Online supporting information:

Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection

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1. Eligibility Criteria

1.1 Inclusion Criteria

- Male or female at least 18 years of age at time of screening.
  - If female, patient must have been either postmenopausal, *or* permanently surgically sterile, *or* practicing at least 1 approved method of birth control (for women of childbearing potential) starting day 1 through at least 30 days after the last dose of glecaprevir/pibrentasvir.
  - For male subjects, no contraception was required.
  - Females of childbearing potential must have had a negative serum pregnancy test result at screening, and a negative urine pregnancy test at day 1.
  - Females of non-childbearing potential (either postmenopausal or permanently surgically sterile) at screening did not require pregnancy testing.
- Screening laboratory result indicating hepatitis C virus (HCV) genotype (GT) 1, 2, 3, 4, 5 or 6 infection.
- Positive anti-HCV antibody and plasma HCV RNA viral load ≥ 1000 IU/mL at screening visit.
- Chronic HCV infection defined as one of the following:
  - Positive for anti-HCV antibody 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 have been HCV treatment-naive (ie, had not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment-experienced (ie, had failed prior treatment with interferon, pegylated interferon with or without ribavirin, or sofosbuvir with ribavirin with or without pegylated interferon), pre- or post-transplant.

  - Previous HCV treatment must have been completed ≥2 months prior to screening.
  - GT3 subjects must have been treatment-naive.
- Body mass index of ≥18.0 kg/m^2 at the time of screening.
- Patients must have been documented as non-cirrhotic defined as meeting one of the following criteria:
  - A liver biopsy within 6 months prior to or during screening demonstrating the absence of cirrhosis, eg, a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤3, Ishak fibrosis score of ≤4.
  - A FibroScan® score of <12.5 kPa within 3 months of screening or during the screening period.
  - Patients with indeterminate FibroScan® score (12.5≤ score <14.6), must have had a qualifying liver biopsy; or a screening FibroTest score of ≤0.48 and aspartate aminotransferase (AST) to platelet ratio index (APRI) <1.
  - Patients with indeterminate FibroTest (0.48< result <0.75), or conflicting FibroTest and APRI results (eg, FibroTest ≤0.48, but APRI ≥1) must have had a qualifying liver FibroScan® or biopsy.
  - Liver biopsy results superseded Fibrotest®/APRI or FibroScan® results and were considered definitive.
  - FibroScan® results superseded Fibrotest®/APRI results for the determination of absence of cirrhosis.
- Patients voluntarily signed and dated an informed consent form, approved by an Institutional Review Board/Independent Ethics Committee prior to the initiation of any screening or study-specific procedures.
- Patients must have been able to understand and adhere to the trial visit schedule and all other protocol requirements.

- Recipient of a cadaveric or living donor liver transplant which was a consequence of HCV infection ≥3 months prior to screening, or patient received a cadaveric or living donor kidney ≥3 months before screening.
    - For patients with a history of hepatocellular carcinoma: patients in receipt of a cadaveric or living donor liver transplant ≥3 months prior to screening as a consequence of hepatocellular carcinoma in the setting of chronic HCV were eligible if there was not a clinical diagnosis of recurrent hepatocellular carcinoma post-liver transplant.
- Patients were currently taking a stable immunosuppressant regimen based on tacrolimus, sirolimus, everolimus, mycophenolate mofetil, azathioprine, cyclosporine and/or mycophenolic acid.
    - Corticosteroids such as prednisone or prednisolone were permitted as components of the immunosuppressant regimen providing the dose was no more than 10 mg/day at the time of screening.
    - Cyclosporine must have been at a maintenance dose of 100 mg or less per day.

1.2 Exclusion Criteria

- Female patient who was pregnant, breastfeeding or was considering becoming pregnant during the trial or for approximately 30 days after the last dose of glecaprevir/pibrentasvir.
- Recent (within 6 months prior to glecaprevir/pibrentasvir administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
- Positive test result at screening for hepatitis B surface antigen or anti-human immunodeficiency virus antibody.

