Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Online Supporting Information

Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment

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Table of contents

ABT-493 was identified by AbbVie and Enanta Pharmaceuticals.

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Eligibility Criteria

Inclusion

- Male or female, at least 18 years of age at time of screening
- Female who is:
    - Practicing total abstinence from sexual intercourse or;
    - Sexually active with female partners only or;
    - Not of childbearing potential or;
    - Uses at least two effective methods of birth control while receiving study drugs
- Sexually active males must be surgically sterile or have male partners only, or must use at least two effective methods of birth control
- Estimated glomerular filtration rate of <30 mL/min/1.73 m^2
- Screening laboratory result indicating HCV genotype 1, 2, 3, 4, 5, or 6 infection
- Patient has positive anti HCV antibody and plasma HCV RNA load ≥1000 IU/mL at screening visit
- Chronic HCV infection defined as one of the following:
    - Positive for anti-HCV Ab or HCV RNA at least 6 months before screening
    - A liver biopsy consistent with chronic HCV infection
    - Abnormal alanine aminotransferase (ALT) levels for at least 6 months before screening
- Patient must be HCV treatment-naïve or have received prior treatment with interferon/pegylated interferon with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated interferon
- Body Mass Index (BMI) is ≥18 kg/m^2 at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m)
- Patient must be documented as non-cirrhotic or having compensated cirrhosis (defined below)
- For patients with cirrhosis: absence of hepatocellular carcinoma as indicated by serum alpha-fetoprotein <100 ng/mL at screening and a negative ultrasound, computed tomography scan, or magnetic resonance imaging within 3 months prior to screening, or a negative ultrasound at screening
- For patients with cirrhosis: Child-Pugh score of ≤6 at screening and no current or past clinical evidence of Child-Pugh B or C classification or clinical history of decompensation, including ascites, bleeding varices, portal hypertension or hepatic encephalopathy
- Patient must voluntarily sign and date informed consent form, approved by an institutional review board/independent ethics committee prior to the initiation of any screening or study-specific procedures
- Patient must be able to understand and adhere to the study visit schedule and all other protocol requirements

Exclusion

- Female who is pregnant, breastfeeding, or planning to become pregnant during the study; or male whose partner is pregnant or planning to become pregnant during the study
- Recent history (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator
- Patients on peritoneal dialysis (removed with amendment 2)
- Positive test result at screening for hepatitis B surface antigen (HBsAg) or anti-human immunodeficiency virus antibody (HIV Ab)
- HCV genotype performed during screening indicating co-infection with more than one HCV genotype
- Patients who failed a previous regimen containing protease inhibitors or NS5A inhibitors

- Clinically significant abnormalities other than HCV infection, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12 lead electrocardiogram that make a patient unsuitable for the study in the opinion of the investigator, including, but not limited to:
    - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma *in situ*) in the past 5 years
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection
- Any cause of liver disease other than chronic HCV infection, including but not limited to the following:
    - Hemochromatosis
    - Alpha-1 antitrypsin deficiency
    - Wilson's disease
    - Autoimmune hepatitis
    - Alcoholic liver disease
    - Seatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental HCV infection
- Screening laboratory analyses showing any of the following abnormal laboratory results:
    - ALT >10 × upper limit of normal (ULN)
    - AST >10 × ULN
    - Total bilirubin ≥3.0 mg/dL
    - Albumin <2.8 g/dL
    - International Normalized Ratio (INR) >2.3, unless patient has known hemophilia or is on a stable anticoagulant regimen affecting INR
    - Hemoglobin <10 g/dL
    - Platelets <40,000 cells per mm^3
    - Absolute Neutrophil Count (ANC) <1000 cells/µL
- History of solid organ transplant, unless the implanted organ has since been removed and patient is no longer on immunosuppressive medication
- Clinical history of acute renal failure in 3 months prior to screening
- Planned renal transplant during the course of the study (treatment and post-treatment)
- Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks, whichever is longer, prior to study drug administration
- The use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 2 months of screening
- Requirement for chronic use of systemic immunosuppressants during the study
- Consideration by the investigator, for any reason, that the patient is unsuitable to receive GLE, PIB, SOF, or DCV
- History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs
- Patients who can't participate in the study per local law

Cirrhosis Determination

No Cirrhosis:

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell (Histologic Activity Index; Fibrosis component), IASL, Scheuer, or Laennec fibrosis score of ≤3, Ishak (modified Knodell) fibrosis score of ≤4; or
    - A FibroScan score of <12.5 kPa within 6 months prior to Screening or during the Screening Period; or
        - Patients with indeterminate FibroScan score (12.5 ≤ score < 14.6) must have qualifying liver biopsy
- A screening FibroTest score of ≤0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) <1;
    - Patients with non-qualifying/conflicting FibroTest and APRI results (e.g., FibroTest ≤0.48, but APRI ≥1) must have a qualifying liver FibroScan or biopsy

Compensated Cirrhosis:

- Histologic diagnosis of cirrhosis on a previous liver biopsy (eg, METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤3 or Ishak fibrosis score of >4)
- Screening FibroTest score ≥0.75 and an APRI >2
    - Patients with indeterminate FibroTest (0.48 < results < 0.75), or conflicting FibroTest and APRI results must have a qualifying liver Fibroscan or biopsy
- Previous FibroScan score ≥14.6 kPa;
    - Patients with indeterminate FibroScan score (12.5 ≤ score < 14.6) must have qualifying liver biopsy

Chronic Kidney Disease Staging and Eligibility

Based on the Modification of Diet in Renal Disease study equation, patients must have had an estimated glomerular filtration rate of less than 30 milliliters per minute per 1.73 meters squared.

- **Stage 4 chronic kidney disease:** estimated glomerular filtration rate between 29 and 15 milliliters per minute per 1.73 meters squared
- **Stage 5 chronic kidney disease:** estimated glomerular filtration rate less than 15 milliliters per minute per 1.73 meters squared

HCV Genotype, Subtype, and RNA Measurement

Plasma samples for HCV genotype and subtype determination will be collected at screening. Genotype and subtype will be assessed using the Versant® HCV Genotype Inno LiPA Assay, version 2.0 or higher. If the LiPA assay is unable to determine genotype, it will be determined by a Sanger sequencing assay of NS5B region.

Plasma HCV RNA levels were determined for each collected sample using the COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0. The lower limit of detection and lower limit of quantification for this assay are both 15 IU/mL.

Resistance-associated Variants

Variants at any of the following amino acid positions were included in the analysis:

- **NS3:** 155, 156, and 168.
- **NS5A:** 24, 28, 30, 31, 58, 92, and 93.

SVR12, Virologic Stopping, and Futility Criteria

Patients that achieved SVR12 were those with HCV RNA less than the lower limit of quantification throughout the SVR12 window (post treatment day 57 to 126) without confirmed quantifiable HCV RNA before that window.

Patients were required to stop treatment with study drugs if they met any of the following criteria:

- Confirmed increase from nadir in HCV RNA, defined as 2 consecutive HCV RNA measurements (>1 $\log_{10}$ IU/mL above nadir) at any time point during treatment
- Confirmed HCV RNA ≥100 IU/mL, defined as 2 consecutive HCV RNA measurements ≥100 IU/mL, after HCV RNA was measured at less than LLOQ during treatment

Pharmacokinetic Analysis:

Optional Intensive Pharmacokinetic Sampling:

N=6 non-cirrhotic subjects with CKD Stage 5 requiring hemodialysis participated in additional pharmacokinetic sampling. On a visit during treatment Week 4, hemodialysis was initiated two hours after study drug administration and continued for approximately 4 hours. During dialysis, plasma samples were collected at 2 hours after study drug administration (immediately prior to dialysis) and from predialyzer (arterial) and postdialyzer (venous) sources at 3, 4, 5, and 6 hours after study drug administration (1, 2, 3, and 4 hours after the start of dialysis, respectively).

Pharmacokinetic Evaluation:

Plasma concentrations of glecaprevir and pibrentasvir were quantified with validated assay methods. The lower limit of quantification for each analyte was 1.0 ng/mL. The area under the curve from the start of dialysis until the last measurable concentration (AUC_t) was determined for arterial and venous plasma samples collected during hemodialysis. Central value ratios and 90% confidence intervals (CI) were estimated by repeated measures analyses of the natural logarithms of AUC_t in venous and arterial plasma using SAS, Version 9.2 (Cary, NC) for all analytes.

