CERTAIN-1: Efficacy and Safety of Glecaprevir/Pibrentasvir in Japanese Patients With Chronic Genotype 1 Hepatitis C Virus Infection With and Without Cirrhosis

Kazuaki Chayama[1], Fumitaka Suzuki[2], Yoshiyasu Karino[3], Yoshiiku Kawakami[1], Ken Sato[4], Tomofumi Atarashi[5], Atsushi Naganuma[6], Tsunamasa Watanabe[7], Yuichiro Eguchi[8], Hitoshi Yoshiji[9], Masataka Seike[10], Yoshiyuki Takei[11], Koji Kato[12], Katia Alves[12], Margaret Burroughs[12], Rebecca Redman[12], David L Pugatch[12], Tami J Pilot-Matias[12], Wangang Xie[12], Hiromitsu Kumada[2]

[1]Hiroshima University Hospital, Hiroshima, Japan; [2]Toranomon Hospital, Tokyo, Japan; [3]JA Hokkaido P.W.F.A.C Sapporo-Kosei General Hospital, Sapporo, Japan; [4]Gunma University Hospital, Maebashi, Japan; [5]JA Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital, Obihiro, Japan; [6]NHO Takasaki General Medical Center, Takasaki, Japan; [7]St. Marianna University School of Medicine, Kawasaki, Japan; [8]Saga University Hospital, Saga, Japan; [9]Nara Medical University Hospital, Nara, Japan; [10]Oita University Hospital, Yufu, Japan; [11]Mie University Hospital, Mie, Japan; [12]AbbVie Inc., North Chicago, Illinois, United States

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INTRODUCTION

- In Japan, 1.5 million individuals are estimated to have chronic hepatitis C virus (HCV) infection,[1–4] with genotype 1 (GT1) accounting for approximately 67% of cases[5]
- The health burden of chronic HCV infection in Japan is expected to rise over the next several years, due to projected disease progression combined with an aging population[6]
- Approved regimens in Japan for the treatment of HCV GT1-infected patients, which constitutes 67% of all HCV infections,[7] require 12 weeks of treatment and some are contraindicated or not recommended in some subpopulations including patients with severe renal impairment and those with the HCV NS5A Y93H polymorphism
- A highly efficacious regimen that can be used to treat HCV GT1-infected patients including those with the HCV NS5A Y93H baseline polymorphism over a shorter treatment duration would help improve the standard of care

Next Generation Direct-acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Collectively: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:[8]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Synergistic antiviral activity

Clinical PK & metabolism:
- Oral dosing of 3 pills once-daily
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg. Glecaprevir was identified by AbbVie and Enanta.

STUDY OBJECTIVE

- Evaluate the safety and efficacy of Glecaprevir/Pibrentasvir (G/P) in HCV GT1-infected Japanese patients including those with compensated cirrhosis

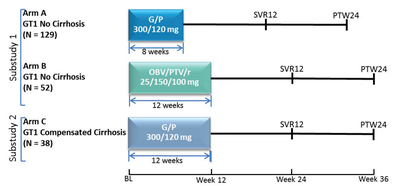
METHODS

- CERTAIN-1 is a phase 3, open-label, multicenter study assessing the safety and efficacy of once-daily G/P in Japanese patients with chronic HCV infection
- HCV GT1-infected patients without cirrhosis were enrolled in Substudy 1
  - Patients without the NS5A Y93H polymorphism were randomized 2:1 to 8 weeks of G/P or 12 weeks of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and were included in the primary efficacy analysis
  - Patients with the NS5A Y93H polymorphism were assigned to the G/P Arm
- HCV GT1-infected patients with compensated cirrhosis were enrolled in Substudy 2 and received 12 weeks of G/P
- The primary efficacy endpoint of Substudy 1 was assessed in the intent-to-treat (ITT)-PS population, defined as the ITT population excluding those with the NS5A Y93H polymorphism at baseline
- Efficacy and safety were assessed in the ITT population, defined as patients who received at least 1 dose of study drug

METHODS (CONTINUED)

- Efficacy was also assessed in the modified ITT (mITT) population which excludes those who did not achieve SVR12 due to reasons other than virologic failure

Figure 1. Study Design



PTW24 = post-treatment Week 24; BL = baseline; OBV/PTV/r = ombitasvir, paritaprevir, and ritonavir.

KEY ELIGIBILITY CRITERIA

Main inclusion criteria:

- Japanese patients aged 18 years or older (no upper limit)
- HCV GT1-infected, with HCV RNA level >1000 IU/mL at the time of screening
- Treatment-naïve or treatment-experienced (IFN-based with or without RBV), DAA naïve
- Patients without cirrhosis (Substudy 1) were required to demonstrate absence of cirrhosis with a liver biopsy (eg, METAVIR — or equivalent — score of ≤3 or an Ishak score of ≤4), a Fibroscan score <12.5 kPa, or FibroTest score ≤0.72 and Aspartate Aminotransferase to Platelet Ratio Index ≤2, or screening Discriminant Score (z) less than zero
- Patients with compensated cirrhosis (Substudy 2) were required to have 1 of the following: a liver biopsy with a METAVIR (or equivalent) score >3 or Ishak fibrosis score >4, a FibroTest score ≥0.73 with an Aminotransferase to Platelet Ratio Index >2, a FibroScan score ≥14.6 kPa or screening Discriminant Score (z) greater than zero

Main exclusion criteria:

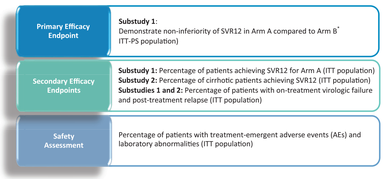
- A positive test result for hepatitis B surface antibody or anti-HIV antibody
- Clinical evidence of Child-Pugh B or C classification or clinical history of decompensated cirrhosis
- Any cause of liver disease other than chronic HCV infection
- Abnormal screening laboratory results **(Table 1)**

Table 1. Abnormal Laboratory Results Exclusion Criteria in Patients Without Cirrhosis and With Compensated Cirrhosis

Assessment	Without Cirrhosis	Compensated Cirrhosis
eGFR*, mL/min/1.73m^2	<30	<30
Serum albumin, g/dL	<LLN	<2.8
INR	≥1.2	≥1.8
Hemoglobin, g/dL	<10	<10
Platelet count, cells/mm^3	<90 000	<50 000

INR, International normalized ratio; LLN, lower limit of normal.
*eGFR, estimated glomerular filtration rate (using the MDRD method modified for Japanese population: eGFR = 194 × Serum Creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 [if female]).

STUDY ENDPOINTS AND ASSESSMENTS



*Non-inferiority achieved if lower bound of 95% CI of the difference in SVR12 (Arm A – Arm B) is above -10%.

RESULTS

PARTICIPANTS

- 181 patients with HCV GT1 infection without cirrhosis were enrolled and treated in Substudy 1; 129 in Arm A (including 23 patients with Y93H polymorphism) and 52 in Arm B
- 38 patients with HCV GT1 infection and compensated cirrhosis were enrolled and treated in Substudy 2

Table 2. Baseline Demographics and Disease Characteristics

Characteristic	Substudy 1 Without Cirrhosis: Arm A G/P 8 weeks N = 129	Substudy 1 Without Cirrhosis: Arm B OBV/PTV/r 12 weeks N = 52	Substudy 2 Compensated Cirrhosis: G/P 12 weeks N = 38
Female, n (%)	82 (64)	38 (73)	21 (55)
Age, median (range), years	64 (21–86)	67 (31–81)	73 (48–85)
BMI, mean ± SD, kg/m^2	24 ± 4	23 ± 4	24 ± 5
IL28B non-CC genotype, n (%)	50 (39)	20 (39)	7 (18)
Treatment-naïve	94 (73)	37 (71)	26 (68)
Treatment-experienced	35 (27)	15 (29)	12 (32)
HCV subtype			
1a	4 (3)	0	0
1b	125 (97)	52 (100)	38 (100)
NS5A Y93H present*	23 (18)	0	9 (24)
HCV RNA, mean ± SD, $\log_{10}$ IU/mL	6.1 ± 0.8	6.2 ± 0.6	6.0 ± 0.8

BMI, body mass index; G/P, Glecaprevir/Pibrentasvir; GT1, genotype 1; *IL28B*, interleukin 28B; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir.
*Presence of Y93H determined by SRL Medisearch Laboratories using direct sequencing, which has an approximate detection threshold of 15%.

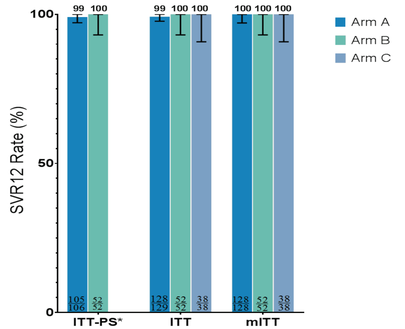
EFFICACY

- The CERTAIN-1 study met the primary endpoint (ITT-PS primary efficacy population)
  - The efficacy results observed in Arms A and B met the criteria for non-inferiority of the 8-week treatment duration of G/P to the 12-week treatment duration of OBV/PTV/r (SVR12 for Arm A – Arm B = -0.9%; 95% CI: -2.8%, 0.9%)

RESULTS (CONTINUED)

- SVR12 was achieved by 105/106 (99.1%) in the ITT-PS primary efficacy population randomized to receive 8 weeks of G/P in Arm A
  - No virologic failures occurred resulting in an SVR12 rate of 100% in the mITT population
  - The single patient not achieving SVR12 was lost to follow-up after achieving SVR4
- SVR12 was achieved by 52/52 (100%) patients enrolled in Arm B and treated with OBV/PTV/r for 12 weeks
- SVR12 was achieved by all 23 (100%) HCV GT1-infected patients with Y93H polymorphism in the 8-week G/P arm
- SVR12 was achieved by all 38 (100%) HCV GT1-infected patients with compensated cirrhosis
- No virologic failures occurred in any patient receiving G/P, with or without compensated cirrhosis, therefore baseline patient and viral characteristics, including the presence of NS5A Y93H as well as other baseline polymorphisms, had no impact on SVR12

Figure 2. SVR12 Rates For Each Arm in the ITT-PS, ITT, and mITT Populations



*The primary efficacy population of Substudy 1, ITT-PS, excludes patients with the HCV Y93H polymorphism.
Arm A: 8-week G/P treatment; Arm B: 12-week OBV/PTV/r treatment; Arm C: 12-week G/P treatment.
ITT = intent-to-treat, mITT = modified ITT (excludes failures due to reasons other than virologic failures).
The error bars represent the 95% confidence intervals.
In Arm A, 1 patient was lost to follow-up.

SAFETY

- Adverse events (AEs) were experienced by 57% and 67% of non-cirrhotic patients in Arms A and B (Substudy 1), respectively, and by 66% in patients with compensated cirrhosis in Substudy 2
- One patient with compensated cirrhosis discontinued treatment at Day 14 due to a Grade 2 AE (drug eruption described as generalized erythematous papular rash) that was assessed as study–drug related by the treating physician
- No serious adverse events occurred in patients treated with G/P
- No cases of liver decompensation occurred in any arm
- Laboratory abnormalities were rare across all treatment arms. For patients (with or without cirrhosis) treated with G/P, no grade ≥3 abnormalities occurred in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels

Table 3. Treatment-emergent Adverse Events

Event	Substudy 1 Without Cirrhosis: Arm A G/P 8 weeks N = 129 n (%)	Substudy 1 Without Cirrhosis: Arm B OBV/PTV/r 12 weeks N = 52 n (%)	Substudy 2 Compensated Cirrhosis: Arm C G/P 12 weeks N = 38 n (%)
Any AE	74 (57)	35 (67)	25 (66)
Any drug-related AE	30 (23)	14 (27)	7 (18)
Any serious AE	0	3 (6)	0
Any DAA-related serious AE	0	1 (2)	0
Any AE leading to D/C of study drug	0	1 (2)	1 (3)
Any AE leading to interruption of study drug	0	1 (2)	0
Common AEs (occurring in ≥5% and ≥2 patients in any arm)			
Nasopharyngitis	20 (16)	7 (14)	3 (8)
Malaise	3 (2)	0	4 (11)
Pruritus	8 (6)	5 (10)	2 (5)
Headache	6 (5)	5 (10)	1 (3)
Hypertension	4 (3)	4 (8)	1 (3)
Blood bilirubin increased	3 (2)	3 (6)	1 (3)
Cystitis	1 (1)	3 (6)	0
Cough	1 (1)	1 (2)	2 (5)
Rash	3 (2)	3 (6)	2 (5)
Atrial fibrillation	0	0	2 (5)
Head discomfort	0	0	2 (5)
Oropharyngeal pain	0	0	2 (5)
Pruritus generalized	0	0	2 (5)

Table 4. Key Post-baseline Laboratory Abnormalities

Laboratory abnormalities	Substudy 1 Without Cirrhosis: Arm A G/P 8 weeks N = 129 n (%)	Substudy 1 Without Cirrhosis: Arm B OBV/PTV/r 12 weeks N = 52 n (%)	Substudy 2 Compensated Cirrhosis: Arm C G/P 12 weeks N = 38 n (%)
Haemoglobin			
Grade 2 (<10–8 g/dL)	2 (1.6)	4 (7.7)	1 (2.6)
Grade ≥3 (<8 g/dL)	0	0	0
Alanine aminotransferase			
Grade 2 (>3–5 × ULN)	1 (0.8)	1 (1.9)	0
Grade ≥3 (>5 × ULN)	0	1 (1.9)	0
Aspartate aminotransferase			
Grade 2 (>3–5 × ULN)	1 (0.8)	1 (1.9)	0
Grade ≥3 (>5 × ULN)	0	0	0
Total bilirubin			
Grade 2 (>1.5–3 × ULN)	2 (1.6)	3 (5.8)	3 (7.9)
Grade ≥3 (>3 × ULN)	0	0	0

ULN = upper limit of the normal range.