- HCV genotype performed during screening indicating co-infection with more than 1 HCV genotype or if HCV genotype was indeterminate.
- Requirement for and inability to safely discontinue the prohibited concomitant medications or supplements at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any glecaprevir/pibrentasvir.
- Clinically significant abnormalities, other than HCV infection, that made the patient an unsuitable candidate for the trial in the opinion of the investigator, including, but not limited to:
    - Active or suspected malignancy.
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, metabolic, or other medical disease or disorder, which was unrelated to the existing HCV infection.
    - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A1C) concentration >8.5% at the screening visit.
- Any cause of liver disease post transplantation 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.
- Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection.
- Clinical history of fibrosing cholestatic hepatitis at any time post-transplant.
- Screening laboratory analyses showing any of the following abnormal laboratory results:

  - ALT and AST >10 × upper limit of normal (ULN).
  - Albumin <3.5 g/dL.
  - Hemoglobin <10 g/dL.
  - Platelets <70,000.
  - Calculated creatinine clearance (Cockcroft-Gault method) of <30 mL/min.
  - Direct bilirubin >2 mg/dL.
  - International Normalized Ratio >1.5 ULN.
- Clinical history of acute renal failure in the 3 months prior to screening.
- Re-transplantation of the liver or kidney.
- Recipient of liver or kidney from a donor with known human immunodeficiency virus infection and/or hepatitis B surface antigen positive.
- Steroid resistant rejection of the transplanted liver or kidney, or a history of rejection treated with high dose steroid within 3 months of screening.
- History of post-transplant complications related to hepatic or renal vasculature.
- 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 was longer) prior to glecaprevir/pibrentasvir administration.
- Receipt of any other investigational or commercially available direct acting anti-HCV agents other than sofosbuvir (eg, telaprevir, boceprevir, simeprevir, paritaprevir, daclatasvir, ledipasvir, ombitasvir, elbasvir, or dasabuvir).
- Consideration by the investigator, for any reason, that the patient was an unsuitable candidate to receive glecaprevir/pibrentasvir.
- History of severe, life-threatening or other significant sensitivity to any excipients of the glecaprevir/pibrentasvir.
- Patients who could not participate in the trial as per local law.

Supporting Table S1. Prevalence of Baseline Polymorphisms in NS3 and NS5A

	NS3†		NS5A†	
HCV subtype*	**Baseline polymorphisms**	**% (n/N)‡**	**Baseline polymorphisms**	**% (n/N)‡**
All GT1	**Any**	**(0/56)**	**Any**	**19.6 (11/56)**
1a	Any	(0/27)	Any	14.8 (4/27)
			M28V	3.7 (1/27)
			H58L/P	11.1 (3/27)
1b	Any	(0/29)	Any	24.1 (7/29)
			R30K/Q	6.9 (2/29)
			L31M	3.4 (1/29)
			P58S/T	10.3 (3/29)
			Y93H	6.9 (2/29)
All GT2	**Any**	**(0/13)**	**Any**	**83.3 (10/12)**
2a	Any	(0/2)	Any	100 (2/2)
			L31M	100 (2/2)
2b	Any	(0/9)	Any	75.0 (6/8)
			M31L	75.0 (6/8)
			P58S	12.5 (1/8)
2c	Any	(0/1)	Any	100 (1/1)
			R30K	100 (1/1)

	NS3†		NS5A†	
HCV subtype*	**Baseline polymorphisms**	**% (n/N)‡**	**Baseline polymorphisms**	**% (n/N)‡**
2i	Any	(0/1)	Any	100 (1/1)
			F28L	100 (1/1)
3a	**Any**	**(0/24)**	**Any**	**20.8 (5/24)**
			P58A/T	8.3 (2/24)
			Y93H	12.5 (3/24)
All GT4	**Any**	**(0/4)**	**Any**	**100 (4/4)**
4a	Any	(0/1)	Any	100 (1/1)
			L30R	100 (1/1)
4d	Any	(0/2)	Any	100 (2/2)
			M31L	50.0 (1/2)
			T58P	100 (2/2)
4r	Any	(0/1)	Any	100 (1/1)
			I28M	100 (1/1)
6a	**Any**	**(0/2)**	**Any**	**100 (2/2)**
			Q24R/K	50.0 (1/2)
			F28L	100 (2/2)
GT1, 2, 3, 4, 6	**Any**	**(0/99)**	**Any**	**32.7 (32/98)**

*HCV subtype was determined by phylogenetic analysis of NS3 and/or NS5A sequences.

†Amino acid positions included in the analysis: 155, 156, 168 in NS3; 24, 28, 30, 31, 58, 92,

93 in NS5A. “Any” indicates number of patients with polymorphisms at any of these amino acid positions.

‡“n” is the number of patients with polymorphism relative to subtype-specific reference sequence; “N” is the total number of patients with available sequence for that target.

