# Online Supporting Information

## Glecaprevir/Pibrentasvir for HCV Genotype 3 Patients with Cirrhosis and Prior Treatment Experience

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### Table of Contents



Glecaprevir was identified by AbbVie and Enanta Pharmaceuticals.

**Supporting Table 1. SURVEYOR-II, Part 3 Inclusion/Exclusion Criteria**

**Inclusion Criteria**

1 Male or Female, ≥18 years at screening

2 Female who is:

- Of childbearing potential and is sexually active with male partner(s):
  - Must agree to use two effective forms of birth control starting from day 1 and through day 30 after completion of study drugs (options below)
    - Intrauterine device
    - Condom with spermicide
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Contraceptive sponge with spermicide
    - Progestin-only contraceptives without ethinyl estradiol
- Postmenopausal for at least 2 years prior to screening
- Surgically sterile or has a vasectomized partner(s)
- Practicing total abstinence as a lifestyle
- Sexually active with female partner(s) only

3 Sexually active males must be surgically sterile or have male partner(s) only, or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control starting from day 1 and through day 30 after completion of study drugs (acceptable methods outlined below)

- Male condom with spermicide and one of the following for the female partner:
  - Intrauterine device
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Contraceptive sponge with spermicide
  - Hormonal contraceptive

4 Screening laboratory result indicating HCV GT3

5 Chronic HCV infection defined as one of the following:

- Positive for anti-HCV antibody or HCV RNA at least 6 months before screening and positive for both at the time of screening

- Positive for anti-HCV antibody or HCV RNA at screening with liver biopsy consistent with chronic HCV infection

6 Patient must meet one of the following criteria:
- Prior HCV treatment naïve
- Prior HCV treatment experienced, with virologic failure or relapse
  - IFN/pegIFN ± RBV
  - SOF + RBV ± pegIFN
  - Treatment completed ≥2 months prior to screening

7 BMI of ≥18 $kg/m^2$

8 If patient is **non-cirrhotic**, they must meet one of the following criteria:
- Liver biopsy within 24 months prior to screening demonstrating the absence of cirrhosis (eg, METAVIR score of ≤3 or Ishak score ≤4)
- Screening FibroTest score of ≤0.48 and APRI <1
  - Patients with indeterminate FibroTest (0.48 < results < 0.75) or conflicting FibroTest and APRI must have a qualifying FibroScan or biopsy
- FibroScan score of <12.5 kPa performed ≤6 months before or during screening
  - Patients with indeterminate FibroScan score must have qualifying liver biopsy

9 If patient is **cirrhotic**, they must meet one of the following criteria:
- Liver biopsy prior to (or during) screening demonstrating cirrhosis (eg, METAVIR score of >3 (including 3/4) or Ishak score >4)
- Screening FibroTest score of ≥0.75 and APRI >2
  - Patients with indeterminate FibroTest (0.48 < results < 0.75) or conflicting FibroTest and APRI must have a qualifying FibroScan or biopsy
- FibroScan score of ≥14.6 kPa performed prior to or during screening
  - Patients with indeterminate FibroScan score (12.5 ≤ score < 14.6) must have qualifying liver biopsy

10 Patient must voluntarily sign and date an informed consent form, approved by an Institutional Review Board/Independent Ethics Committee prior to the initiation of any screening or study-specific procedures

