRI > 2 ; **or** a FibroTest result that is ≥ 0.73 and an APRI ≤ 2 ; **or** a Discriminant Score = 0, must have a liver biopsy performed within 24 months prior to screening showing evidence of cirrhosis, or in the absence of an available biopsy result within 24 months prior to screening, may undergo a liver biopsy during screening to demonstrate the presence of cirrhosis. The result of the liver biopsy will be considered the decisive result for patient eligibility and patients may be enrolled only if the biopsy performed within the previous 24 months or during the Screening period shows evidence of cirrhosis.

- Patients enrolled in Substudy 2 will have compensated cirrhosis defined by a Child-Pugh score of ≤ 6 at Screening.

Main Exclusion:

- Positive test result at screening for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).
- As per central clinical laboratory results, patient's HCV subgenotype at Screening is not subgenotype 1b, cannot be determined or indicates co-infection of subgenotype 1b with any other HCV genotype.
- Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational or commercially available anti-HCV therapy (other than interferon (alpha, beta or pegIFN) with or without RBV) including previous exposure to telaprevir, boceprevir, simeprevir, ABT-450, ABT-267.

For non-cirrhotic patients ONLY:

- Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior biopsy showing cirrhosis, e.g., a Metavir score or New Inuyama score >3 or an Ishak score of > 4.
- Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 5 × ULN
- Estimated Glomerular filtration rate adjusted for Japanese population (eGFR_j) < 50 mL/min/1.73m² as estimated by the MDRD method, according to the following formula: $eGFR_j = 194 \times \text{Serum Creatinine}^{-1.094} \times \text{Age}^{-0.287} (\times 0.739, \text{ if female})$
- Albumin < Lower limit of normal (LLN)
- International normalized ration (INR) > 1.5. Patients with a known inherited blood disorder and an INR > 1.5 may be enrolled only with approval of the AbbVie Study Designated Physician.
- Hemoglobin < LLN
- Platelets < 90,000 cells/mm³
- Absolute neutrophil count (ANC) < 1500 cells/μL
- Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

For cirrhotic patients ONLY:

- Any current or past clinical evidence of a Child-Pugh B or C Classification or any clinical history of liver decompensation, such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
- Presence of hepatocellular carcinoma on imaging technique (either a positive ultrasound confirmed by CT/MRI or a positive CT scan or MRI) within 3 months prior to screening or during screening
- Alanine aminotransferase (ALT) > 7 × upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 7 × ULN
- eGFR_j < 50 mL/min/1.73m² as estimated by the MDRD method corrected for the Japanese population.
- Albumin < 2.8 g/dL
- International normalized ration (INR) > 2.3 (patients with a known inherited blood disorder and INR > 2.3 may have been enrolled with approval of the Sponsor Study Designated Physician).
- Hemoglobin < LLN
- Platelets < 60,000 cells per mm³
- Absolute neutrophil count (ANC) < 1500 cells/μL
- Total bilirubin ≥ 3.0 mg/dL

Data imputation for HCV RNA endpoints

Missing data were imputed via a flanking imputation method, whereby the closest HCV RNA value before or after the study visit window was used. If a HCV RNA value at a post-baseline visit was missing, but the patient had an undetectable or unquantifiable HCV RNA level at both the preceding value and succeeding value, the HCV RNA level was imputed as undetectable or unquantifiable, respectively, at that visit. In addition, if the patient had an unquantifiable HCV RNA level at the preceding value and an undetectable HCV RNA level at the succeeding value, or vice versa, the HCV RNA level was imputed as unquantifiable at this visit. For SVR12

analyses, if there was no value in the appropriate window after the flanking imputation, a backward imputation approach was used such that if the nearest HCV RNA value after the SVR window was unquantifiable or undetectable, then it was used to impute the response in the SVR window. Patients with missing HCV RNA data in the analysis window after imputations were considered as failures.

Serious Adverse Events

Serious adverse events were defined as events that resulted in the death of the patient, were considered by the investigator to be life-threatening, resulted in hospitalization or prolongation of hospitalization, or resulted in persistent or significant disability/incapacity. Any important medical event requiring medical or surgical intervention to prevent serious outcome or any congenital anomaly was also considered a serious adverse event.

Supplemental Table 1. Summary of Approximate Patient Numbers Expected to be Enrolled by Subpopulation.

Subpopulation	Double-Blind OBV/PTV/r	Double-Blind Placebo	Open-Label OBV/PTV/r	Total
Non-cirrhotic naïve patients	125	60	--	185
Naïve, high viral load, IFN-eligible	100	50	--	150
Naïve, IFN-ineligible	20	10	--	30
Naïve, low viral load	≤5	≤5	--	~5
Non-cirrhotic experienced patients	60	30	--	90
Experienced, relapser	20	10	--	30
Experienced, nonresponder	20	10	--	30
Experienced, IFN-intolerant	20	10	--	30
Cirrhotic	--	--	37	37
Total	~185	~90	~37	~312

OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; IFN, interferon.