CONCLUSIONS

- SVR12 was achieved in 99.1% of Japanese patients with HCV GT1 infection without cirrhosis and without the HCV NS5A Y93H polymorphism at baseline following 8 weeks of treatment with G/P, no patient experienced virologic failure
  - Non-inferiority compared to 12 weeks of treatment with OBV/PTV/r was achieved
  - High SVR rates were achieved regardless of patient and disease characteristics
- All 23 patients with GT1 infection and the HCV Y93H polymorphism without cirrhosis achieved SVR12 following 8 weeks of treatment with G/P
- All 38 patients with GT1 infection and compensated cirrhosis achieved SVR12 following 12 weeks of treatment with G/P
- G/P administered for 8 or 12 weeks was well tolerated and demonstrated a favorable safety profile, with no serious AEs and low rates of liver-related laboratory abnormalities
  - No patient experienced a grade 3 total bilirubin
  - No patient experienced laboratory abnormalities indicating liver disease progression
  - No cases were consistent with Drug-induced Liver Injury (DILI)
  - No patient experienced hepatic decompensation
- The once daily, RBV-free investigational G/P may provide an 8-week treatment option for HCV GT1-infected DAA treatment-naïve non-cirrhotic Japanese patients without the need for pretreatment testing for the Y93H polymorphism, and a 12-week treatment option for GT1-infected Japanese patients with compensated cirrhosis

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DISCLOSURES

AbbVie sponsored the study (NCT02707952), contributed to its design, the collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the publication. All authors had access to relevant data.

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abbvie

Efficacy and Safety of Glecaprevir/Pibrentasvir in Japanese Patients With Chronic Genotype 2 Hepatitis C Virus Infection With and Without Cirrhosis

Kazuaki Chayama[1], Fumitaka Suzuki[2], Ken Sato[3], Tomofumi Atarashi[4], Tsunamasa Watanabe[5], Hidenori Toyoda[6], Masanori Atsukawa[7], Atsushi Naganuma[8], Kazuo Notsumata[9], Yukio Osaki[10], Makoto Nakamuta[11], Koichi Takaguchi[12], Satoru Saito[13], Koji Kato[14], David L Pugatch[14], Margaret Burroughs[14], Rebecca Redman[14], Katia Alves[14], Tami J Pilot-Matias[14], Bo Fu[14], Hiromitsu Kumada[2]

[1]Hiroshima University Hospital, Hiroshima, Japan; [2]Toranomon Hospital, Tokyo, Japan; [3]Gunma University Hospital, Maebashi, Japan; [4]JA Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital, Obihiro, Japan; [5]St. Marianna University School of Medicine, Kawasaki, Japan; [6]Ogaki Municipal Hospital, Ogaki, Japan; [7]Nippon Medical School Chiba Hokusoh Hospital, Inzai, Japan; [8]NHO Takasaki General Medical Center, Takasaki, Japan; [9]Fukuiken Saiseikai Hospital, Fukui, Japan; [10]Osaka Red Cross Hospital, Osaka, Japan; [11]NHO Kyushu Medical Center, Fukuoka, Japan; [12]Kagawa Prefectural Central Hospital, Takamatsu, Japan; [13]Yokohama City University Hospital, Yokohama, Japan; [14]AbbVie Inc., North Chicago, Illinois, United States

Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver, 19–23 April 2017, Amsterdam, the Netherlands

INTRODUCTION

- In Japan, 1.5 million individuals are estimated to have chronic hepatitis C virus (HCV) infection,[1–4] with genotype 2 (GT2) accounting for approximately 30% of cases[5]
- The Japanese HCV patient population tends to be older and have a higher rate of advanced liver disease compared to patients in the United States and Europe, and as such the health burden of HCV infection is expected to rise in the coming years[6,7]
- The current standard of care for HCV GT2-infected patients in Japan requires co-administration with ribavirin (RBV): sofosbuvir (SOF) + RBV for 12 weeks or OBV/PTV/r + RBV for GT2a HCV-infected patients without cirrhosis for 16 weeks[8]
- RBV is associated with adverse events, notably anemia, and is contraindicated in Japan for use in patients with renal impairment (CrCl ≤50 mL/min). In addition, SOF is contraindicated in patients with severe renal impairment[9]
- A once-daily, potent, safe and RBV-free regimen with high efficacy for treatment of HCV GT2, regardless of baseline patient demographics or viral characteristics can help improve the standard of care for HCV GT2-infected patients in Japan

Next Generation Direct-acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:[10]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Synergistic antiviral activity

Clinical PK & metabolism:
- Oral dosing of 3 pills once-daily
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg. Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVE

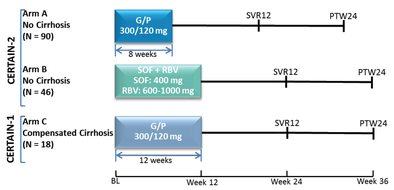
- Evaluate the safety and efficacy of Glecaprevir/Pibrentasvir (G/P) in HCV GT2-infected Japanese patients including those with compensated cirrhosis

METHODS

- CERTAIN-1 and CERTAIN-2 are phase 3, open-label, multicenter studies assessing the safety and efficacy of G/P (300/120mg) once daily in Japanese patients with HCV infection
- Patients without cirrhosis enrolled in CERTAIN-2 had HCV GT2 infection and were randomized 2:1 to treatment with 8 weeks with G/P (Arm A) or 12 weeks with SOF (400 mg QD) + RBV (600–1000 mg weight-based, divided BID) (Arm B)
- A cohort of patients enrolled in CERTAIN-1 (Arm C) had GT2 infection and compensated cirrhosis and were assigned to treatment with G/P for 12 weeks
- Safety and efficacy were assessed in the intent-to-treat (ITT) population, defined as all patients who received at least 1 dose of study drug. Efficacy was also assessed in the modified ITT (mTT) population, defined as the ITT population excluding patients who failed to achieve SVR12 for reasons other than virologic failure

METHODS (CONTINUED)

Figure 1. Study Design



PTW24 = post-treatment Week 24; BL = baseline.
RBV dosing: 600–1000 mg weight-based, divided BID.

KEY ELIGIBILITY CRITERIA

Main inclusion criteria:

- Japanese patients aged 18 years or older (no upper limit)
- HCV GT2 infected with HCV RNA level >1000 IU/mL at the time of screening
- Treatment-naïve or treatment-experienced (IFN-based with or without RBV)
- Patients without cirrhosis (CERTAIN-2) were required to demonstrate absence of cirrhosis with a liver biopsy (eg, METAVIR — or equivalent — Score of ≤3 or an Ishak score of ≤4), a Fibroscan score <12.5 kPa, or FibroTest score ≤0.72 and Aspartate Aminotransferase to Platelet Ratio Index ≤2, or screening Discriminant Score (z) less than zero
- Patients with compensated cirrhosis (CERTAIN-1) were required to have 1 of the following: a liver biopsy with a METAVIR (or equivalent) score >3 or Ishak score >4, a FibroTest score ≥0.73 with an Aminotransferase to Platelet Ratio Index >2, a FibroScan score ≥14.6 kPa or screening Discriminant Score (z) greater than zero

Main exclusion criteria:

- A positive test result for hepatitis B surface antigen or anti-HIV antibody
- Clinical evidence of Child-Pugh B or C classification or clinical history of decompensated cirrhosis
- Any cause of liver disease other than chronic HCV-infection
- Abnormal screening laboratory results **(Table 1)**

Table 1. Abnormal Laboratory Results Exclusion Criteria for Patients Without Cirrhosis and Patients With Compensated Cirrhosis

Assessment	Without Cirrhosis	Compensated Cirrhosis
eGFR*, mL/min/1.73m^2	N/A	<30
CrCl, mL/min	≤50	N/A
Serum albumin, g/dL	<LLN (3.3 g/dL)	<2.8
INR	≥1.2	≥1.8
Hemoglobin, g/dL	<12	<10
Platelet count, cells/mm^3	<90 000	<50 000

INR, International normalized ratio; LLN, lower limit of normal. CrCl, creatinine clearance.
*eGFR, estimated glomerular filtration rate (using the MDRD method modified for Japanese population: eGFR = 194 × Serum Creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female)).

STUDY ENDPOINTS AND ASSESSMENTS

Primary Efficacy Endpoint	**CERTAIN-2:** Demonstrate non-inferiority of SVR12 in Arm A compared to Arm B* (ITT population)
Secondary Efficacy Endpoints	**CERTAIN-2:** Percentage of patients achieving SVR12 for Arm A (ITT population) **CERTAIN-1:** Percentage of cirrhotic patients achieving SVR12 (ITT population) **CERTAIN-1 & CERTAIN-2: Per**centage of patients with on-treatment virologic failure and post-treatment relapse (ITT population)
Safety Assessment	Percentage of patients with treatment-emergent adverse events (AEs) and laboratory abnormalities (ITT population)

*Non-inferiority achieved if lower bound of 95% CI of the difference in SVR12 (Arm A – Arm B) is above -10%.

RESULTS

PARTICIPANTS

- 136 patients with HCV GT2 infection without cirrhosis were enrolled in CERTAIN-2 and randomized 2:1 to Arms A (n = 90) and B (n = 46), respectively
- 18 patients with HCV GT2 infection and compensated cirrhosis were enrolled in Arm C of CERTAIN-1
- Consistent with the demographics of HCV infections in Japan, the majority of patients in all treatment arms were female, elderly and infected with HCV GT2a

Table 2. Baseline Demographics and Disease Characteristics

Characteristic	CERTAIN-2 Without Cirrhosis: Arm A G/P 8 weeks N = 90	CERTAIN-2 Without Cirrhosis: Arm B SOF + RBV 12 weeks N = 46	CERTAIN-1 Compensated Cirrhosis: Arm C G/P 12 weeks N = 18
Female, n (%)	48 (53)	25 (54)	11 (61)
Age, median (range), years	57 (26-83)	58 (21-84)	70 (49-85)
BMI, mean ± SD, kg/m^2	22.9 ± 3.3	23.0 ± 4.2*	22.2 ± 3.5
HCV subtype†			
2a, n (%)	65 (72)	30 (65)	10 (56)
2b, n (%)	25 (28)	16 (35)	8 (44)
IL28B non-CC genotype, n (%)	23 (26)	9 (20)	3 (17)
HCV RNA, mean ± SD, $\log_{10}$ IU/mL	6.0 ± 0.8	6.1 ± 0.8	5.3 ± 1.0
Treatment-experienced, n (%)	15 (17)	8 (17)	7 (39)

BMI, body mass index; G/P, Glecaprevir/Pibrentasvir; *IL28B*, interleukin 28B; SOF+RBV, sofosbuvir+ ribavirin.
*N = 45.
†HCV subtype determined by phylogenetic analysis of baseline NS3/4A and/or NS5A sequence.