11 Patient must be able to understand and adhere to the study visit schedule and all other protocol requirements

12 For patients with compensated cirrhosis:

- Must be HCC negative as indicated by ultrasound, CT scan, or MRI 3 months prior to screening, or by ultrasound at screening

| **Exclusion Criteria** | |
|---|---|
| 1 | History of severe, life-threatening or other sensitivity to any drug |
| 2 | Female who is pregnant, planning to become pregnant during study, or breastfeeding; or male whose partner is pregnant or planning to become pregnant during study |
| 3 | Recent (≤6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to protocol in the opinion of the investigator |
| 4 | Positive test result at screening for HBV surface antigen or HIV antibody |
| 5 | HCV GT test performed during screening indicating co-infection with more than one HCV GT |
| 6 | Requirement for an inability to safely discontinue prohibited medications or supplements at least 2 weeks or 10 half-lives (whichever is longer) prior to first dose of study drug |
| 7 | Positive result of a urine drug screen at the screening visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result (including methadone and buprenorphine ± naloxone) associated with documented and medically appropriate short-term use or chronic stable use of medication in that class or single positive results on a urine screen for alcohol. If methadone or buprenorphine ± naloxone use is for opioid replacement therapy, patient must be on stable therapy for ≥6 months prior to screening |
| 8 | Clinically significant abnormalities other than HCV infection based upon medical history, physical examination, vital signs, laboratory profile, and a 12-lead ECG that make the subject an unsuitable candidate in the opinion of the investigator, including, but not limited to:<br>● Uncontrolled diabetes defined by a glycated hemoglobin level >8.5% at screening<br>● History of, active, or suspected malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years<br>● Uncontrolled cardiac, respiratory (except mild asthma), gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to existing HCV infection |
| 9 | Any cause of liver disease other than chronic HCV infection, including but not limited to:<br>● Hemochromatosis<br>● α-1-antitrypsin deficiency |

- Wilson's disease
- Autoimmune hepatitis
- Alcoholic liver disease
- Drug-related liver disease
- Steatosis or steatohepatitis on liver biopsy considered to be the primary cause of liver disease rather than coincidental HCV infection

10 Screening laboratory analyses showing any of the following abnormal results:

- ALT >10 × ULN
- AST >10 × ULN
- Calculated creatinine clearance of <50 mL/min
- Albumin <LLN for non-cirrhotic patients or <2.8 g/dL for cirrhotic patients
- INR >1.5 for non-cirrhotic patients or >2.3 for patients with cirrhosis (unless patient is on a stable anticoagulant or has known hemophilia)
- Hemoglobin <11 g/dL for women or <12 g/dL for men
- Platelets <90,000 cells/$mm^3$ for non-cirrhotic patients or <60,000 cells/$mm^3$ for cirrhotic patients
- ANC <1,000 cells/mL
- Direct bilirubin >ULN for non-cirrhotic patients or total bilirubin >3 × ULN for cirrhotic patients

11 History of solid organ transplantation

12 Clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate using Fridericia's correction formula >450 msec at screening or study day 1

13 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

14 Current or previous enrollment in this study or another study of any anti-HCV agent; patients who previously participated in trials of investigational anti-HCV agents may be enrolled with the approval of the AbbVie Study Designated Physician if they can produce documentation that they received placebo only, IFN or pegIFN with or without RBV only, or SOF plus RBV with or without pegIFN only

15 The use of colony stimulating factors (eg, GCSF) or erythropoietin ≤2 months from screening

16 ≤1,000 IU/mL or unquantifiable or undetectable HCV RNA at screening

17 Previous use of any HCV DAA, except SOF

18 Consideration by the investigator that the subject is an unsuitable candidate to receive co-formulated G/P, for any reason

19 For patients with compensated cirrhosis:
- Past clinical evidence of Child-Pugh B or C classification
- Clinical history of liver decompensation, including:
  - Ascites
  - Bleeding varices
  - Use of beta-blockers or diuretics for portal hypertension or ascites
  - Hepatic encephalopathy

20 Patients that cannot participate in the study per local law

21 Requirement for chronic use of systemic immunosuppressants during the study, including but not limited to:
- Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks)
- Azathioprine
- Monoclonal antibodies (eg, influximab)

ALT, alanine aminotransferase; ANC, absolute neutrophil count; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CT, computed tomography; DAA, direct-acting antiviral; ECG, electrocardiogram; GCSF, granulocyte colony stimulating factor; G/P, coformulated glecaprevir/pibrentasvir; GT, genotype; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; INR, international normalized ratio; LLN, lower limit of normal; MRI, magnetic resonance imaging; pegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal

