Contents

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 × [gamma-globulin (%)] + 0.001 × [hyaluronate (µg×l-1)] - 0.075 × [platelet (× 104 cells/mm3)] - 0.413 × 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 × [gamma-globulin (%)] + 0.001 × [hyaluronate (µg×l-1)] - 0.075 × [platelet (× 104 cells/mm3)] - 0.413 × 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 Inuyma 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 (eGFRj) < 50 mL/min/1.73m2 as estimated by the MDRD method, according to the following formula: eGFRj = 194 × Serum Creatinine-1.094 × Age-0.287 (× 0.739, 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
- eGFRj < 50 mL/min/1.73m^2 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 mm^3
- 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).

	Substudy 1 Patients without cirrhosis		**Substudy 2 Patients with compensated cirrhosis**
n/N (%)	**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 (>= 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
Substudy 1: Patients without cirrhosis- Group A (DB OBV/PTV/r)									
1	On-treatment virologic failure	Treatment-experienced (IFN-intolerant)	Male	54	26.0	CT	NA	7.45637	5.80821
2	Relapse	Treatment-naive (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
Substudy 1: Patients without cirrhosis- Group B (OL OBV/PTV/r)									
7	On-treatment virologic failure	Treatment-experienced (relapser)	Male	74	22.8	CC	NA	7.05308	3.42160
8	Relapse	Treatmen-naïve (IFN-ineligible)	Female	73	24.3	CT	NA	7.41497	<1.17609
Substudy 2: Patients with cirrhosis- Group C (OL OBV/PTV/r)									
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.

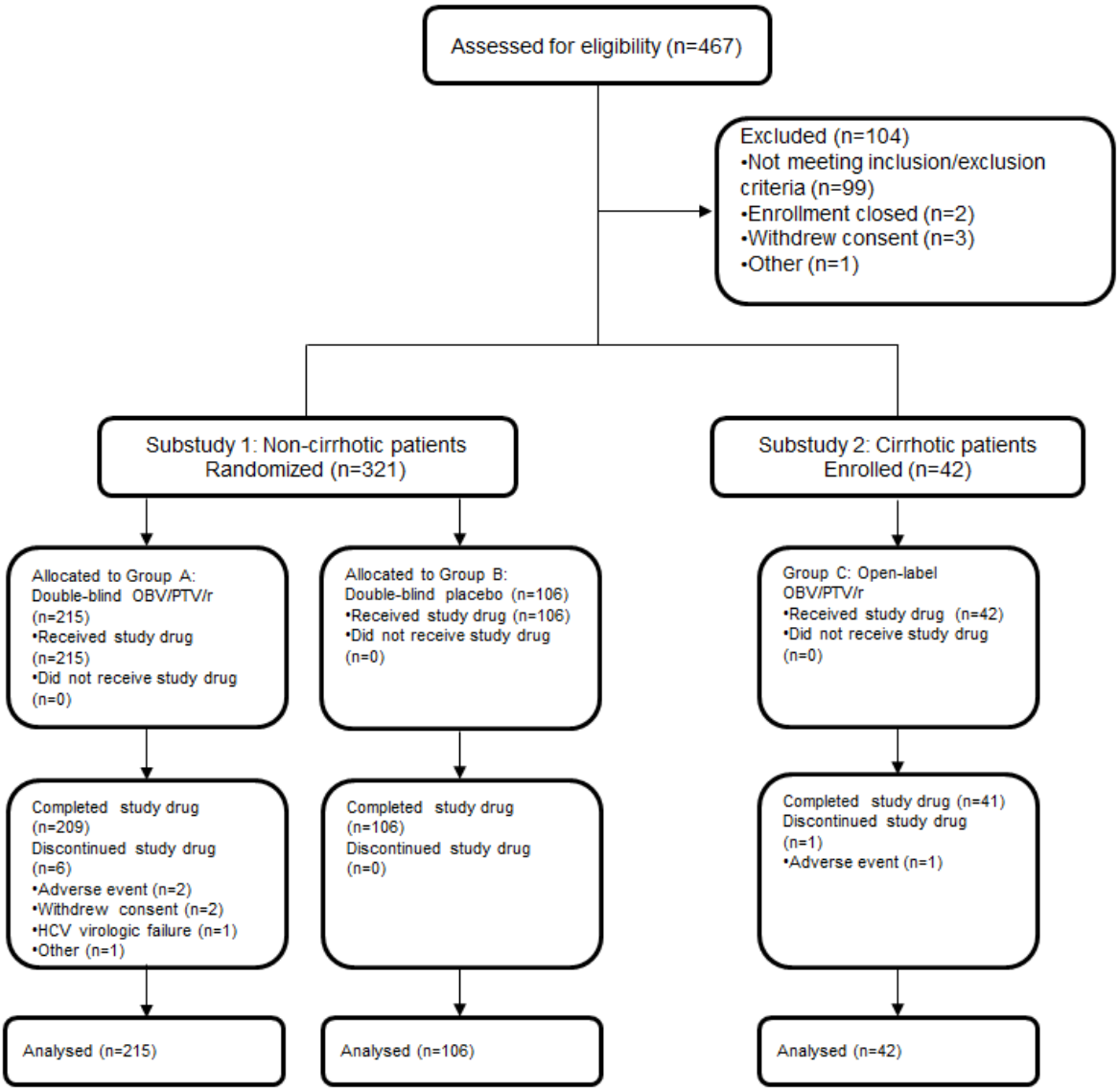
	Substudy 1 Patients without cirrhosis			Substudy 2 Patients with compensated cirrhosis	All Patients
n/N (%)	Group A DB OBV/PTV/r	Group B OL OBV/PTV/r	Group A (DB) + Group B (OL) OBV/PTV/r	Group C OL OBV/PTV/r	Group A (DB) + Group B (OL) + Group C (OL) OBV/PTV/r
Lowest CCB dosage*					
Yes	2/20 (10.0)	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 of 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.