Online Supporting Information

Glecaprevir/Pibrentasvir in Patients with Chronic HCV Genotype 3 Infection: An Integrated Phase 2/3 Analysis

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Glecaprevir was identified by AbbVie and Enanta Pharmaceuticals.

Key Patient Eligibility Criteria*

At least 18 years of age

Chronic hepatitis C virus genotype 3 infection (HCV RNA at least 1,000 IU/mL at screening)

Absence of coinfection with hepatitis B virus or infection with multiple HCV genotypes

Absence of cirrhosis or presence of compensated (Child-Pugh A) cirrhosis

HCV treatment naïve or experienced with interferon or pegylated IFN with or without ribavirin, or sofosbuvir plus ribavirin with or without pegylated IFN

Patients with stage 4 or 5 chronic kidney disease (EXPEDITION-4), HIV coinfection (EXPEDITION-2), or post-liver/kidney transplant (MAGELLAN-2) were included

*Differences in criteria between Phase 2 and Phase 3 studies are listed in Table S1.

Cirrhosis Determination (Phase 3 studies and SURVEYOR-II Part 2)

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 (eg, FibroTest ≤0.48, but APRI ≥1) must have a qualifying liver FibroScan or biopsy

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); or
- Previous FibroTest score ≥0.75 and an APRI >2; or

  - 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

Note: SURVEYOR-II Part 1 (Phase 2) enrolled patients without cirrhosis only and used same criteria except for FibroTest and APRI cutoffs (Table S1) and no specification of indeterminate ranges for FibroTest or FibroScan.

Resistance Analyses

For HCV resistance analysis, we define a polymorphism as a baseline amino acid difference relative to the appropriate reference sequence. Regions encoding full-length NS3/4A or NS5A were sequenced by next generation sequencing from available baseline samples from all patients, and on the first available post-baseline sample with HCV RNA ≥ 1000 IU per milliliter from patients who experienced virologic failure. Detection of polymorphisms at baseline and substitutions at the time of virologic failure was done using a 15% detection threshold. For patients who experienced virologic failure, polymorphisms at baseline and substitutions at the time of failure were examined using an extended list of amino acid positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, 168 in NS3, and 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A.

Table S1. Differential Patient Eligibility Criteria in Phase 2 or 3 Clinical Trials

	Phase 2 Trials	Phase 3 Trials
General characteristics		
Age	18 – 70	≥18
BMI (kg/m^2)	≥18 to <38	≥18
HCV RNA (IU/mL)	>10,000	≥1,000
Prior treatment experience	IFN, pegIFN, RBV	IFN, pegIFN, RBV, SOF
Absence of cirrhosis*		
Fibroscan (kPa)	<12.5	<12.5
Fibrotest	≤0.72	≤0.48
APRI	≤2	<1
Positive urine drug test exclusionary?	Yes	No

APRI, AST-to-platelet ratio index ; BMI, body-mass index; IFN, interferon; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir

*Fibrotest and APRI criteria for SURVEYOR-2 Part 2 (Phase 2) were the same used in phase 3 trials

Table S2. Patients Excluded in the mITT Analysis

	Treatment History	Cirrhosis Status	Treatment Duration	Reason for Non-Response	DAA Adherent*?
1	Naïve	No cirrhosis	12 weeks	Treatment discontinuation	No
2	Naïve	No cirrhosis	8 weeks	Missing SVR12 data	No
3	Naïve	No cirrhosis	8 weeks	OTVF	No (#17 in Table 4)
4	Naïve	No cirrhosis	12 weeks	Treatment discontinuation	Yes
5	Naïve	No cirrhosis	12 weeks	Missing SVR12 data	No
6	Naïve	No cirrhosis	12 weeks	Treatment discontinuation	No
7	Naïve	No cirrhosis	8 weeks	Missing SVR12 data	Yes
8	Naïve	No cirrhosis	12 weeks	Missing SVR12 data	Yes
9	Naïve	No cirrhosis	12 weeks	Treatment discontinuation	No
10	Naïve	No cirrhosis	12 weeks	Relapse	No (#12 in Table 4)
11	Naïve	No cirrhosis	12 weeks	Missing SVR12 data	No
12	Naïve	No cirrhosis	12 weeks	Missing SVR12 data	No
13	Naïve	Cirrhosis	12 weeks	OTVF	No (#21 in Table 4)
14	Naïve	No cirrhosis	8 weeks	Missing SVR12 data	Yes
15	Experienced†	No cirrhosis	12 weeks	Relapse	No (#1 in Table 4)
16	Naïve	No cirrhosis	12 weeks	Missing SVR12 data	Yes
17	Naïve	Cirrhosis	12 weeks	Missing SVR12 data	No
18	Naïve	No cirrhosis	8 weeks	Missing SVR12 data	No
19	Experienced†	Cirrhosis	16 weeks	OTVF	No (#9 in Table 4)

SVR12, sustained virologic response 12 weeks post-treatment; OTVF, on-treatment virologic failure

* DAA adherence was calculated as the percentage of tablets taken (determined by pill counts at study visits from week 4, 8, 12 [where applicable] and 16 [where applicable]) relative to the total expected number of tablets, where adherence needed to be between 80% and 120% at each 4-week dispensation interval (values below 80% and above 120% were considered non-adherent)

† Experienced with pegIFN/RBV