## HCV Genotype, Subtype, and RNA Measurement

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

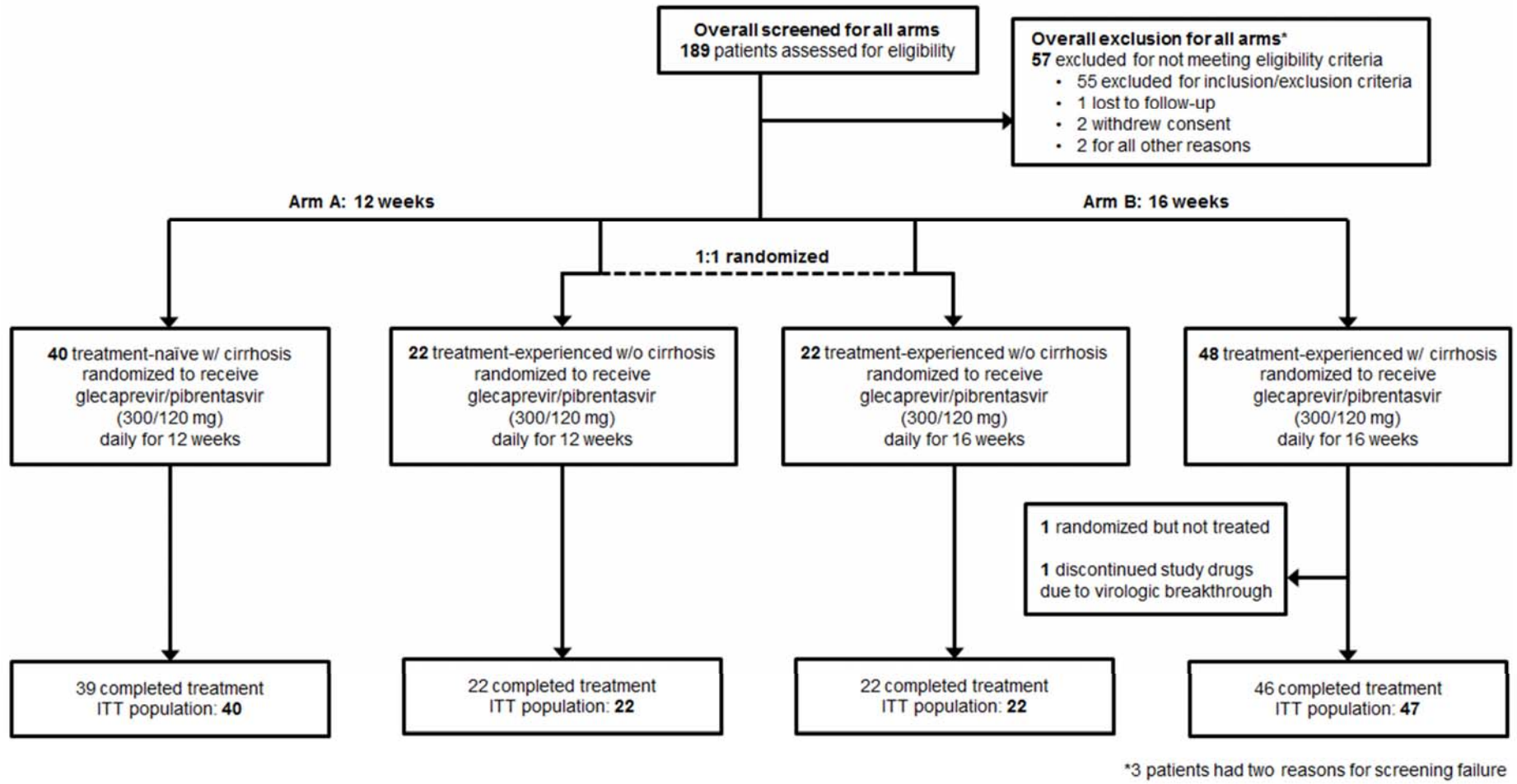
Plasma HCV RNA levels were determined for each collected sample using the COBAS® TaqMan real-time reverse transcriptase PCR, v2.0. For HCV GT3, the lower limit of detection for this assay was 15 IU/mL, while the lower limit of quantification was 25 IU/mL.