Supporting Table S2. Glecaprevir/pibrentasvir Efficacy in Patient Subgroups

Patient or disease characteristic	**SVR12 % (n/N; 95% CI)***
Overall	98.0 (98/100; 93.0–99.4)
Sex	
Male	97.3 (73/75; 90.8–99.3)
Female	100 (25/25; 86.7–100)
Age	
<65 years	98.6 (73/74; 92.7–99.8)
≥65 years	96.2 (25/26; 81.1–99.3)
Body mass index	
<30 kg/m^2	98.6 (72/73; 92.6–99.8)
≥30 kg/m^2	96.3 (26/27; 81.7–99.3)
Baseline fibrosis stage	
F0–F1	97.5 (78/80; 91.3–99.3)
F2	100 (6/6; ND)
F3	100 (14/14; 78.5–100)
HCV genotype	
1	100 (57/57; 93.7–100)
2	100 (13/13; 77.2–100)
3	91.7 (22/24; 74.2–97.7)
4	100 (4/4; ND)
6	100 (2/2; ND)

Patient or disease characteristic	**SVR12 % (n/N; 95% CI)***
HCV treatment experience	
Naïve	97.0 (64/66; 89.6–99.2)
Experienced	100 (34/34; 89.8–100)
Interferon-based	100 (32/32; 89.3–100)
Sofosbuvir-based	100 (1/1; ND)
Pre-transplant	100 (24/24; 86.2–100)
Post-transplant	100 (10/10; 72.2–100)
Immunosuppressant medication type	
Tacrolimus	98.5 (67/68; 92.1–99.7)
Cyclosporine	100 (13/13; 77.2–100)
Other†	94.7 (18/19; 75.4–99.1)
Presence of baseline polymorphisms‡	
None	100 (65/65)
NS3-only	—
NS5A-only	96.9 (31/32)
NS3+NS5A	—

*Intention-to-treat analysis. The 95% CIs were calculated using the Wilson's score method (ND for subgroups with <10 patients).

†Other category includes azathioprine, everolimus, mycophenolic acid, prednisolone, prednisone, and sirolimus.

‡Modified intention-to-treat analysis. Amino acid positions included in the analysis: 155, 156, and 168 in NS3; 24, 28, 30, 31, 58, 92, and 93 in NS5A.

CI, confidence interval; HCV, hepatitis C virus; ND, not done; SVR12, sustained virologic response at post-treatment week 12.

Supporting Table S3. Serious Adverse Events

Patient	**Serious adverse event***	**Study day onset†**	**Relationship to glecaprevir/pibrentasvir**
1	Pyelonephritis	23	No reasonable possibility
	Neutropenia	43	No reasonable possibility
	Pyelonephritis	112 (27)	No reasonable possibility
2	Groin infection	42	No reasonable possibility
	Sepsis	42	No reasonable possibility
	Vascular pseudoaneurysm ruptured	42	No reasonable possibility
	Pneumonia	87 (3)	No reasonable possibility
	Sepsis	99 (15)	No reasonable possibility
3	Immunosuppressant drug level increased	46	No reasonable possibility
	Liver function test increased	46	No reasonable possibility
	Renal impairment	46	No reasonable possibility
4	Respiratory tract infection	73	No reasonable possibility
5	Urinary tract infection	15	No reasonable possibility
	Renal impairment	18	No reasonable possibility
	Sepsis	46	No reasonable possibility
	Urinary tract infection	46	No reasonable possibility
	Renal failure	85	No reasonable possibility
6	Sinusitis	2	Reasonable possibility

7	Cerebrovascular accident	50 (1)	No reasonable possibility
8	Hepatic function abnormal	113 (29)	Reasonable possibility

*MedDRA Preferred Term version 19.1.

†Numbers in parentheses indicate days since last dose of glecaprevir/pibrentasvir.

Supporting Table S4. Immunosuppressant Medication Dosage Change

Immunosuppressant medication dosage change, n (%)	**Day 3**	**Week 1**	**Day 10**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 12**
Cyclosporine								
Increase	2 (2)	1 (1)	0	2 (2)	2 (2)	2 (2)	2 (2)	1 (1)
Decrease	3 (3)	1 (1)	4 (4)	2 (2)	3 (3)	0	0	1 (1)
Sirolimus								
Increase	0	0	0	0	0	0	0	0
Decrease	0	0	0	0	0	0	0	0
Everolimus								
Increase	2 (2)	0	0	0	1 (1)	1 (1)	0	1 (1)
Decrease	0	0	0	2 (2)	2 (2)	0	2 (2)	2 (2)
Tacrolimus								
Increase	14 (14)	3 (3)	6 (6)	5 (5)	11 (11)	12 (12)	2 (2)	9 (9)
Decrease	9 (9)	10 (10)	7 (7)	15 (15)	11 (11)	6 (6)	10 (10)	9 (9)

Number and percentage of patients with immunosuppressant medication dosage change at each post-baseline visit during the glecaprevir/pibrentasvir treatment period (safety population, N = 100).