Supplementary Material

High Efficacy Rates of ABT-493 and ABT-530 Treatment in Patients with HCV Genotype 1 or 3 Infection and Compensated Cirrhosis

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ABT-493 was identified by AbbVie and Enanta Pharmaceuticals.

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Key SURVEYOR-I Eligibility Criteria

Inclusion

- Male or female between 18 and 70 years of age, inclusive, at time of screening.
- Screening laboratory result indicating HCV GT1 infection.
- Chronic HCV infection 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-HCV Ab 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 (or a liver biopsy performed prior to enrollment with evidence of chronic HCV infection).
- Patient must meet one of the following criteria:
    - Treatment-naïve: patient has never received treatment for HCV infection.
    - Peginterferon/ribavirin experienced:
        - On-treatment failure: patient received PR for the treatment of HCV, did not discontinue due to intolerance or an adverse event, and failed to achieve an undetectable HCV RNA at the end of PR treatment; or
        - Relapse: patient received anti-HCV therapy with PR, did not discontinue due to intolerance or an adverse event, and had detectable HCV RNA during treatment follow-up.
    - Note: previous HCV treatment must have been completed ≥2 months prior to screening.
- Body Mass Index (BMI) is from ≥18 to <38 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).
- Patients must have been documented as having cirrhosis defined as meeting one of the following criteria (per local standard):
    - A liver biopsy within 24 months prior to or during screening demonstrating the presence of cirrhosis, eg, a METAVIR Score of >3 (including 3/4 or 3 – 4), Ishak score of >4; or
    - FibroScan score ≥14.6 kPa within 6 months of screening or during screening, or
        - Patients with indeterminate FibroScan score (12.5 – <14.6) must have qualifying liver biopsy.
    - A screening FibroTest result that is ≥0.75 and an APRI >2
        - Patients with conflicting FibroTest and APRI results must have a qualifying FibroScan or liver biopsy.
- HCV RNA >10,000 IU/mL at screening.

Exclusion

- Absence of a positive test result at screening for hepatitis B surface antigen (HBsAg) and anti-human immunodeficiency virus antibody (HIV Ab).
- HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
- Screening laboratory analyses showing any of the following abnormal laboratory results:
    - ALT >5 × ULN.

- AST >5 × ULN.
- Calculated creatinine clearance of <50 mL/min.
- Albumin <LLN.
- International normalized ratio (INR) >1.5.
- Hemoglobin <LLN.
- Platelets <90,000 cells per mm^3.
- Absolute neutrophil count (ANC) <1500 cells/µL (<1200 cells/µL for patients of black race or patients of African descent who are black).
- Indirect bilirubin ≥1.5 × ULN.
- Direct bilirubin >ULN.

- History of solid organ transplant.
- Previous use of any HCV direct-acting antiviral.

Key SURVEYOR-II Eligibility Criteria

Inclusion

- Male or female between 18 and 70 years of age, inclusive, at time of screening.
- Screening laboratory result indicating HCV GT3 infection.
- Chronic HCV infection defined as one of the following:
  - Positive for anti-HCV Ab or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV Ab 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 (or a liver biopsy performed prior to enrollment with evidence of chronic HCV infection).
- Patient must meet one of the following criteria:
  - Treatment-naïve: patient has never received treatment for HCV infection.
  - Treatment-experienced (selected-dose arms):
    - PegIFN/RBV on-treatment failure: patient received pegIFN/RBV for the treatment of HCV, did not discontinue because of intolerance or an adverse event of the treatment, and failed to achieve an undetectable HCV RNA level at the end of treatment; or
    - PegIFN/RBV post-treatment relapse: patient received pegIFN/RBV for the treatment of HCV, did not discontinue because of intolerance or an adverse event of the treatment, and had undetectable HCV RNA at the end of treatment but detectable HCV RNA during treatment follow-up.
    - Note: previous HCV treatment must have been completed ≥2 months prior to screening.
- Body Mass Index (BMI) is from ≥18 to <38 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).
- Patients must have been documented as having cirrhosis defined as meeting one of the following criteria (per local standard):

- A liver biopsy prior to or during screening demonstrating the presence of cirrhosis, eg, a METAVIR Score of >3 (including 3/4 or 3 – 4), Ishak score of >4; or
- FibroScan score ≥14.6 kPa within 6 months of screening or during screening, or
  - Patients with indeterminate FibroScan score (12.5 – <14.6) must have qualifying liver biopsy.
- A screening FibroTest result that is ≥0.75 and an APRI >2
  - Patients with conflicting FibroTest and APRI results must have a qualifying FibroScan or liver biopsy.

- HCV RNA >10,000 IU/mL at screening.