## Resistance Analysis Methods and Definitions

For HCV resistance analysis, a polymorphism was defined as a baseline amino acid difference relative to the appropriate subtype-specific reference sequence, and a substitution as a treatment-emergent amino acid difference relative to the patient's baseline viral sequence. An amino acid variant was considered an amino acid change due to either a baseline polymorphism or a treatment-emergent substitution. Regions encoding full-length NS3/4A or NS5A were sequenced by next generation sequencing from available baseline samples from all patients, and from the first available post-baseline sample with HCV RNA ≥1000 international units per milliliter from the patients who experienced virologic failure. Baseline polymorphisms and treatment-emergent substitutions were identified using a 15% detection threshold at amino acid positions 155, 156, 168 in NS3, and 24, 28, 30, 31, 58, 92, 93 in NS5A.

Baseline polymorphisms relative to a subtype-specific reference sequence for all patients, and treatment-emergent substitutions relative to the patient's baseline sequence for patients who experienced virologic failure were identified using the following set of amino acid positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A. These are positions at which substitutions have been observed in vitro or clinically in NS3 or NS5A in any genotype with drugs for the respective inhibitor class.

**Supporting Figure 1. Progression of patients through SURVEYOR-2, Part 3 (PRISMA diagram)**



**Supporting Table 2. On-treatment response, HCV RNA below LLOQ**

| | Arm A (12 weeks G/P) | | Arm B (16 weeks G/P) | |
|---|---|---|---|---|
| | | 1:1 Randomized | | |
| Time of measurement | Treatment-naïve w/ cirrhosis N = 40 | Treatment-experienced w/o cirrhosis N = 22 | Treatment-experienced w/o cirrhosis N = 22 | Treatment-experienced w/ cirrhosis N = 47 |
| **On-treatment response, n/N (%)** | | | | |
| Week 4 | 40/40 (100) | 22/22 (100) | 22/22 (100) | 44/46 (96) |
| Week 8 | 40/40 (100) | 22/22 (100) | 22/22 (100) | 46*/47 (98) |
| Week 12 | 37/37 (100) | 21/21 (100) | 22/22 (100) | 46*/47 (98) |
| Week 16 | – | – | 22/22 (100) | 45/45 (100) |
| Final treatment visit | 40/40 (100) | 22/22 (100) | 22/22 (100) | 46*/47 (98) |

CI, confidence interval; LLOQ, lower limit of quantification; n, patients with positive on-treatment response; N, total patients with available data
Positive on-treatment response was considered as HCV RNA below LLOQ (25 IU/mL)
Final treatment visit was ≤2 days after last dose of study drug
* One patient was determined non-compliant and had on-treatment virologic failure (breakthrough) with HCV RNA becoming >LLOQ at week 8