Patient Reported Outcomes:

Patient reported outcomes were also measured in this trial (see protocol); those assessments will be analyzed and reported in a separate, future publication.

Figure S1

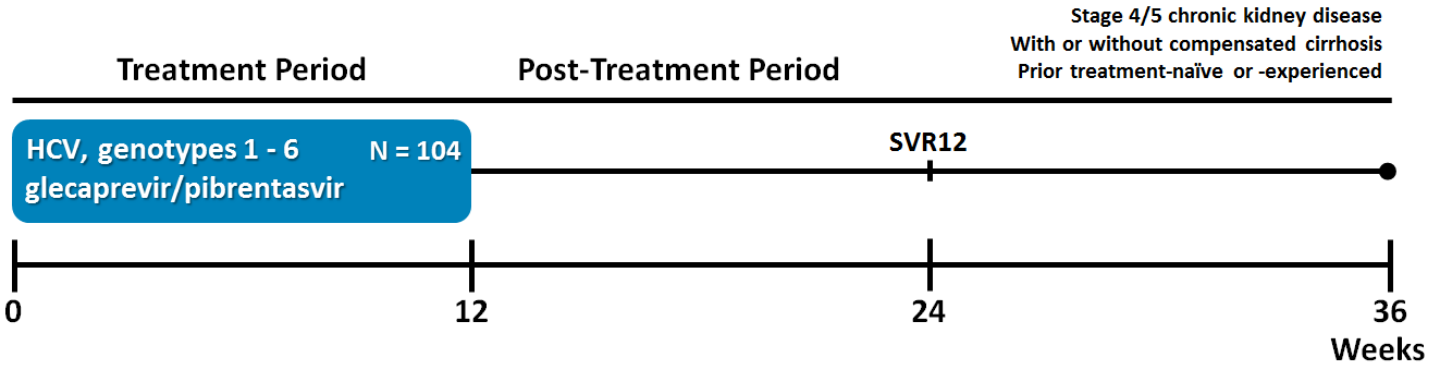

Figure S1. EXPEDITION-4 study design. Patients were prospectively enrolled and had stage 4/5 chronic kidney disease with or without compensated cirrhosis; those with prior interferon/pegylated interferon with or without ribavirin, or sofosbuvir with ribavirin with or without pegylated interferon treatment experience were eligible. The study included a single arm where patients received co-formulated glecaprevir/pibrentasvir for 12 weeks. SVR12 was achieved by those patients that did not have virologic failure or relapse by study week 24.