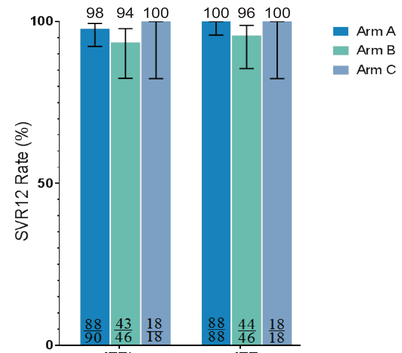
EFFICACY

- The CERTAIN-2 study met the primary endpoint (ITT primary efficacy population): G/P for 8 weeks was non-inferior to SOF + RBV for 12 weeks
  - The difference in SVR12 between Arms A and B (4.3; 95% CI:-3.5, 12.1) met the criteria for non-inferiority as the lower bound of the 95% CI was above the predefined threshold of -10%
- SVR12 was achieved by 88/90 (97.8%) patients enrolled in Arm A and treated with G/P for 8 weeks (ITT population)
  - No virologic failures occurred
  - One patient not achieving SVR12 was lost to follow-up after achieving SVR4, while the other prematurely discontinued study drug due to an adverse event (AE) (nausea and vomiting) after 18 days of treatment with undetectable HCV RNA at the time of discontinuation

RESULTS (CONTINUED)

- SVR12 was achieved by 43/46 (93.5%) patients enrolled in Arm B and treated with SOF + RBV for 12 weeks (ITT population)
  - Two patients had virologic relapse by post-treatment Week 12, the third patient not achieving SVR12 prematurely discontinued treatment
- 100% (18/18) HCV GT2-infected patients with compensated cirrhosis enrolled in CERTAIN-1 Arm C and treated with G/P for 12 weeks achieved SVR12

Figure 2. SVR12 Rates For Each Arm in the ITT and mITT Populations



*ITT = intent-to-treat, mITT = modified ITT (excludes failures due to reasons other than virologic failures).
Arm A: 8-week G/P treatment; Arm B: 12-week SOF+RBV treatment; Arm C: 12-week G/P treatment.
In Arm A, 1 patient was lost to follow-up and 1 patient discontinued study drug.
In Arm B, 2 patients had a relapse and 1 patient discontinued study drug.
The error bars represent the 95% confidence intervals.

SAFETY

- The lower rates of AEs in Arm A compared to Arm B are statistically significant (P = .002 and P <.001 for all AEs and drug-related AEs, respectively; **Table 3**)
  - AEs that occurred at a statistically significant lower rate in Arm A than Arm B (P <.05) were anaemia, blood bilirubin increase and hyperuricaemia
- Two patients (2%) in Arm A experienced serious adverse events, spontaneous pneumothorax in 1 patient and unstable angina in the other, neither event was assessed by the treating physician as being related to G/P
- One patient (1%) in Arm A discontinued study drug due to a drug-related AE (nausea and vomiting) after 18 days of treatment
- One patient (2%) in Arm B discontinued study drug due to a drug-related AE (Malaise) after 12 days of treatment
- No liver decompensation events occurred in any arm
- One patient in CERTAIN-1 (Arm-C) discontinued study drug due to a Grade 2 drug-related AE (drug eruption, on Day 12, characterized as a patchy purpuric rash and eczema) which was resolved on Day 29
- Post-baseline abnormalities in key laboratory parameters were rare across all treatment arms **(Table 4)**
  - No Grade ≥3 abnormalities occurred in hemoglobin, alanine aminotransferase or aspartate aminotransferase levels in patients treated with G/P
  - One patient with compensated cirrhosis treated with G/P had a Grade 3 elevation in total bilirubin (predominantly indirect bilirubin) at Week 1, which returned to baseline (Grade 2) at the Day 15 visit, with no concomitant ALT elevation
  - Post-baseline Grade ≥2 levels in hemoglobin and total bilirubin were statistically significantly lower in patients in Arm A compared to Arm B
  - One patient in Arm B treated with SOF+RBV had a Grade 3 elevation in total bilirubin levels lasting for approximately 58 days

Table 3. Treatment-emergent Adverse Events

Event	CERTAIN-2 Without Cirrhosis: Arm A G/P N = 90 n (%)	CERTAIN-2 Without Cirrhosis: Arm B SOF + RBV N = 46 n (%)	CERTAIN-1 Compensated Cirrhosis: Arm C G/P N = 18 n (%)
Any AE*	43 (48)	35 (76)	12 (67)
Any drug-related AE†	16 (18)	23 (50)	7 (39)
Any serious AE	2 (2)‡	2 (4)§	0
Any study–drug related serious AE	0	1 (2)	0
Any AE leading to D/C of study drug	1 (1.1)‖	1 (2.2)¶	1 (6)
Any AE leading to interruption of study drug	0	2 (4.3)**	0
Common AEs (occurring in ≥5% and ≥2 patient in any group)			
Anaemia††	0	16 (35)	1 (6)
Pruritus	3 (3)	2 (4)	4 (22)
Blood bilirubin increased††	1 (1)	7 (15)	2 (11)
Nasopharyngitis	9 (10)	5 (11)	2 (11)
Malaise	5 (6)	4 (9)	1 (6)
Headache	6 (7)	1 (2)	0
Nausea	3 (3)	3 (7)	0
Stomatitis	1 (1)	3 (7)	0
Hyperuricaemia§§	0	3 (7)	0

*Difference between Arm A and Arm B is statistically significant (P = .002).
†Difference between Arm A and Arm B is statistically significant (P <.001).
‡Pneumothorax spontaneous and angina unstable.
§Pneumonia and Castleman's disease, the former assessed as not drug-related and the latter as drug related.
‖Nausea and vomiting.
¶Malaise.
**Pneumonia and anaemia, the latter assessed as study-drug related.
††Difference between Arm A and Arm B is statistically significant (P <.001).
‡‡Difference between Arm A and Arm B is statistically significant (P = .002).
§§Difference between Arm A and Arm B is statistically significant (P = .037).

Table 4. Key Post-baseline Laboratory Abnormalities

Laboratory abnormalities	CERTAIN-2 Without Cirrhosis: Arm A G/P N = 90 n (%)	CERTAIN-2 Without Cirrhosis: Arm B SOF + RBV N = 46 n (%)	CERTAIN-1 Compensated Cirrhosis: Arm C G/P N = 18 n (%)
Haemoglobin			
Grade 2 (<10–8 g/dL)*	1 (1)	4 (9)	2 (11)
Grade ≥3 (<8 g/dL)	0	1 (2)	0
Alanine aminotransferase			
Grade 2 (>3–5 × ULN)	0	0	0
Grade ≥3 (>5 × ULN)	0	0	0
Aspartate aminotransferase			
Grade 2 (>3–5 × ULN)	0	0	1 (6)
Grade ≥3 (>5 × ULN)	0	0	0
Total bilirubin			
Grade 2 (>1.5–3 × ULN)†	4 (4)	9 (22)	2 (11)
Grade ≥3 (>3 × ULN)	0	1 (2)	1 (6)

ULN, upper limit of the normal range.
*Difference in Grade ≥2 between Arm A and B was statistically significant (P = .017).
†Difference in Grade ≥2 between Arm A and B was statistically significant (P = .005).

CONCLUSIONS

- 97.8% SVR12 was achieved in HCV GT2-infected Japanese patients without cirrhosis following 8 weeks of treatment with G/P
  - No virologic failures occurred
  - The 8-week G/P treatment regimen was non-inferior to the 12 week SOF + RBV regimen
  - High SVR rates were achieved regardless of patient and disease characteristics
- 100% SVR12 was achieved in HCV GT2-infected patients with compensated cirrhosis following 12 weeks of treatment with G/P
- G/P administered for 8 and 12 weeks was well tolerated, with no drug-related serious AEs reported and low rates of liver-related laboratory abnormalities
  - 1 patient experienced a Grade 3 total bilirubin with indirect predominance and without concurrent ALT elevation or other laboratory abnormalities indicating liver disease progression (eg, no concomitant increases in INR or decreases in albumin)
  - No cases were consistent with Drug-induced Liver Injury (DILI)
  - No patients experienced hepatic decompensation
- G/P is an investigational, once daily, all-oral, RBV-free treatment regimen with high rates of SVR12 and favorable tolerability profile in HCV GT2-infected Japanese patients including those with compensated cirrhosis, and shorter treatment duration for HCV GT2-infected patients without cirrhosis than current standard of care regimens

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Safety of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1–6 Hepatitis C Virus Infection: An Integrated Analysis

FRI-238

Jean-Francois Dufour[1], Eli Zuckerman[2], Neddie Zadeikis[3], Christophe Hezode[4], Seung Woon Paik[5], Pietro Andreone[6], Ola Weiland[7], Jihad Slim[8], Steven L Flamm[9], Timothy Morgan[10], Hugo Vargas[11], Simone Strasser[12], Ashley Brown[13], Yao Yu[3], Ariel Porcalla[3], Federico J Mensa[3]

[1]University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland; [2]Carmel Medical Center Liver Institute, Haifa, Israel; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]Hôpital Henri Mondor, Université Paris-Est, Créteil, France; [5]Samsung Medical Center, Seoul, Republic of Korea; [6]Dipartimento di Scienze Mediche e Chirurgiche, University of Bologna, Bologna, Italy; [7]Karolinska University Hospital Huddinge, Karolinska Institutet, Stockholm, Sweden; [8]St. Michael's Medical Center, Newark, New Jersey, United States; [9]Northwestern Feinberg School of Medicine, Chicago, Illinois, United States; [10]Veteran's Affairs Long Beach Healthcare System, Long Beach, California, United States; [11]Mayo Clinic, Phoenix, Arizona, United States; [12]Royal Prince Alfred Hospital, Sydney, New South Wales, Australia; [13]Imperial College Healthcare, London, United Kingdom

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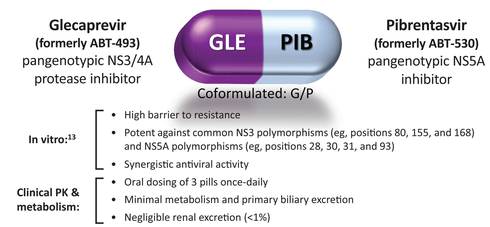
BACKGROUND

- Chronic hepatitis C virus (HCV) infection is a major cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease[1]; achieving a sustained virologic response (SVR) is associated with reduced risk of developing cirrhosis, hepatic decompensation, HCC, and death[2]
- Glecaprevir (formerly ABT-493), an NS3/4A protease inhibitor, and pibrentasvir (formerly ABT-530), an NS5A inhibitor, are direct-acting antivirals (DAAs) being developed as a once-daily, fixed-dose combination regimen (G/P) to treat genotype (GT) 1–6 HCV infection **(Figure 1)**
- In phase 2 studies and a large registrational programme, G/P achieved SVR12 rates of 95% or greater in patients infected with GT 1–6 and demonstrated a favourable safety profile without relevant laboratory abnormalities or alanine aminotransferase (ALT) elevations[3–12]
- Here we report results of an integrated safety analysis of 2265 patients treated with G/P 300/120 mg once daily, regardless of formulation, in phase 2 or 3 studies

Figure 1. Next Generation Direct-acting Antivirals



G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Note in the phase 2 SURVEYOR-I and SURVEYOR-II studies, once daily GLE (300 mg) + PIB (120 mg) were administered separately.
Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVES

- To describe the safety of G/P in patients treated for 8, 12, or 16 weeks across eight phase 2 or 3 studies, including all major HCV genotypes
  - This analysis focuses primarily on patients without cirrhosis; however, safety data are also presented for those patients with compensated cirrhosis to allow comparison of the safety profiles; detailed safety and pharmacokinetic (PK) information for patients with compensated cirrhosis is being presented separately (Gane E, et al. EASL 2017, Poster number: THU-263)

METHODS

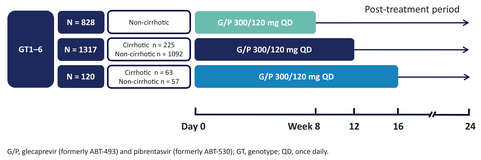
STUDY DESIGN

- Eight global, multicentre, open-label or double blind and placebo controlled phase 2 and 3 clinical trials were included in this analysis:
  - ENDURANCE-I (NCT02604017): phase 3, randomised study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT1 infection
  - ENDURANCE-II (NCT02640482): phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT2 Infection
  - ENDURANCE-III (NCT02640157): phase 3, randomised, active-controlled study to compare efficacy and safety of G/P with sofosbuvir (SOF) co-administered with daclatasvir in adults with chronic HCV GT3 infection (Foster GR, et al. EASL 2017, Oral presentation number: GS-006)
  - ENDURANCE-IV (NCT02636595): phase 3, single-arm study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT4, GT5, or GT6 infection
  - EXPEDITION-I (NCT02642432): phase 3, single-arm study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic HCV GT1, GT2, GT4, GT5, or GT6 infection and compensated cirrhosis (Forns X, et al. EASL 2017, Oral presentation number: GS-005)

METHODS (CONTINUED)

  - MAGELLAN-I (NCT02446717): phase 2, randomised study to evaluate the efficacy, safety, and PK of co-administration of GLE and PIB or G/P ± ribavirin (RBV) in adults with chronic HCV infection who failed a prior DAA-containing therapy (Poordad F, et al. EASL 2017, Oral presentation number: PS-156). Patients who received RBV were excluded from this integrated analysis
  - SURVEYOR-I (NCT02243280): phase 2 study to evaluate the efficacy, safety, and PK of co-administration of GLE and PIB ± RBV in subjects with HCV GT1, GT4, GT5, or GT6 infection. Patients who received RBV were excluded from this integrated analysis
  - SURVEYOR-II (NCT02243293): phase 2/3, randomised, multi-part study to evaluate the efficacy, safety, and PK of co-administration of GLE and PIB ± RBV in subjects with chronic HCV GT2–6 infection. Patients who received RBV were excluded from this integrated analysis
- Patients were assigned to treatment arms of 8-, 12-, or 16-week duration, as defined in the study protocols **(Figure 2)**

Figure 2. Phase 2 and 3 Multicenter Studies of GT1–6 HCV-infected Patients Without Cirrhosis or With Compensated Cirrhosis



G/P, glecaprevir (formerly ABT-493) and pibrentasvir (formerly ABT-530); GT, genotype; QD, once daily.