**Supporting Table 3. SVR12 by presence of baseline polymorphisms in NS3 and NS5A[a]**

| | | Arm A (12 weeks G/P) | | Arm B (16 weeks G/P) | |
|---|---|---|---|---|---|
| | | 1:1 Randomized | | | |
| Target | Baseline Polymorphism | Treatment-naïve w/ cirrhosis N = 38 | Treatment-experienced w/o cirrhosis N = 22 | Treatment-experienced w/o cirrhosis N = 21 | Treatment-experienced w/ cirrhosis N = 47 |
| | | n/N (%) SVR12 | | | |
| NS3 | Without any NS3 | 34/34 (100) | 16/18 (89) | 18/19 (95) | 37/38 (97) |
| | With any NS3[c] | 4/4 (100) | 4/4 (100) | 2/2 (100) | 8[b]/9 (89) |
| NS5A | Without any NS5A | 29/29 (100) | 16/16 (100) | 18/18 (100) | 39/41 (95) |
| | With any NS5A[c] | 9/9 (100) | 4/6 (67) | 2/3 (67) | 6/6 (100) |
| | A30M/R/S/T/V | 4/4 (100) | 1/1 (100) | 1/1 (100) | 4/4 (100) |
| | A30K | – | 0/1 (0) | 0/1 (0) | – |
| | Y93H | 4/4 (100) | 2/3 (67) | – | 1/1 (100) |

[a]Analysis includes patients with available baseline sequencing data and excludes patients without SVR12 due to non-virologic reasons
[b]Patient without SVR12 had drug exposures 50% lower than average at most study visits
[c]Includes baseline polymorphisms present in ≥15% of viral population as detected by next generation sequencing at NS3 positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168; and NS5A positions: 24, 28, 29, 30, 31, 32, 58, 92, and 93

**Supporting Table 4. Prevalence of baseline polymorphisms in NS3 and NS5A[a]**

| | | Arm A (12 weeks G/P) | | Arm B (16 weeks G/P) | |
|---|---|---|---|---|---|
| | | | 1:1 Randomized | | |
| Target | Baseline Polymorphism[b] | Treatment-naïve w/ cirrhosis N = 39 | Treatment-experienced w/o cirrhosis N = 22 | Treatment-experienced w/o cirrhosis N = 21 | Treatment-experienced w/ cirrhosis N = 47 |
| | | n (%) | | | |
| NS3 | Any | 4 (10) | 4 (18) | 2 (10) | 9 (19) |
| | A166S/T | 4 (10) | 4 (18) | 2 (10) | 8 (17) |
| | Q168K/R | 1 (4) | – | – | 1 (2) |
| NS5A | Any | 9 (23) | 6 (27) | 3 (14) | 6 (13) |
| | S24A | – | 1 (5) | – | – |
| | M28V | 1 (3) | – | – | 1 (2) |
| | A30M/R/S/T/V | 4 (10) | 1 (5) | 1 (5) | 4 (9) |
| | A30K | – | 1 (5) | 1 (5) | – |
| | V31M | – | 1 (5) | 1 (5) | – |
| | P58R/S | 3 (8) | – | – | 1 (2) |
| | E92G | 1 (3) | – | – | – |
| | Y93H | 4 (10) | 3 (14) | – | 1 (2) |

[a]Data missing for 1 patient in Arm A (column 1) and 1 patient in Arm B (column 3)

[b]Baseline polymorphisms shown were present in ≥15% of viral population as detected by next generation sequencing at NS3 positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168; and NS5A positions: 24, 28, 29, 30, 31, 32, 58, 92, and 93

**Supporting Table 5. Summary of Treatment-emergent Serious Adverse Events**

| G/P Treatment Duration | MedDRA 19.0 Preferred Event Term | Onset | Resolved | Grade | Relatedness to Study Drug | Interruption of G/P Treatment? |
|---|---|---|---|---|---|---|
| 12 weeks | Colon Cancer | Day 45 | – | Grade 3 | No relation | No |
| 12 weeks | Schizophrenia | Day 71 | Day 99 | Grade 4 | No relation | No |
| 16 weeks | Angina Pectoris | Day 9 | Day 14 | Grade 3 | No relation | No |
| 16 weeks | Squamous Cell Carcinoma of the Skin | Day 37 | Day 91 | Grade 3 | No relation | No |
| 16 weeks | Umbilical Hernia | Day 81 | Day 88 | Grade 3 | No relation | No |
| 16 weeks | Parapneumonic Effusion | Day 88 | Day 97 | Grade 4 | No relation | No |