Figure S2

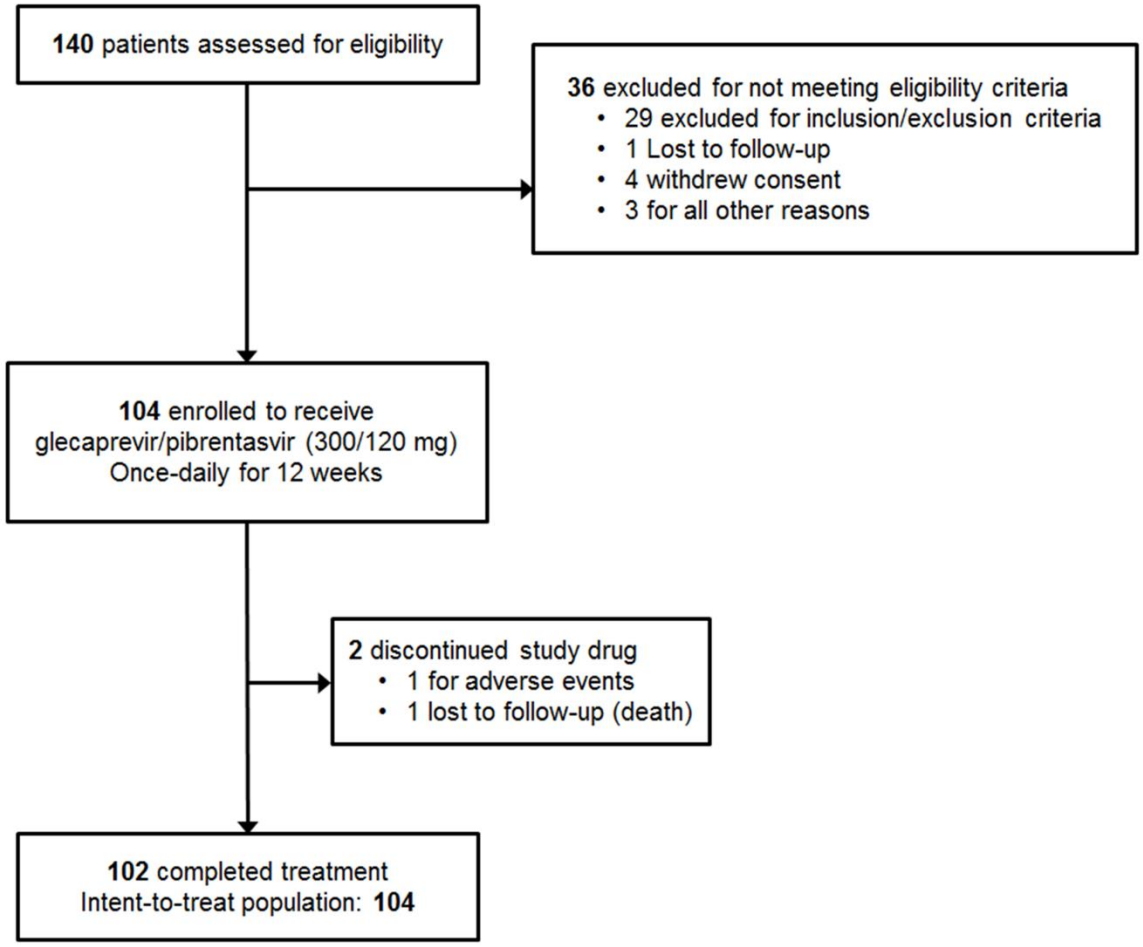

Figure S2. EXPEDITION-4 PRISMA Diagram. This is a flow diagram of patient screening, enrollment, and treatment in the study.

Table S1. Common patient comorbidities*

Condition, n (%)	N = 104
Hypertension	89 (86)
Anemia	47 (45)
Diabetes mellitus	43 (41)
Eye disease/disorder	25 (24)
Obesity	20 (19)
Drug abuse	20 (19)
Hyperlipidemia	17 (16)
Constipation	15 (14)
Gastroesophageal reflux	14 (14)
Coronary artery disease	13 (13)
Hypothyroidism	12 (12)
Post-menopausal	12 (12)
Osteoarthritis	11 (11)
Musculoskeletal pain	11 (11)
Depression	11 (11)

*Kidney impairment and renal disease not listed

Table S2. Treatment-emergent Cardiovascular-related Serious Adverse Events

All Patients (n = 104)				
Cardiovascular Event	**Age (years)**	**Hemodialysis**	**Cardiovascular History**	**Blood Pressure at Baseline**
Hypertensive Crisis; hypertension	68	Yes	Type 2 Diabetes; hypertension	180/80
Congestive cardiac failure; hypertensive cardiomyopathy; pulmonary edema; hypertensive crisis	63	No	Hypertension; hypercholesterolemia	197/94*
Pulmonary edema; mitral valve stenosis; fluid overload	45	Yes	Hypertension; hyperlipidemia; valvular heart disease; type 2 diabetes	112/70
Congestive cardiac failure	57	No	Hypertension; diabetes mellitus; cardiomyopathy	127/84
Congestive cardiac failure	57	Yes	Ischemic cardiomyopathy; congestive heart failure; type 2 diabetes; hypertension; valvular heart disease; hyperlipidemia; bilateral pulmonary effusions	142/69
Cerebral hemorrhage	41	Yes	Hypertension; type 2 diabetes	170/95

Two cardiovascular serious adverse events were not listed due to traumatic or iatrogenic etiologies
*Baseline blood pressure values not available; screening blood pressure values listed

Table S3. Mean Change from Baseline in Blood Pressure During Study Period

Systolic Blood Pressure (mmHg)	All Patients (n = 104)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	104	136.0	–	–
Week 1	101	136.3	0.4	17.2
Week 2	103	136.0	-0.1	17.5
Week 4	103	132.7	-3.3	21.4
Week 8	103	132.7	-3.2	21.6
Week 12	98	134.6	-1.7	22.4
Final Treatment Visit	104	134.5	-1.5	22.0
Post-treatment Week 4	99	134.4	-1.6	21.8
Post-treatment Week 8	102	134.4	-1.2	23.9
Final Post-treatment Visit	104	131.3	-4.8	24.5