KEY ELIGIBILITY CRITERIA

- Eligible patients were treatment-naive or treatment-experienced with prior pegylated interferon (pegIFN)/RBV or SOF + RBV ± pegIFN or in the MAGELLAN-1 study, experienced with a NS5A and/or protease inhibitor-containing regimen. Patients were ≥18 years of age with no upper limit, with compensated liver disease, and without HIV (except ENDURANCE-1) or HBV co-infection
- Compensated cirrhosis was confirmed at screening by:
  - Child-Pugh score ≤6, and no current or past clinical evidence of Child-Pugh B or C classification, or clinical history of liver decompensation
  - Documentation of one of the following:
    - Histological diagnosis from liver biopsy
    - FibroTest score ≥0.75 and aspartate aminotransferase (AST): platelet ratio index (APRI) >2
    - FibroScan score ≥ 14.6 kPa
- Patients documented as non-cirrhotic were defined as meeting one of the following criteria:
  - Histological diagnosis from liver biopsy demonstrating the absence of cirrhosis
  - FibroTest score <12.5 kPa or indeterminate FibroTest score ≥12.5 –<14.6 kPa with a qualifying liver biopsy
  - FibroTest score ≤0.48 and AST–APRI <1 or indeterminate FibroTest score >0.48–<0.75 kPa, or conflicting APRI results with a qualifying liver biopsy
- At screening, patients must not have co-infection with >1 HCV GT; HCC; ALT, or AST levels >10 × the upper limit of normal (ULN) (or >5 × ULN in SURVEYOR-I); creatinine clearance <50 mL/min; or international normalised ratio (INR) >2.3 (unless subject has known haemophilia or is on a stable anticoagulant regimen affecting INR); albumin <2.8 g/dL; total bilirubin >3.0 × ULN
- Patients at screening must have had platelets ≥60 000 cells per mm^3 (≥120 000 cells per mm^3 in SURVEYOR-I and SURVEYOR-II) and ≥90 000 cells per mm^3 in patients with compensated cirrhosis and without, respectively

STUDY ASSESSMENTS

- Percentage of patients with SVR12 (HCV RNA <LLOQ 12 weeks after the last dose of study drug)
- Adverse events (AEs), including serious adverse events (SAEs) and those leading to treatment discontinuation and death, and clinical laboratory parameters were monitored throughout the treatment and immediate post-treatment periods (within 30 days after treatment completion)
- Safety analyses included pooled AEs and laboratory data from all patients who received at least 1 dose of study drug in the studies specified

RESULTS

- A total of 2265 patients were enrolled from 25 countries and included in this safety analysis
- Baseline demographic and clinical characteristics stratified by cirrhotic status are shown in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Patients without cirrhosis n = 1977	Patients with compensated cirrhosis n = 288	Total N = 2265
Male, n (%)	1057 (54)	182 (63)	1239 (55)
Age, median (range), years	53 (19–84)	58 (26–88)	54 (19–88)
White race, n (%)	1590 (81)	244 (85)	1834 (81)
BMI, median (range), kg/m^2	26 (17–66)	28 (18–55)	26 (17–66)
HCV genotype, n (%)			
1	821 (42)	112 (39)	933 (41)
2	426 (22)	34 (12)	460 (20)
3	517 (26)	115 (40)	632 (28)
4	144 (7)	18 (6)	162 (7)
5	29 (2)	2 (1)	31 (1)
6	40 (2)	7 (2)	47 (2)
Treatment-naive, n (%)	1406 (71)	174 (60)	1580 (70)
Treatment-experienced, n (%)	571 (29)	114 (40)	685 (30)
PRS-experienced	485 (25)	87 (30)	572 (25)
NS5A- and/or PI-experienced	86 (4)	27 (9)	113 (5)
Baseline fibrosis stage, n (%)			
F0–F1	1593 (81)	0	1593 (71)
F2	154 (8)	0	154 (7)
F3	226 (12)	2 (<1)	228 (10)
F4	0	286 (99)	286 (13)
Missing	4	0	4
Baseline HCV RNA level, log_{10} IU/mL, median (range)	6.2 (0.8–7.8)	6.2 (3.1–7.4)	6.2 (0.7–7.8)
Baseline platelet, $10^{\wedge 9}$/L, n (%)			
<100	6 (<1)	68 (24)	74 (3)
≥100	1971 (99)	220 (76)	2191 (97)
Baseline eGFR, mL/min/1.73 m^2, n (%)			
<30	0	0	0
≥30–<60	27 (1)	8 (3)	35 (2)
≥60–<90	930 (49)	115 (46)	1045 (46)
≥90	925 (49)	129 (51)	1054 (46)
Missing	95	36	131

BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; PI, protease inhibitor; PRS, pegIFN/RBV or SOF + RBV ± pegIFN.

RESULTS (CONTINUED)

EFFICACY

- Overall, 97% (1926/1977) of patients without cirrhosis achieved SVR12 (intent-to-treat); high SVR12 rates were achieved irrespective of HCV GT

SAFETY

ADVERSE EVENTS

- Overall, 68% (1529/2265) of patients reported experiencing ≥1 AE of any type; 67% (1316/1977) of non-cirrhotic patients experienced an AE **(Table 2)**
- The most commonly reported AEs (>10%) were headache and fatigue
- Most AEs were mild in severity, and the frequency and severity were similar in patients with compensated cirrhosis compared with those without cirrhosis
- Only 1 patient experienced an SAE considered by the investigator to be possibly DAA-related (transient ischemic attack) on Day 11; the patient discontinued treatment on Day 12 and the SAE resolved the same day. The patient did not return for SVR12 **(Table 2)**
- Eight (0.4%) patients without cirrhosis experienced an AE that led to discontinuation of study drug; of which 3 patients discontinued study drugs due to AEs assessed as being possibly related to DAA treatment
- All deaths were considered not related to the study drug

Table 2. Summary of Adverse Events

Event	Non-cirrhotic patients n = 1977	Patients with compensated cirrhosis n = 288	Total N = 2265
Any AE, n (%)	1316 (67)	213 (74)	1529 (68)
AE occurring in ≥10% of patients, n (%)			
Headache	363 (18)	47 (16)	410 (18)
Fatigue	272 (14)	58 (20)	330 (15)
Any SAE	31 (2)	17 (6)	48 (2.1)
DAA-related SAE	1 (<0.1)	0	1 (<0.1)
Any AE leading to discontinuation of study drug*	8 (0.4)	0	8 (0.4)
Any DAA-related AE with ≥grade 3†	4 (0.2)	0	4 (0.2)
Any fatal AE	2 (0.1)	0	2 (<0.1)
Death‡	5 (0.3)	1 (0.3)	6 (0.3)

*Of the total 8 patients, 3 patients experienced a total of 9 DAA-related AEs leading to study drug discontinuation, including abdominal pain, diarrhoea, dyspepsia, nausea, fatigue, malaise, dizziness, headache, and transient ischaemic attack; †four (0.2%) patients experienced any DAA-related AE with ≥grade 3, including upper abdominal pain, asthenia, migraine, and increased ALT, AST, and GGT; ‡causes of death, all n = 1: pneumonia, accidental overdose, adenocarcinoma, hepatic cancer metastatic, cerebral haemorrhage, alcohol poisoning, and toxicity to various agents. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; SAE, serious adverse event.

LABORATORY ABNORMALITIES

- Two (<0.1%) patients experienced grade 3 elevations in ALT from baseline (>5 × ULN, grade higher than baseline)
  - Across the phase 2 and 3 studies, four (<0.1%) patients experienced a post-nadir grade 3 in ALT (>5 × ULN). All 4 patients were non-cirrhotic and elevations were considered not clinically relevant or most likely associated with etiologies unrelated to study drug (passage of gallstone)
- No cases consistent with drug-induced liver injury occurred **(Table 3)**
- Six patients (0.3%) without cirrhosis experienced grade 3 (>3 × ULN) elevations of total bilirubin. Most of these were transient elevations of predominantly indirect bilirubin without associated ALT increase in patients with indirect hyperbilirubinaemia at baseline (Gilbert's syndrome) **(Table 3)**
- No patients discontinued prematurely due to laboratory abnormalities

Table 3. Summary of Laboratory Abnormalities

Laboratory abnormalities	Non-cirrhotic patients n/N (%)	Patients with compensated cirrhosis n/N(%)	Total n/N(%)
ALT ≥grade 3 (>5 × ULN)*	2/1975 (0.1)	0	2/2263 (<0.1)†
Total bilirubin ≥grade 3 (>3 × ULN)*	6/1975 (0.3)	2/288 (0.7)	8/2263 (0.4)‡

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
*Increased grade from baseline result; †One patient experienced grade 3 and above ALT (>5 × ULN) elevations concomitant with total bilirubin (>2 × ULN) elevations 1 day post-treatment. Laboratory abnormalities were consistent with an obstructive pattern, most likely due to transient passage of a biliary stone; ‡Most elevations were predominantly indirect bilirubin without associated ALT increase in patients with indirect hyperbilirubinemia at baseline (Gilbert's syndrome).

CONCLUSIONS

- In patients with HCV GT1–6 infection treated in phase 2 and 3 clinical studies, G/P achieved 97% (1926/1977) SVR12 in non-cirrhotic patients and 97% (279/288) SVR12 in cirrhotic patients. G/P was well tolerated, with very low rates of discontinuations and DAA-related SAEs
- The safety profile in subjects with cirrhosis was similar to those in subjects without cirrhosis (see also Gane E, et al. EASL 2017, Poster number: THU-263)
- Grade ≥3 laboratory abnormalities more severe than baseline were infrequent

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JF Dufour: Advisor for Bristol-Myers Squibb, Gilead, Janssen Cilag, Jennerex, Merck, Novartis, Roche; speaker: Bayer, Boehringer Ingelheim, Novartis, Roche.

E Zuckerman: Speaker/consultant for AbbVie, Merck, Gilead, Bristol-Meyers Squibb, Roche, Neopharm.

C Hezode: Clinical investigator/speaker/consultant for AbbVie, BMS, Gilead, Janssen Pharmaceuticals, MSD, Roche.

SW Paik: Research support from AbbVie, Bristol-Meyers Squibb, Gilead, GlaxoSmithKline, MSD, Novartis Roche.

P Andreone: Research support from Roche, MSD, Gilead Sciences, BMS; advisory committees for Roche, MSD, Janssen Cilag, AbbVie, Boehringer Ingelheim, Gilead Sciences, Intercept, BMS; consultant for MSD, BMS.

O Weiland: Clinical investigator/advisor/speaker: Merck, BMS, Janssen, Gilead, AbbVie, Medivir.

J Slim: Speaker for AbbVie, BMS, Gilead, Merck, Janssen, Genentech.

SL Flamm: Speaker/consultant for AbbVie, Gilead, BMS, Merck; grant/research support from AbbVie, Gilead, BMS, Merck.

T Morgan: Participant in clinical trials sponsored by AbbVie, BMS, Gilead, Merck.

H Vargas: Participant in clinical trials sponsored by AbbVie, Gilead, Merck.

S Strasser: Advisor/speaker for AbbVie, Gilead, BMS, MSD.

A Brown: Advisor/speaker/recipient of research grants from AbbVie, Bristol-Meyers Squibb, Janssen, Gilead, MSD.

N Zadeikis, Y Yu, A Porcalla, FJ Mensa: Employees of AbbVie and may hold stock or options.