Supplemental Table 2. Rates of Rapid Virologic Response (RVR), End of Treatment Response, and Sustained Virologic Response 4 Weeks Post-treatment (SVR4).

n/N (%)	Substudy 1 Patients without cirrhosis		Substudy 2 Patients with compensated cirrhosis
	Group A DB OBV/PTV/r N=215	Group B OL OBV/PTV/r N=106	Group C OL OBV/PTV/r N=42
RVR	208/215 (96.7)	105/106 (99.1)	39/42 (92.9)
EOTR	208/215 (96.7)	105/106 (99.1)	41/42 (97.6)
SVR4	205/215 (95.3)	104/106 (98.1)	40/42 (95.2)

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; IFN, interferon.

RVR was defined as HCV RNA < LLOQ in the week 4 window. EOTR was defined as HCV RNA < LLOQ in the week 12 window. SVR4 was defined as HCV RNA < LLOQ in the SVR4 window (4 weeks after the last actual dose of study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window.

Supplemental Table 3. Characteristics of Patients Who Experienced Virologic Failure.

Patient	Reason for non-response	Prior IFN treatment status	Sex	Age (y)	BMI (kg/m ²)	IL28B Genotype	Baseline Fibrosis Stage	HCV RNA (log ₁₀ U/mL)	
								Baseline	Final Treatment Visit
<i>Substudy 1: Patients without cirrhosis- Group A (DB OBV/PTV/r)</i>									
1	On-treatment virologic failure	Treatment-experienced (IFN-intolerant)	Male	54	26.0	CT	NA	7.45637	5.80821
2	Relapse	Treatment-naïve (IFN-eligible)	Male	47	25.4	CC	NA	7.22789	<1.17609
3	Relapse	Treatment-naïve (IFN-eligible)	Male	54	20.6	CC	NA	7.15836	<1.17609
4	Relapse	Treatment-naïve (IFN-ineligible)	Female	66	23.1	CC	NA	6.97267	<1.17609
5	Relapse	Treatment-naïve (IFN-eligible)	Male	60	23.0	CC	NA	7.38382	<1.17609
6	Relapse	Treatment-experienced (IFN-intolerant)	Female	56	20.6	CT	NA	7.44716	<1.17609
<i>Substudy 1: Patients without cirrhosis- Group B (OL OBV/PTV/r)</i>									
7	On-treatment virologic failure	Treatment-experienced (relapser)	Male	74	22.8	CC	NA	7.05308	3.42160
8	Relapse	Treatment-naïve (IFN-ineligible)	Female	73	24.3	CT	NA	7.41497	<1.17609
<i>Substudy 2: Patients with cirrhosis- Group C (OL OBV/PTV/r)</i>									
9	On-treatment virologic failure	Treatment-experienced (nonresponder)	Female	69	22.6	CC	F4	7.71767	7.28103
10	Relapse	Treatment-experienced (relapser)	Female	66	22.3	CC	F4	6.88423	<1.17609
11	Relapse	Treatment-experienced (nonresponder)	Female	59	27.7	CC	F4	6.71600	<1.17609

IFN, interferon; BMI, body-mass index; DB, double-blind; OL, open-label; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir. NA, not available (these patients were enrolled based on discriminant score).

Supplemental Table 4. Frequency of Treatment-Emergent Edema-related Adverse Events by Calcium Channel Blocker Use.

	Substudy 1 Patients without cirrhosis			Substudy 2 Patients with compensated cirrhosis
n/N (%)	Group A DB OBV/PTV/r	Group B DB Placebo	Group B OL OBV/PTV/r	Group C OL OBV/PTV/r
Calcium channel blocker use				
Yes	13/51 (25.5)	0/24	5/23 (21.7)	4/10 (40.0)
No	2/164 (1.2)	0/82	0/83	0/32

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir.

n/N, number of patients with edema-related adverse events/total number of patients within calcium channel blocker use subgroup. Edema-related adverse events were defined as peripheral edema, edema, face edema, or pulmonary edema.

Supplemental Table 5. Frequency of Treatment-Emergent Edema-related Adverse Events According to Calcium Channel Blocker Dose.