Diastolic Blood Pressure (mmHg)	All Patients (n = 104)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	104	78.2	–	–
Week 1	101	79.2	0.9	9.3
Week 2	103	78.4	0.3	10.0
Week 4	103	77.3	-1.0	11.2
Week 8	103	76.9	-1.4	12.5
Week 12	98	76.6	-1.7	10.5
Final Treatment Visit	104	76.5	-1.6	10.3
Post-treatment Week 4	99	77.1	-1.4	11.6
Post-treatment Week 8	102	76.2	-1.6	12.1
Final Post-treatment Visit	104	75.9	-2.3	11.9

Table S4. Clinically Relevant Blood Pressure Values

Vital Sign, n (%)	N = 104
Systolic Blood Pressure (mmHg)	
≤90 and ≥20 decreased from BL	7 (7)
≥180 and ≥20 increased from BL	7 (7)
Diastolic Blood Pressure (mmHg)	
≤50 and ≥15 decreased from BL	4 (4)
≥105 and ≥15 increased from BL	6 (6)

BL, baseline; mmHg, millimeters of mercury

Table S5. Mean Change from Baseline in GFR and ALT During Study Period

GFR (mL/sec/1.73m^2)	All Patients (n = 104)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	104	0.176	–	–
Week 1	100	0.173	-0.001	0.452
Week 2	101	0.179	0.001	0.040
Week 4	101	0.173	0.002	0.039
Week 8	100	0.178	0.002	0.040
Week 12	96	0.171	-0.003	0.041
Final Treatment Visit	104	0.172	-0.004	0.040
Post-treatment Week 4	98	0.175	-0.003	0.040
Final Post-treatment Visit	101	0.175	-0.003	0.039

ALT (U/L)	All Patients (n = 104)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	104	33.6	–	–
Week 1	100	19.4	-14.3	13.6
Week 2	101	17.2	-16.2	15.4
Week 4	101	15.3	-18.1	15.1
Week 8	100	14.6	-19.5	16.4
Week 12	96	14.6	-19.1	18.4
Final Treatment Visit	104	14.0	-19.6	17.0
Post-treatment Week 4	98	13.3	-20.0	17.1
Final Post-treatment Visit	101	13.2	-19.9	17.0

Table S6. Mean Change from Baseline in GFR and ALT During Study Period

GFR (mL/sec/1.73m^2)	Patients without Dialysis (n = 19)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	19	0.343	–	–
Week 1	18	0.326	-0.012	0.035
Week 2	19	0.346	0.002	0.056
Week 4	17	0.321	-0.017	0.029
Week 8	19	0.330	-0.013	0.024
Week 12	17	0.325	-0.013	0.052
Final Treatment Visit	19	0.326	-0.017	0.051
Post-treatment Week 4	19	0.336	-0.007	0.047
Final Post-treatment Visit	19	0.336	-0.007	0.047

ALT (U/L)	Patients without Dialysis (n = 19)			
Visit	N	Mean	Mean Change from Baseline	Standard Deviation
Baseline	19	42.4	–	–
Week 1	18	29.4	-13.5	21.2
Week 2	19	24.2	-18.2	22.3
Week 4	17	19.5	-21.7	20.5
Week 8	19	17.6	-24.7	23.4
Week 12	17	21.1	-20.5	31.0
Final Treatment Visit	19	16.9	-25.5	25.0
Post-treatment Week 4	19	16.5	-25.8	25.9
Final Post-treatment Visit	19	15.6	-26.7	25.5

Table S7. Arterial and Venous Drug Parameters During Hemodialysis

Analyte	Pharmacokinetic Parameter	Central Value		Ratio of Central Values (90% Confidence Interval)
		Venous (test)	Arterial (reference)	
Glecaprevir	C_{max} (ng/mL)	698	722	0.97 (0.91 – 1.03)
	AUC_t (ng·h/mL)	1680	1690	0.99 (0.95 – 1.04)
Pibrentasvir	C_{max} (ng/mL)	115	114	1.02 (0.99 – 1.04)
	AUC_t (ng·h/mL)	349	330	1.06 (1.03 – 1.08)

C_{max}, maximum measured concentration; AUCt, area under the concentration-time curve between the start and end of dialysis