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Pharmacokinetics and Safety of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1–6 Hepatitis C Virus Infection and Compensated Cirrhosis: An Integrated Analysis

THU-263

Edward Gane[1], Fred Poordad[2], Joaquin Valdes[3], Chih-Wei Lin[3], Wei Liu[3], Armen Asatryan[3], Stanley Wang[3], Catherine Stedman[4], Susan Greenbloom[5], Tuan Nguyen[6], Magdy Elkhashab[7], William Harlan[8], Marcus-Alexander Wörns[9], Albert Tran[10], Jean-Pierre Mulkay[11], Yao Yu[3], Ariel Porcalla[3], Federico J Mensa[3]

[1]Liver Unit, Auckland City Hospital, Auckland, New Zealand; [2]The Texas Liver Institute, University of Texas Health, San Antonio, Texas, United States; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]Christchurch Hospital and University of Otago, Christchurch, New Zealand; [5]Toronto Digestive Disease Associates, Toronto, Ontario, Canada; [6]Research and Education, Inc., San Diego, California, United States; [7]Toronto Liver Centre, Toronto, Ontario, Canada; [8]Asheville Gastroenterology Associates, Asheville, North Carolina, United States; [9]Universitaetsmedizin der Johannes Gutenberg University, Mainz, Germany; [10]University Hospital of Nice, Digestive Centre, Nice, France; [11]Hôpital CHU Saint-Pierre, Brussels, Belgium

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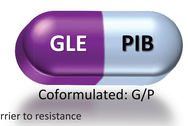
BACKGROUND

- Patients with chronic hepatitis C virus (HCV) infection and cirrhosis are at greatest risk of progression to liver decompensation and death[1,2]
- Achievement of a sustained virologic response (SVR) with chronic HCV treatment reduces the risk of hepatic decompensation events, end-stage liver disease, hepatocellular carcinoma, and liver-related mortality[3]
- Glecaprevir (formerly ABT-493), an NS3/4A protease inhibitor (PI), and pibrentasvir (formerly ABT-530), an NS5A inhibitor, are direct-acting antivirals (DAAs) being developed as a once-daily, fixed-dose combination regimen (G/P) to treat genotypes (GTs) 1–6 chronic HCV infection, including those with compensated cirrhosis **(Figure 1)**
- G/P has been studied in a large registrational program, in which high (≥95%) SVR rates and low rates of virologic failure were achieved in a broad range of patient populations across all major genotypes[4–12]
- Here we report results of an integrated safety and pharmacokinetic (PK) analysis of 308 patients with compensated cirrhosis treated with G/P 300 mg/120 mg without ribavirin (RBV) in phase 2 and 3 studies

Figure 1. Next Generation Direct-acting Antivirals



G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Note in the phase 2 SURVEYOR-I and SURVEYOR-II studies, once daily GLE (300 mg) + PIB (120 mg) were administered separately.
Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVES

- To describe the safety and PK properties of G/P in patients with compensated cirrhosis treated for 12 or 16 weeks across four phase 2 and 3 studies
  - Detailed safety information for patients without cirrhosis is being presented separately (Dufour JF et al. EASL 2017, Poster number: FRI-238)

METHODS

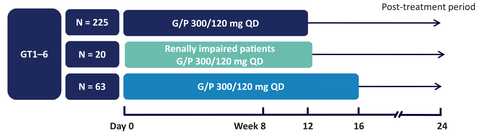
STUDY DESIGN

- Arm(s) from 4 global, open-label multicenter, phase 2 and 3 clinical trials that evaluated the efficacy, safety, and/or PK of HCV-infected patients with compensated cirrhosis treated with G/P were included in this analysis:
  - EXPEDITION-I (NCT02642432): phase 3, single-arm, evaluated G/P for 12 weeks in HCV GT1, 2, 4, 5, or 6-infected adults (Forns X, et al. EASL 2017, Oral presentation number: GS-005)
  - EXPEDITION-IV (NCT02651194): phase 3, single-arm study to evaluate the efficacy and safety of G/P for 12 weeks in renally impaired adults with chronic HCV GT1–6 infection
  - SURVEYOR-II (NCT02243293) study arms O, Q, and R: phase 2, partially randomized study evaluated co-administration of GLE and PIB, or G/P, for 12 or 16 weeks in treatment-naive or treatment-experienced GT3-HCV-infected adults

METHODS (CONTINUED)

  - MAGELLAN-I (NCT02446717) study arms D and E: phase 2, randomized, study evaluated G/P for 12 or 16 weeks in HCV GT1- or GT4-infected adults who failed a prior DAA-containing therapy (Poordad F, et al. EASL 2017, Oral presentation number: PS-156)
- Patients were assigned to treatment arms of 12- or 16-week duration, as defined in the study protocols **(Figure 2)**

Figure 2. Phase 2 and 3 Multicenter Studies of GT1–6 HCV-infected Patients With Compensated Cirrhosis



G/P, glecaprevir (formerly ABT-493) and pibrentasvir (formerly ABT-530); QD, once daily.

KEY ELIGIBILITY CRITERIA

- Eligible patients for studies EXPEDITION-I and SURVEYOR-II were treatment-naive or treatment-experienced with prior interferon (IFN) or pegylated interferon (pegIFN)/± RBV or SOF + RBV ± pegIFN or in the MAGELLAN-I study, experienced with a PI and/or NS5A inhibitor-containing regimen. Patients were ≥18 years of age, and had no HIV or hepatitis B virus co-infection
- Compensated cirrhosis was confirmed at screening by:
  - Child-Pugh score ≤6 and no current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation
  - Documentation of one of the following:
    - Histologic diagnosis from liver biopsy
    - FibroTest score ≥0.75 and AST–to-platelet ratio index (APRI) >2
    - FibroScan score ≥14.6 kPa
- At screening, patients must not have had co-infection with >1 HCV GT or diagnosed with hepatocellular carcinoma (HCC). Patients enrolled across the studies must not have the following lab eligibility criteria: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >10 × the upper limit of normal (ULN) (or >5 × ULN in SURVEYOR-II arm O); creatinine clearance <50 mL/min (EXPEDITION-I, SURVEYOR-I and -II, and MAGELLAN-I) or eGFR ≥30 mL/min/1.73 m^2 (EXPEDITION-IV); or international normalized ratio (INR) >2.3 (unless subject has known hemophilia or is on a stable anticoagulant regimen affecting INR; or >1.35 in SURVEYOR-II Arm O); albumin <2.8 g/dL; total bilirubin >3.0 ULN (or direct bilirubin >ULN in SURVEYOR-II Arm O)
- Patients with compensated cirrhosis at screening did not have platelets <40 000 cells per mm^3 (EXPEDITION-4), <60 000 cells per mm^3 (EXPEDITION-1) and <90 000 cells per mm^3 (phase 2 studies)

STUDY ASSESSMENTS

- Adverse events (AEs), including serious adverse events (SAEs) and those leading to treatment discontinuation and death, and clinical laboratory parameters were monitored throughout the treatment and immediate post-treatment periods (within 30 days of treatment completion)
- Safety analyses included pooled AEs and laboratory data from all patients who received at least one dose of study medications in the studies specified
- PK exposure in patients with compensated cirrhosis was estimated using population PK analyses approach. Plasma concentrations were analyzed using non-linear mixed-effects modeling with NONMEM 7.3. Exposure (steady-state area under the curve) of each agent was obtained using post-hoc estimations for individual subjects from population PK analyses

RESULTS

- A total of 308 patients with compensated cirrhosis were included in this integrated PK and safety analysis
- Baseline demographic and disease characteristics are shown in **Table 1**
- Most patients were of white race, were male, were treatment-naive and had a baseline Child-Pugh score of 5

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Patients with compensated cirrhosis N = 288	Patients with severe renal impairment N = 20
Male, n (%)	182 (63)	17 (85)
Age, median (range), years	58 (26–88)	61 (34–77)
White race, n (%)	244 (85)	17 (85)
BMI, median (range), kg/m^2	28 (18–55)	26 (18–45)
HCV genotype, n (%)		
1	112 (39)	11 (55)
2	34 (12)	4 (20)
3	115 (40)	1 (5)
4	18 (6)	4 (20)
5	2 (<1)	0
6	7 (2)	0
Treatment-naive, n (%)	174 (60)	8 (40)
Treatment-experienced, n (%)	114 (40)	12 (60)
PRS-experienced	87 (30)	12 (60)
NS5A- and/or PI-experienced	27 (9)	0
Baseline Fibrosis stage*, n (%)		
F0-F1	0	0
F2	0	2 (10.5)
F3	2 (<1)	0
F4	286 (99)	17 (89.5)
Missing	0	1
Screening Child-Pugh Score		
5	261 (91)	15 (75)
6	27 (9)	5 (25)
Baseline Child-Pugh Score		
5	249 (87)	15 (75)
≥6†	38 (13)	5 (25)
Missing	1	0
Baseline HCV RNA level (log_{10} IU/mL), median (range)	6.2 (3–7)	5.9 (4–7)
Baseline platelet counts (10^3/L), n (%)		
<100	68 (24)	2 (10)
≥100	220 (76)	18 (90)
Baseline albumin (g/L), n (%)		
<35	21 (7)	2 (10)
≥35	267 (93)	18 (90)
Baseline total bilirubin (µmol/L), (n%)		
<34.2	282 (98)	20 (100)
≥34.2	6 (2)	0
Baseline eGFR (mL/min/1.73 m^2)		
<30	0	20 (100)
≥30–<60	8 (3)	0
≥60–<90	115 (46)	0
≥90	129 (51)	0
Missing	36	0

BMI, body mass index; eGFR, estimated glomerular function; HCV, hepatitis C virus; PI, protease inhibitor;
PRS, IFN or pegIFN/± RBV or SOF + RBV ± pegIFN.
*Baseline fibrosis stage was defined for subjects with non-missing liver biopsy scores, FibroScan scores, or FibroTest scores; cirrhosis status was determined as collected in EDC; †One patient had a CP score of 7.

SAFETY

- Overall, 74% (213/288) of patients with compensated cirrhosis experienced ≥1 AE of any type **(Table 2)** with the most commonly reported AEs (≥10%) being fatigue and headache
- Most AEs were mild or moderate in severity. No patient with compensated cirrhosis, and without severe renal impairment (N = 288) experienced a DAA-related SAE, a DAA-related AE grade ≥ 3, or an AE leading to discontinuation of study drug
- One patient experienced an AE with a sign of hepatic decompensation. The patient had a previous history of esophageal varices and experienced esophageal variceal bleeding on Day 22 without worsening of hepatic function and without progression to hepatic failure. The event was not deemed to be related to the study drug and resolved; the patient achieved SVR12 with completion of treatment with G/P
- Two patients died post-treatment, both due to an AE considered not related to study drug (cerebral hemorrhage)

Table 2. Summary of Adverse Events

Event, n (%)	Patients with compensated cirrhosis N = 288	Patients with compensated cirrhosis and CP score 5 N = 261	Patients with compensated cirrhosis and CP score 6 N = 27	Patients with severe renal impairment N = 20
Any AE	213 (74)	196 (75)	17 (63)	20 (100)
Any SAE	17 (6)	14 (5)	3 (11)	11 (55)
DAA-related SAE	0	0	0	0
Any AE leading to discontinuation of study drug	0	0	0	2 (10)
Any fatal AE	0	0	0	1 (5)
Death	1 (0.3)	1 (0.4)	0	1 (5)
AE consistent with hepatic decompensation	1 (0.3)*	0	1 (4)	0
AEs occurring in ≥10% of patients in the N = 288 cirrhotic population				
Fatigue	58 (20)	53 (20)	5 (19)	1 (5)
Headache	47 (16)	44 (17)	3 (11)	1 (5)

AE, adverse event; CP, Child-Pugh; DAA, direct-acting antiviral; SAE, serious adverse event.
*Patient experienced an AE with a sign of hepatic decompensation. The patient had previous history of esophageal varices and met the Hepatic Decompensation and Hepatic Failure PMQ search criteria. The event was not deemed to be related to the study drug.

LABORATORY ABNORMALITIES

- Post-baseline grade ≥3 laboratory abnormalities were infrequent; there were no grade 3 ALT increases and no cases consistent with drug-induced liver injury **(Table 3)**

Table 3. Summary of Post-baseline Laboratory Abnormalities

Post-baseline laboratory abnormalities, n/N (%)	Patients with compensated cirrhosis N = 288	Patients with compensated cirrhosis and CP score 5 N = 261	Patients with compensated cirrhosis and CP score 6 N = 27	Patients with severe renal impairment N = 20
Hemoglobin ≥grade 3 (<8 g/dL)	1 (0.3)*	0	1 (3.7)	1 (5)
ALT ≥grade 3 (>5 × ULN)	0	0	0	0
AST ≥grade 3 (>5 × ULN)	0	0	0	0
Total bilirubin ≥grade 3 (>3 × ULN)	2 (0.7)†	1 (0.4)	1 (3.7)	1 (5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CP, Child-Pugh; ULN, upper limit of normal.
*One patient experienced a ≥ grade 3 hemoglobin elevation on Day 29 of treatment. The elevation reduced to grade 2 post-treatment;
†One patient experienced ≥ grade 3 total bilirubin elevation at Days 10, 87, and 115 of treatment, which reduced to grade 2 post-treatment and were predominantly indirect. One patient experienced ≥ grade 3 total bilirubin elevation at Days 15, 44, 71, and post treatment. The elevations were predominantly indirect or mixed hyperbilirubinemia and resolved post treatment. Bilirubin elevations were not associated with ALT increases in either patient.