Exclusion

- Absence of a positive test result at screening for hepatitis B surface antigen (HBsAg) and anti-human immunodeficiency virus antibody (HIV Ab).
- HCV genotype performed during screening indicating co-infection with more than one HCV genotype.
- Screening laboratory analyses showing any of the following abnormal laboratory results:
  - ALT >5 × ULN.
  - AST >5 × ULN.
  - Calculated creatinine clearance of <50 mL/min.
  - Albumin <LLN.
  - INR >1.5.
  - Hemoglobin <LLN.
  - Platelets <90,000 cells per mm^3.
  - ANC <1500 cells/µL (<1200 cells/µL for patients of black race or patients of African descent who are black).
  - Direct bilirubin >ULN.
- History of solid organ transplant.
- Previous use of any HCV direct-acting antiviral.

Virologic Stopping and Futility Criteria

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.
- Failure to achieve unquantifiable HCV RNA levels by week 6.
- Confirmed quantifiable HCV RNA level at any point after an unquantifiable level.

Supplemental Table 1. Baseline NS3 and NS5A Substitutions Detected in Patients with HCV Genotype 1 Infection

	Genotype 1 ABT-493 200 mg ABT-530 120 mg N = 27
NS3 substitutions, n (%)	
V55A	2 (7)
Q80K	4 (15)
S122G	2 (7)
I170V	4 (15)
NS5A substitutions, n (%)	
M28V	2 (7)
Q30R	1 (4)
R30Q (GT1b)*	1 (4)
L31M	1 (4)

GT, genotype.
*** Only 1 GT1b-infected patient had a baseline HCV sequence substitution; all other substitutions were found in GT1a-infected patients.**
Baseline substitutions were detected by population sequencing (threshold for detection ~15%). NS3 protease or NS5A inhibitor baseline resistance-associated substitutions for HCV GT1 are more clearly defined than other genotypes and were assessed based on the specific amino acid substitutions at the signature positions described below.
GT1 NS3 substitutions:
GT1a: V36A/G/I/L/M, F43L, T54A/S, V55A/I, Y56H, Q80K/R, V107I, S122G/R, I132V, R155(all), A156(all), V158I, D168(all), and I170F/T/V.
GT1b: V36A/G/I/L/M, T54A/C/G/S, V55A, Y56H/L, Q80K/R, V107I, S122A/D/G/I/N/T, R155(all), A156(all), V158I, D168(all), V170A/T, and M175L.
GT1 NS5A substitutions:
GT1a: M28(all), Q30(all), L31(all), P32L, H58D/R, and Y93(all).
GT1b: L28(all), P29S/del, R30G/H/P/Q, L31(all), P32L/del, P58A/S, Q62D, A92E/K, and Y93(all).

Supplemental Table 2. Baseline NS3 and NS5A Substitutions Detected in Patients with HCV Genotype 3 Infection

	Genotype 3 ABT-493 300 mg ABT-530 120 mg N = 28	Genotype 3 ABT-493 300 mg ABT-530 120 mg RBV 800 mg N = 27
NS3 substitutions, n (%)		
Y56F	1 (4)	0
Q80K	1 (4)	0
A166S/T	6 (21)	4 (15)
Q168K	1 (4)	0
NS5A substitutions, n (%)		
A30K/T (GT3a)	2 (7)	3 (11)
K30M (GT3b)*	1 (4)	NA
L31M (GT3a)	0	1 (4)
V31M (GT3b)*	1 (4)	NA
P58S	1 (4)	1 (4)
Y93H	1 (4)	3 (11)

GT, genotype; NA, not applicable because no GT3b-infected patients were enrolled in this arm.
*** Only 1 GT3b-infected patient was enrolled and had 2 baseline NS5A substitutions; all other amino acid substitutions were found in GT3a-infected patients.**
Baseline substitutions were detected by population sequencing (threshold for detection ~15%) for all GT3 patients expect the one GT3b-infected patient, which were detected by next generation sequencing using a detection threshold of 15%.
Less is known about GT3 baseline resistance-associated substitutions, thus any amino acid substitutions at the signature positions as described below were included:
NS3: 36, 56, 80, 155, 156, 166, and 168.
NS5A: 24, 28, 29, 30, 31, 32, 58, 92, and 93.

Supplemental Table 3. Characteristics of Patients Experiencing Virologic Failure

											Amino Acid Substitutions*			
											NS3		NS5A	
PtID	**Sex**	**Age**	**BL HCV RNA, log_{10} IU/mL**	**GT**	**BMI**	**Platelet Count, $\times 10^9$**	**Albumin, g/dL**	**Fibroscan Result, kPa**	**Prior PR Treatment Experience**	**Reason for non-SVR**	**Baseline**	**At failure**	**Baseline**	**At failure**
1	F	60	6.2	1a	29.6	98	3.6	20.9	Naïve	Relapse	I170V	I170V	L31M	L31M Y93N
2	M	59	7.1	3a	26.9	192	4.4	25.7	Relapse	Relapse	A166S	None	None	M28G

PtID, patient ID; GT, genotype; BMI, body mass index measured as kg/m^2; PR, peginterferon/RBV.
*** Amino acid substitution(s) as determined by population sequencing with a detection threshold of approximately 15%.**