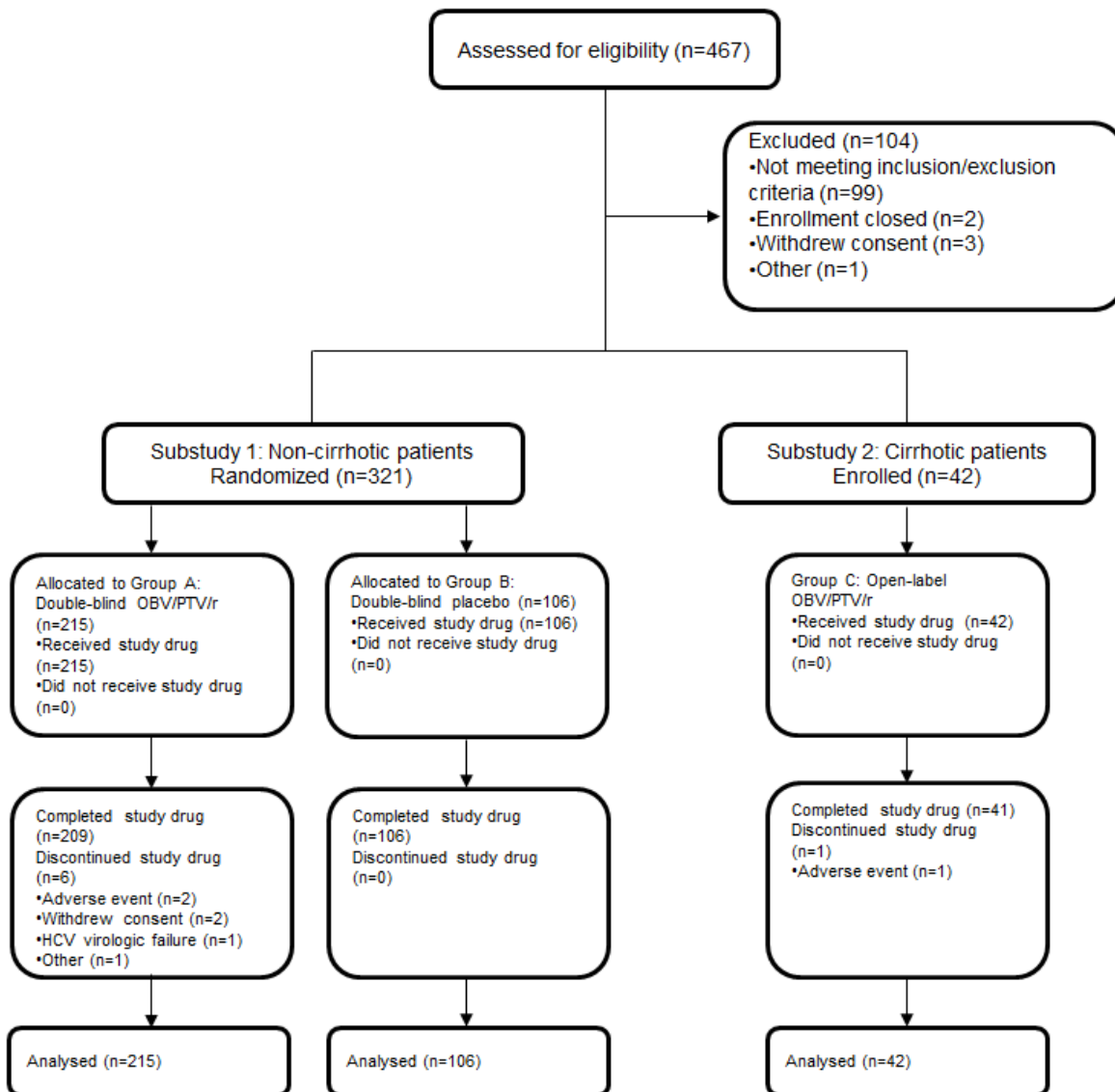
	Substudy 1 Patients without cirrhosis			Substudy 2 Patients with compensated cirrhosis	All Patients
n/N (%)	Group A DB OBV/PTV/r	Group B OL OBV/PTV/r	Group A (DB) + Group B (OL) OBV/PTV/r	Group C OL OBV/PTV/r	Group A (DB) + Group B (OL) + Group C (OL) OBV/PTV/r
Lowest CCB dosage*					
Yes	2/20 (10.0)	1/8 (12.5)	3/28 (10.7)	0/2	3/30 (10.0)
No	11/31 (35.5)	4/15 (26.7)	15/46 (32.6)	4/8 (50.0)	19/54 (35.2)

DB, double-blind; OL, open-label; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; CCB, calcium channel blocker.

n/N, patients with edema-related adverse events/total number of patients in subgroup. Edema-related adverse events were peripheral edema, edema, face edema, or pulmonary edema.

*Lowest dose of CCB was defined as the lowest CCB dose that could be administered based on the relevant prescribing information. CCB dose was assessed either (1) at the time of the edema-related AE or (2) if there was no edema-related AEs, as the dose of CCB that was administered for > 50% of the study duration.

Supplemental Figure 1. Patient Disposition.



OBV, ombitasvir; PTV, paritaprevir; r, ritonavir.

For those patients who were excluded or discontinued study drug, each reason for exclusion or discontinuation is given. Therefore, the sum of the counts given for the reasons may be greater than the overall number of patients excluded or patients who discontinued study drug. All 106 patients in Arm B also completed open-label study drug and were included in analyses. There was one patient each in Arm B and C who experienced on-treatment virologic failure; neither of these patients prematurely discontinued study drug as they experienced rebound late in treatment and did not have confirmation of increased viral load until after study drug completion.