PHARMACOKINETICS

- GLE exposure in patients with compensated cirrhosis was approximately 2.2-fold higher than exposure in patients without cirrhosis **(Table 4)**
- PIB exposure in patients with compensated cirrhosis was similar to that previously reported in patients without cirrhosis **(Table 4)**

Table 4. AUC_{24} Values for GLE and PIB in Patients With and Without Compensated Cirrhosis

Patient cirrhosis status	N	AUC_{TD}ss (ng*h/mL) Geometric Mean (%CV) GLE	AUC_{TD}ss (ng*h/mL) Geometric Mean (%CV) PIB
Non-cirrhotic patients	1804*	4800 (198)	1430 (63)
Patients with compensated cirrhosis	288	10 700 (124)	1530 (50)

*N derived from patients without cirrhosis enrolled into phase 2 and 3 studies across the registrational program.

CONCLUSIONS

- In HCV GT1–6-infected patients with compensated cirrhosis treated in phase 2 and phase 3 clinical studies, G/P was well tolerated, with no DAA-related SAEs and no AEs leading to discontinuation of study drug
- Most AEs were mild or moderate in severity. The GLE exposure was higher in patients with cirrhosis compared with those without cirrhosis; however, on-treatment laboratory abnormalities of grade ≥3 were rare, and no ALT elevations occurred
- Despite higher GLE exposure in patients with compensated cirrhosis, the safety profile was similar to those in patients without cirrhosis. Reported AEs (>10%) were consistent between patients with cirrhosis and without cirrhosis (see also Dufour JF, et al. EASL 2017, Poster number: FRI-238)

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DISCLOSURES

E Gane: Advisor for AbbVie, Gilead, Achillion, Novartis, Roche, Merck, Janssen.

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S Greenbloom: Participant in AbbVie-sponsored clinical trials.

C Stedman: Grant/research support from Gilead; consultant/advisor for Janssen, AbbVie, Gilead, MSD.

W Harlan: Participant in AbbVie-sponsored clinical trials.

A Tran: PI for AbbVie, Merck, Gilead, BMS studies.

T Nguyen: Grant/research support from Gilead, BMS, Idenix Pharmaceuticals; advisor/speaker for Gilead, BMS.

M Elkhashab: Participant in AbbVie-sponsored clinical trials.

MA Wörns: Advisor for AbbVie, BMS; speaker for AbbVie, BMS, Gilead, Janssen.

JP Mulkay: Research grants from Janssen, Gilead; advisor for Janssen, Gilead, MSD, BMS, AbbVie; speaker for BMS, Gilead.

J Valdes, C Lin, W Liu, Y Yu, A Asatryan, S Wang, A Porcalla, FJ Mensa: Employees of AbbVie and may hold stock or options.

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Pooled Resistance Analysis in HCV Genotype 1–6 Infected Patients Treated With Glecaprevir/Pibrentasvir in Phase 2 and 3 Clinical Trials

FRI-205

Preethi Krishnan, Gretja Schnell, Rakesh Tripathi, Teresa Ng, Thomas Reisch, Jill Beyer, Tatyana Dekhtyar, Michelle Irvin, Wangang Xie, Lois Larsen, Federico Mensa, Tami Pilot-Matias, and Christine Collins

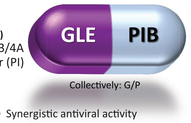
Research and Development, AbbVie Inc., North Chicago, Illinois, United States

Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver, 19–23 April 2017, Amsterdam, the Netherlands

BACKGROUND

Next Generation Direct-acting Antivirals

Glecaprevir (formerly ABT-493) pangenotypic NS3/4A protease inhibitor (PI)



Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

In vitro:
- Synergistic antiviral activity
- High barrier to resistance
- Potent against common NS3 and NS5A polymorphisms

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P (100/40 mg) dosed once daily for a total dose of 300/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

- Eight Phase 2 and 3 studies evaluated the safety and efficacy of G/P without RBV at a dose of 300/120 mg for 8, 12, or 16 weeks in HCV genotype (GT) 1–6 infected patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or -experienced to pegIFN, RBV and/or sofosbuvir **(Table 1)**. Pooled SVR12 rates by HCV genotype, treatment duration, prior treatment experience and cirrhosis status are shown in **Table 2**
- Fewer than 1% (22/2256) of the patients experienced virologic failure
- A pooled resistance analysis grouped by HCV genotype, treatment duration, prior treatment experience and cirrhosis status was conducted. Patients with prior NS5A-inhibitor and/or PI experience (MAGELLAN-I study) were analyzed separately (see Poster SAT-204)

Table 1. Phase 2 and 3 Studies Included in the Pooled Resistance Analyses (Combination Regimen of GLE 300 mg QD and PIB 120 mg QD)

Study	HCV Genotype	Study Design and Population	Duration	Total Enrolled and Treated (N)	Number of Sequences Analyzed[a]
SURVEYOR-1	1, 4, 5, 6	Open-label; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; no cirrhosis	8 and 12 weeks	66	66
SURVEYOR-2	2, 3, 4, 5, 6	Open-label; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; with or without compensated cirrhosis	8, 12, and 16 weeks	524	498
ENDURANCE-1	1	Open-label; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; no cirrhosis	8 and 12 weeks	703	680
ENDURANCE-2	2	Double-blind; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; no cirrhosis	12 weeks	202	190
ENDURANCE-3	3	Open-label; treatment-naive; no cirrhosis	8 and 12 weeks	390	384
ENDURANCE-4	4, 5, 6	Open-label; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; no cirrhosis	12 weeks	121	110
EXPEDITION-1	1, 2, 4, 5, 6	Open-label; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; with compensated cirrhosis	12 weeks	146	142
EXPEDITION-4	1, 2, 3, 4, 5, 6	Open-label; severe renal impairment; treatment-naive or treatment-experienced to pegIFN + RBV ± SOF; with or without compensated cirrhosis	12 weeks	104	96

[a]Indicates number of patients with NS3/4A or NS5A sequences available for analysis. 90 out of 2256 baseline sequences were not available.

Table 2. SVR12 [% (n/N)] in Pooled Analysis of Phase 2 and 3 Studies (Combination Regimen of GLE 300 mg QD and PIB 120 mg QD, ITT Population)

	No Cirrhosis				With Compensated Cirrhosis		No Cirrhosis	With Compensated Cirrhosis
	8 Weeks		12 Weeks		12 Weeks		16 Weeks	
HCV GT	TN	TE-PRS	TN	TE-PRS	TN	TE-PRS	TE-PRS	TE-PRS
GT1	99 (245/248)	99 (138/139)	>99 (241/242)	100 (159/159)	97 (69/71)	97 (29/30)	—	—
GT2	99 (172/174)	91 (21/23)	99 (167/169)	100 (65/65)	100 (26/26)	100 (9/9)	—	—
GT3	95 (177/186)	—	96 (258/270)	90 (44/49)	99 (64/65)	—	96 (21/22)	94 (48/51)
GT4–6	92 (45/49)	100 (9/9)	100 (120/120)	98 (50/51)	100 (20/20)	100 (9/9)	—	—

TN = treatment-naïve; TE-PRS = treatment-experienced to pegIFN + RBV ± SOF.

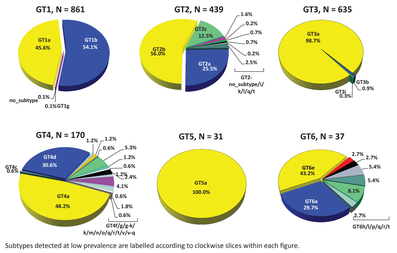
METHODS

- Next Generation Sequencing (NGS)
  - HCV RNA was reverse-transcribed and amplified using RT-PCR and nested PCR followed by library preparation using the Nextera XT sample preparation kit. Paired end sequencing was conducted for full length NS3/4A and NS5A using the Illumina MiSeq platform
  - HCV subtype assignment
    - For each sample analyzed by NGS, a consensus sequence was generated for each target gene from the NGS nucleotide sequences, with an ambiguity setting of 0.25
    - Phylogenetic analyses were conducted using the available full-length HCV NS3/4A and/or NS5A consensus nucleotide sequences in order to confirm the subtype assignment
- Data Analysis
  - NGS data were analyzed at detection thresholds of 2% and 15% relative to the subtype specific reference sequence. Conclusions from analyses using 2% vs 15% detection threshold were similar, therefore, only the analyses conducted at 15% detection threshold are presented in this poster
  - Patients who did not achieve SVR12 for reasons other than virologic failure (such as early treatment discontinuations or missing SVR12 data) were excluded from the analyses

RESULTS

HCV SUBTYPE DISTRIBUTION IN POOLED ANALYSIS OF PHASE 2 AND 3 STUDIES

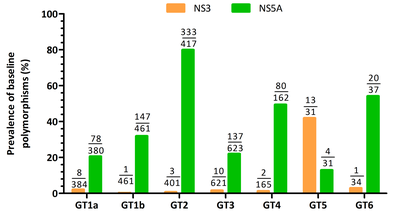
Figure 1. Prevalence of HCV Subtypes by Phylogenetic Analysis of NS3/4A and/or NS5A Baseline Sequences



Subtypes detected at low prevalence are labelled according to clockwise slices within each figure.

PREVALENCE OF BASELINE POLYMORPHISMS IN POOLED ANALYSIS OF PHASE 2 AND 3 STUDIES

Figure 2. Overall Prevalence of Baseline Polymorphisms by Genotype

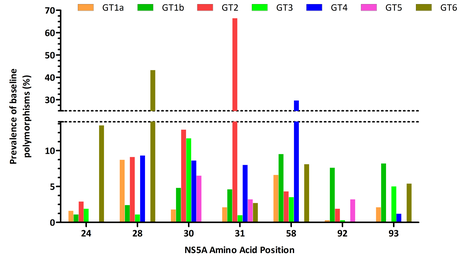


Includes polymorphisms at amino acid positions 155, 156, 168 in NS3, and 24, 28, 30, 31, 58, 92, 93 in NS5A relative to the subtype specific reference sequence.

- Polymorphisms at amino acid positions (155, 156, 168) in NS3 were rare (< 3%) in GT1-4, and 6. In GT5a, the high prevalence of polymorphisms in NS3 was driven by the presence of D168E in 41.9% (13/31) of the samples

RESULTS (CONTINUED)

Figure 3. Prevalence of Baseline Polymorphisms in NS5A



- Prevalence of polymorphisms at amino acid positions (24, 28, 30, 31, 58, 92, 93) in NS5A ranged between 12.9% and 26.8% in GT1, 3, and 5, and ranged between 49.7% and 79.8% in GT2, 4, and 6. Prevalence of baseline polymorphisms in NS5A in each genotype is shown in **Figure 3**
  - The high incidence of baseline NS5A polymorphisms was driven by the common L/M31 polymorphism in GT2a and GT2b, and R30K in GT2c; polymorphisms at position 58 in GT4a-, 4d- and 4f; and polymorphisms at position 28 in GT6
- Within each genotype and drug target, the prevalence of baseline polymorphisms was similar in patients across treatment durations, prior treatment experience, cirrhosis status, or geographic region (data not shown)

PATIENTS EXPERIENCING VIROLOGIC FAILURE IN POOLED ANALYSIS OF PHASE 2 AND 3 STUDIES

- 22 patients experienced virologic failure **(Table 3)**
  - Among the 2 GT1a-infected patients, 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had treatment-emergent Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A
  - Among the 2 GT2a-infected patients, no baseline or treatment-emergent substitutions were observed in NS3 or NS5A
  - Baseline polymorphisms and treatment-emergent substitutions in GT3-infected virologic failures are summarized in **Table 4**
  - Resistance conferred by substitutions detected in patients experiencing virologic failure to GLE or PIB in the in vitro replicon system are shown in **Table 5**

Table 3. Description of Virologic Failures in Pooled Analysis of Phase 2 and 3 Studies

GT	Duration (Weeks)	Prior Treatment Experience	Cirrhosis (Y/N)	Number of Virologic Failures and Outcomes
1a	8	TE-PRS	N	1 OTVF
1a	12	TE-PRS	Y	1 Relapse
2a	8	TE-PRS	N	2 Relapse
3a	8	TN	N	1 OTVF, 5 Relapse
3a	12	TN	N	1 OTVF, 1 Relapse
3b	12	TN	N	1 Relapse
3a	12	TE-PRS	N	1 OTVF, 4 Relapse
3a	16	TE-PRS	Y	1 OTVF, 2 Relapse
3a	16	TE-PRS	N	1 Relapse

GT = HCV subtype by phylogenetic analysis; OTVF = on treatment virologic failure; TN = treatment-naïve; TE-PRS = treatment-experienced to pegIFN + RBV ± SOF; Y/N = yes/no.

Table 4. Baseline Polymorphisms and Treatment-Emergent Substitutions in GT3-infected Virologic Failure Patients

	Baseline Polymorphisms[a] % (n/N)					Treatment-emergent Substitutions[a] % (n/N)			
	8 weeks	12 weeks	16 weeks	All Durations		8 weeks	12 weeks	16 weeks	All Durations
NS3									
Any[b]	17 (1/6)	25 (2/8)	25 (1/4)	22 (4/18)	Any[b]	67 (4/6)	63 (5/8)	50 (2/4)	61 (11/18)
A166S	17 (1/6)	13 (1/8)	25 (1/4)	17 (3/18)	Y56H/N	33 (2/6)	38 (3/8)	25 (1/4)	33 (6/18)
Q168R	—	13 (1/8)	—	6 (1/18)	Q80K/R	17 (1/6)	38 (3/8)	—	22 (4/18)
					A156G	17 (1/6)	—	25 (1/4)	11 (2/18)
					Q168L/R	33 (2/6)	38 (3/8)	25 (1/4)	33 (6/18)
NS5A									
Any[b]	67 (4/6)	88 (7/8)	75 (3/4)	78 (14/18)	Any[b]	83 (5/6)	88 (7/8)	100 (4/4)	89 (16/18)
A30K	67 (4/6)	50 (4/8)	25 (1/4)	50 (9/18)	M28G	—	—	25 (1/4)	6 (1/18)
V31M[c]	—	13 (1/8)	—	6 (1/18)	A30G/K	—	25 (2/8)	25 (1/4)	17 (3/18)
Y93H	—	38 (3/8)	50 (2/4)	28 (5/18)	L31F	—	13 (1/8)	25 (1/4)	11 (2/18)
					P58T	—	25 (2/8)	—	11 (2/18)
					Y93H	83 (5/6)	88 (7/8)	75 (3/4)	83 (15/18)

n = number of patients with the variants; N = number of patients experiencing virologic failure.
[a]Variants at amino acid positions of interest for NS3/4A protease and NS5A inhibitor class were analyzed. Baseline polymorphisms that remained at similar levels or were enriched at the time of failure within a patient's viral population are listed. Treatment-emergent substitutions that were not present at baseline or were enriched relative to baseline (by at least 20% within the patient's viral population) are listed.
[b]Any, indicates number of patients with any of the listed variants.
[c]Variant relative to subtype specific reference sequence in GT3b-infected virologic failure.

Table 5A. In Vitro Activity of GLE Against Amino Acid Substitutions in NS3

	NS3 Amino Acid Substitutions	GLE, Fold EC_{90} change
GT1a	A156V	NA
	Y56H	NA
	Q80R	21
	A156G	1654
GT3a	S166A	NA
	S166T	4.7
	Q168L	13
	Q168R	54
	Y56H + Q168R	1387

NA = not available due to poor replication capacity of the variant.

Table 5B. In Vitro Activity of PIB Against Amino Acid Substitutions in NS5A

	NS5A Amino Acid Substitutions	PIB, Fold EC_{90} change
GT1a	Q30R	1.7
	L31M	1.1
	H58D	1.1
	Y93N	7
	Q30R + L31M	3
	Q30R + Y93N	131
	L31M + H58D	23
	Q30R + L31M + H58D	1704
GT3a	M28G	NA
	A30K	1.1
	L31F	NA
	Y93H	2.3
	A30K + Y93H	69
	L31F + Y93H	NA

NA = not available due to poor replication capacity of the variant.

- Treatment-emergent substitutions were detected in both targets in majority of the patients. Though single substitutions did not confer resistance, multiple substitutions in NS5A, which were detected at the time of failure in most patients, conferred resistance to PIB
- Neither NS5A A30K nor Y93H confer resistance to PIB in GT3a, while the combination confers 69-fold resistance. In patients experiencing virologic failure with pre-existing A30K, acquiring Y93H at the time of failure requires a single nucleotide change. The acquisition of an A30K substitution requires a 2 nucleotide change from the wild type sequence and was therefore rarely detected as a treatment-emergent substitution

IMPACT OF BASELINE POLYMORPHISMS ON TREATMENT OUTCOME

- The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR12 rates for patients infected with GT1 or GT2
- There were no virologic failures among GT4, GT5, or GT6-infected patients
- Four GT3-infected patients experiencing virologic failure had NS3-A166S or Q168R, and 14 had NS5A-A30K or Y93H at baseline **(Table 4)**. The prevalence of these polymorphisms is shown in **Figure 4**. The impact of these polymorphisms on treatment outcome is shown in **Table 6**

Figure 4. Prevalence of Specific Baseline Polymorphisms in GT3-Infected Patients

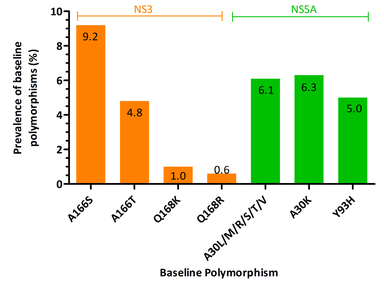


Table 6. Impact of A166S or Q168R in NS3 and/or A30K or Y93H in NS5A at Baseline on Treatment Outcome in GT3-Infected Patients

		No Cirrhosis				Cirrhosis	
		Treatment-naïve		Treatment-experienced		Treatment-naïve	Treatment-experienced
	Baseline Polymorphism	8 Weeks	12 Weeks	12 Weeks	16 Weeks	12 Weeks	16 Weeks
		SVR12 % (n/N)					
	OVERALL SVR12[a]	**97 (175/181)**	**99 (254/257)**	**90 (44/49)**	**95 (20/21)**	**100 (63/63)**	**94 (48/51)**
NS3	With A166S	82 (14/17)[b]	100 (21/21)	80 (4/5)[d]	100 (2/2)	100 (6/6)	67 (4/6)
	Without A166S	98 (161/164)	99 (231/234)	91 (40/44)	95 (18/19)	100 (57/57)	98 (44/45)
	With Q168R	(0/1)[b]	50 (1/2)[c]	·	·	·	100 (1/1)
	Without Q168R	97 (175/180)	99 (251/253)	90 (44/49)	95 (20/21)	100 (63/63)	94 (47/50)
NS5A	With A30K	78 (14/18)[b]	93 (13/14)[c]	25 (1/4)[d]	(0/1)	100 (1/1)	·
	Without A30K	99 (161/163)	99 (241/243)	96 (43/45)	100 (20/20)	100 (62/62)	94 (48/51)
	With Y93H	100 (10/10)	91 (10/11)[c]	50 (2/4)	·	100 (5/5)	100 (1/1)
	Without Y93H	97 (165/171)	99 (244/246)	93 (42/45)	95 (20/21)	100 (58/58)	94 (47/50)

[a]SVR12 rate in patients with available NS3/4A and/or NS5A baseline sequence.
[b]One patient experiencing virologic failure had NS3-A166S/Q168R + NS5A-A30K (though NS3-A166S/Q168R were not detectable at the time of failure in this patient); 1 virologic failure patient had NS3-A166S + NS5A-A30K; two SVR12 achieving patients had NS3-A166S + NS5A-A30K at baseline.
[c]One patient experiencing virologic failure had NS3-Q168R + NS5A-A30K/Y93H at baseline.
[d]One patient experiencing virologic failure had NS3-A166S + NS5A-A30K at baseline.

- Four of the 7 patients experiencing virologic failure with A166S and/or Q168R in NS3 at baseline also had polymorphisms in NS5A; and in 3 of the 7 patients these NS3 polymorphisms were not detectable at the time of failure. Baseline polymorphisms in NS3 did not have an impact on SVR12 in GT3-infected patients
- With the exception of treatment-experienced patients treated for 12 weeks, the presence of A30K or Y93H in NS5A at baseline had minimal impact on overall efficacy

SUMMARY

Among 2256 treatment-naïve and pegIFN, RBV and/or SOF treatment-experienced patients without cirrhosis or with compensated cirrhosis treated with G/P without RBV at a dose of 300/120 mg for 8, 12, or 16 weeks:

- 38 HCV subtypes were identified
- Fewer than 1% (22 patients) experienced virologic failure
  - 2 GT1 failures: 1 had treatment-emergent substitutions A156V in NS3 and Q30R/L31M/H58D in NS5A, and 1 had Q30R/H58D (while Y93N was present at baseline and post-treatment) in NS5A
  - 2 GT2 failures: no treatment-emergent substitutions were observed in NS3 or NS5A
  - 18 GT3 failures: treatment-emergent substitutions Y56H/N, Q80K/R, A156G, or Q168L/R in NS3 were observed in 11 patients; treatment-emergent substitutions M28G, A30G/K, L31F, P58T, or Y93H in NS5A were observed in 16 patients
- The presence of baseline polymorphisms in NS3 and/or NS5A did not have an impact on SVR12 rates for GT1-, GT2-, GT4-, GT5-, or GT6-infected patients
- Baseline polymorphisms in NS3 and NS5A did not have an impact on SVR12 in GT3-infected patients with the exception of treatment-experienced patients treated for 12 weeks. A 16-week regimen in GT3 treatment-experienced patients may be required to achieve SVR rates ≥95%

DISCLOSURES

All authors are AbbVie employees and may hold AbbVie stock and/or stock options.

The design, study conduct, analysis, and financial support of the clinical trials were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the content.

abbvie

Resistance Selection Using Glecaprevir and Pibrentasvir in Replicons of Major HCV Genotypes

THU-305

Teresa Ng, Liangjun Lu, Thomas Reisch, Preethi Krishnan, Gretja Schnell, Rakesh Tripathi, Jill Beyer, Tatyana Dekhtyar, Michelle Irvin, Tami Pilot-Matias, Christine Collins

AbbVie Inc., North Chicago, Illinois, United States

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BACKGROUND

AbbVie's NEXT GENERATION HCV DIRECT-ACTING ANTIVIRALS (DAAs)

- Glecaprevir[a] (GLE; formerly ABT-493): NS3/4A protease inhibitor (PI)
- Pibrentasvir (PIB; formerly ABT-530): NS5A inhibitor
- *In vitro*, GLE and PIB have each demonstrated[1,2]
  - Potent antiviral activity against all major HCV genotypes (GTs)
  - High genetic barrier to development of resistance
  - Potent against common NS3 and NS5A polymorphisms
  - Synergistic antiviral activity when combined with each other
- Safety and efficacy of the combination regimen of GLE/PIB (300/120 mg) have been evaluated in Phase 2 and 3 studies in patients infected with HCV GTs 1–6[3]

[a]GLE was identified by AbbVie and Enanta

Table 1. Antiviral Activity of GLE and PIB

	Stable HCV Replicon EC_{50}, nM							
DAA	GT1a	GT1b	GT2a	GT2b	GT3a	GT4a	GT5a	GT6a
GLE	0.85	0.94	2.2	4.6	1.9	2.8	0.12[a]	0.86
PIB	0.0018	0.0043	0.0023	0.0019	0.0021	0.0019	0.0014	0.0028

[a]Transient replicon results.

OBJECTIVES

- To determine the *in vitro* resistance profiles of GLE or PIB in major HCV genotypes
  - To select and characterize resistance-associated substitutions
  - To determine genetic barrier to resistance

METHODS

- Drug-resistant replicon colony selection
  - 1×10^6 subgenomic stable replicon cells with G418 and GLE or PIB for ~3 weeks at 10-fold or 100-fold over EC_{50}
    - Selection with GLE
      - Non-chimeric replicons GT1a-H77, GT1b-Con1, and GT2a-JFH-1
      - Chimeric replicon (GT1b-Con1 or GT2a-JFH-1 backbone) containing NS3 or NS3/4A from GT2b, 3a, 4a, or 6a
      - Stable replicon cell line with NS3 from GT5 not available
    - Selection with PIB
      - Non-chimeric replicons GT1a-H77 and GT1b-Con1
      - Chimeric replicon (GT1b-Con1 backbone) containing NS5A domain I from GT2a, 2b, 3a, 4a, 5a, or 6a
  - After drug selection, substitutions in HCV drug targets in surviving replicon colonies were identified by DNA sequencing after RT-PCR
    - ~20–30 colonies, or all if fewer colonies, from each treatment condition were analyzed
- Sequence analysis
  - Amino acid positions at which substitutions have been observed with drugs for the inhibitor classes
    - NS3
      - **GT1a:** 36, 43, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, and 170
      - **GT1b:** 36, 54, 55, 56, 80, 107, 122, 155, 156, 158, 168, 170, and 175
      - **GT3a:** 36, 43, 54, 55, 56, 80, 155, 156, 166, and 168
      - **GT2a, 2b, 4a, and 6a:** 36, 43, 54, 55, 56, 80, 155, 156, and 168
    - NS5A
      - **GT1a:** 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93
      - **GT1b:** 24, 28, 29, 30, 31, 32, 54, 58, 62, 92, and 93
      - **GT2a, 2b, 3a, 4a, 5a, and 6a:** 24, 28, 29, 30, 31, 32, 58, 92, and 93
  - Substitutions at other positions detected in >2 colonies in each selection condition are also reported
- Phenotypic analyses were performed by introducing substitutions into corresponding wild-type replicons and testing susceptibility to GLE or PIB in transient replicon assays

RESULTS

GLE Resistance Analysis

Table 2. Selection of NS3 Amino Acid Substitutions by GLE in Replicon Cell Lines With Protease From HCV GTs 1–4 and GT6

	Colony Survival (%)[b]			Prevalence in Replicon Selection[c]			
HCV Subtype[a]	10× EC_{50}	100× EC_{50}	NS3 Amino Acid Substitution	10× EC_{50}	100× EC_{50}	Fold Change in GLE EC_{50}[d]	Replication Efficiency[e], %
1a	0.043	0.0029	Q41R	8[f]/28	—	1.6	36
			A156T	3[f]/28	9[f]/17	1361	5.2
			A156V[g]	—	3/17	NV	<0.5
			Q41R + I170V	5/28	—	NV	<0.5
			V71A + I170V	3/28	—	3.3	1.0
			Q89R + A156T	—	5[f]/17	3585	1.0
			Q89R + D168A	3/28	—	—	—
1b	0.047	0.03	A156T	5[f]/25	5[f]/25	640	19
			A156V	8[f]/25	9[f]/25	1786	9.2
			P89L + A156V	8[f]/25	6[f]/25	4243	119
			A156S + D168V	3/25	—	—	—
			A156V + D168V	—	5/25	5244	17
2a[h]	>0.05	>0.05	A156T	15[f]/24	5/23	216	—
			A156V	9[f]/24	18[f]/23	1143	—
2b[i]	>0.05	>0.05	A156T	21/23	16/20	148	—
			A156V	2/23	4[f]/20	1455	—
3a	0.1	0.0003	A156G[g]	—/—	1/3	1654	—
			Y56H[j] + Q168R[k]	—/—	2/3	1387	—
4a	0.0015	0.0018	A156T	27[f]/36	8[f]/9	1436	—
			A156V	9/36	1/9	3106	—
6a	0.018	0	D168G	3[f]/25	—	191	—
			D168H	10/25	—	146	—
			D168V	7[f]/25	—	38	—
			D168H + M179T + A192V	3/25	—	—	—

[a]GT5a stable replicon not available.
[b](Number of surviving colonies/number of input replicon cells) × 100; number of input replicon cells: 1×10^6 cells except for GT3a 10× EC_{50} selection (1×10^4 cells).
[c]Number of times the amino acid substitution(s) detected/total number of colonies analyzed.
[d]Relative to GLE EC_{50}s for the respective wild-type replicons in transient transfection assays: GT1a = 0.21 nM, GT1b = 0.47 nM, GT2a = 2.5 nM, GT2b = 3.1 nM, GT3a = 0.55 nM, GT4a = 0.67 nM, and GT6a = 0.15 nM.
[e]Relative to replication efficiency of wild-type replicons (100%).
[f]GT2a JFH-1 replicon used for GT2a selection, and a GT2a JFH-1 chimeric replicon with GT2b protease used for GT2b selection.
[g]Highlighted substitution, alone or in combination with other substitution(s), detected in at least 1 patient who experienced virologic failure with treatment of GLE/PIB in Phase 2 or 3 study.[3]
[h]Number of times the amino acid substitution(s) by itself (themselves) or in combination with other substitution(s) detected.
[i]None of the substitutions were detected in >2 colonies.
[j]Denominator indicates total number of colonies that survived selection out of 1×10^6 input cells.
NV = not viable (replication efficiency <0.5%).

- GLE generally selected low number of colonies in replicons of different genotypes at >10× EC_{50}s
- High colony counts observed with selections using replicons with GT2a JFH-1 backbone due to exceptionally high replication rates[4]
- Common NS3 resistance-associated substitutions selected by GLE
  - **GT1a, 1b, 2a, 2b, and 4a:** A156T/V
  - **GT3a:** A156G, and Y56H + Q168R
  - **GT6a:** D168G/H/V
  - A156T/V generally have very low replication efficiency
- Other NS3 substitutions that confer resistance to other NS3/4A PIs were not selected by GLE because they do not confer resistance to GLE **(Tables 3 and 4)**

Table 3. Activity of GLE Against Common GT1 NS3 Resistance-associated Substitutions

HCV Subtype	NS3 Amino Acid Substitution	Fold Change in GLE EC_{50}[a]
1a	V36M	1.4
	F43L	0.3
	T54S	1.0
	V55I	0.2
	Y56H	1.0
	Q80K	0.9
	R155K	0.5
	D168A	4.0
	D168E	1.3
	D168V	4.4
	I170T	0.5
1b	T54A	1.0
	V55A	0.4
	R155K	0.6
	D168A	1.5
	D168E	0.9
	D168V	3.2
	V170A	1.1

[a]Relative to GLE EC_{50}s for the respective wild-type replicons in transient transfection assays: GT1a = 0.21 nM, and GT1b = 0.47 nM.

- GLE is active against common HCV GT1 NS3 amino acid substitutions that confer resistance to other NS3/4A PIs

Table 4. Activity of GLE Against Common GT 2–4 and GT6 NS3 Resistance-associated Substitutions

HCV Subtype	NS3 Amino Acid Substitution	Fold Change in GLE EC_{50}[a]
2a	D168A	1.9
	D168E	3.3
	D168V	2.0
2b	D168A	1.3
	D168E	2.1
	D168V	2.9
3a	R155K	0.5
	Q168R	54
4a	R155C	2.6
	D168V	9.7
4d	D168V	1.9
6a	D168Y	109

[a]Relative to GLE EC_{50}s for the respective wild-type replicons in transient transfection assays: GT2a = 2.5 nM, GT2b = 3.1 nM, GT3a = 0.55 nM, GT4a = 0.67 nM, GT4d = 0.15 nM, and GT6a = 0.15 nM.

- GLE is active against most of the common HCV GT 2–4 and GT6 NS3 amino acid substitutions that confer resistance to other NS3/4A PIs

PIB Resistance Analysis

Table 5. Selection of NS5A Amino Acid Substitutions by PIB in Replicon Cell Lines With NS5A From HCV GTs 1–6[1]

	Colony Survival (%)[a]			Prevalence in Replicon Selection[b]			
HCV Subtype	10× EC_{50}	100× EC_{50}	NS5A Amino Acid Substitution	10× EC_{50}	100× EC_{50}	Fold Change in PIB EC_{50}[c]	Replication Efficiency[d], %
1a	0.0065	0.0002	Q30D[e]	—	1/4[f]	94	50
			Q30 deletion	—	1/4[f]	3549	0.5
			Y93D	—	1/4[g]	NV	<0.5
			Y93H	18/20	—	6.7	18
			Y93N[h]	1/20	—	7.1	25
			H58D[i] + Y93H	—	1/4[g]	2238	13
1b	0	ND	—	—	—	—	—
2a	0.00015	0	F28S + M31I	2/3[g]	—	14 448	—
			P29S + K30G	1/3[g]	—	2.3	—
2b	0	0	—	—	—	—	—
3a	0.0003	0	Y93H[j]	3/3[k]	—	2.3	—
4a	0	0	—	—	—	—	—
5a	0	0	—	—	—	—	—
6a	0	0	—	—	—	—	—

[a](Number of surviving colonies/number of input replicon cells) × 100.
[b]Number of times the amino acid substitution(s) was detected/total number of colonies analyzed.
[c]Relative to PIB EC_{50}s for the respective wild-type replicons in transient transfection assays: GT1a = 0.72 pM, and GT1b = 0.99 pM, and GT3a = 0.65 pM.
[d]Relative to replication efficiency of wild-type replicon (100%).
[e]Substitution with double nucleotide changes.
[f]Highlighted substitution, alone or in combination with other substitution(s), detected in at least 1 patient who experienced virologic failure with treatment of GLE/PIB in Phase 2 or 3 study.[3]
[g]Denominator indicates total number of colonies that survived selection out of 2×10^6 input cells.
[h]Denominator indicates total number of colonies that survived selection out of 1×10^6 input cells.
ND = not determined; NV = not viable (replication efficiency <0.5%).

- PIB demonstrates high genetic barrier to resistance
  - Selection of no or very few drug-resistant colonies in GT 1–6 replicon cells
  - Selection of substitutions requiring 2 nucleotide changes (eg, Q30D, dual amino acid substitutions)
- NS5A resistance-associated substitutions selected by PIB
  - **GT1a:** All but Q30D (2 nucleotide changes) had low (≤25%) replication efficiency; most common were Y93H and Y93N, each confers ≤7-fold resistance to PIB
  - **GT2a:** Only 3 colonies survived selection, each containing 2 amino acid substitutions in NS5A
  - **GT3a:** Only 3 colonies survived selection, each containing Y93H, which confers <3-fold resistance to PIB
  - **GTs 1b, 2b, 4a, 5a, and 6a:** No drug-resistant colonies were selected
- Most substitutions that confer resistance to other NS5A inhibitors were not selected by PIB because they do not confer resistance to PIB **(Tables 6 and 7)**

Table 6. Activity of PIB Against Common GT1 NS5A Resistance-associated Substitutions[1]

HCV Subtype	NS5A Amino Acid Substitution	Fold Change in PIB EC_{50}[a]
1a	M28T	2.1
	M28V	1.8
	Q30E	2.4
	Q30H	1.0
	Q30R	1.7
	L31M	1.1
	L31V	1.3
	P32L	1.7
	H58D	1.1
	Y93C	1.7
	Y93H	6.7
	Y93N	7.1
1b	L28T	0.9
	Y93H	0.6
	Y93N	0.6

[a]Relative to PIB EC_{50}s for the respective wild-type replicons in transient transfection assays: GT1a = 0.72 pM, and GT1b = 1.9 pM.

- PIB is active against common HCV GT1 amino acid substitutions that confer resistance to other NS5A inhibitors

Table 7. Activity of PIB Against Common GT 2–6 NS5A Resistance-associated Substitutions[1]

HCV Subtype	NS5A Amino Acid Substitution	Fold Change in PIB EC_{50}[a]
2a[b]	T24A	1.3
	F28S	1.2
2b[c]	L28F	0.8
	L31M	1.2
	L31V	0.5
3a	M28T	1.7
	Y93H	2.3
4a	L28V	1.1
	L30H	1.3
5a	L28I	1.1
	L31F	2.1
	L31V	0.8
6a	L31V	1.0
	T58A	1.4
	T58N	1.8

[a]Relative to PIB EC_{50}s for the respective wild-type replicons in transient transfection assays: GT2a = 0.99 pM, GT2b = 1.2 pM, GT3a = 0.65 pM, GT4a = 0.78 pM, GT5a = 0.93 pM, and GT6a = 1.0 pM.
[b]The 2a wild-type replicon has M31 in NS5A.
[c]The 2b wild-type replicon has L31 in NS5A.

- PIB is active against common HCV GT 2–6 amino acid substitutions that confer resistance to other NS5A inhibitors

SUMMARY

- GLE and PIB each demonstrated a high genetic barrier to resistance in major HCV genotypes *in vitro*, consistent with the low virologic failure rate (overall <1%) observed in Phase 2 and 3 studies with GLE/PIB (300/120 mg) regimen in patients infected with GTs 1–6[3]
  - GLE predominantly selected NS3 A156 substitutions in GTs 1–4 and D168 substitutions in GT6 *in vitro*
    - In most HCV subtypes, A156 substitutions have low replication efficiency and are unlikely to persist
    - Substitutions important for the HCV NS3/4A PI class at other positions in NS3 have little or no impact on GLE activity
  - PIB selected few NS5A substitutions *in vitro*
    - No viable colonies selected in most genotypes (GTs 1b, 2b, 4a, 5a, and 6a)
    - Few colonies selected in GTs 1a, 2a, and 3a
    - Single NS5A substitutions in GTs 1–6 important for the NS5A inhibitor class have little or no impact on the activity of PIB

DISCLOSURES

All authors are AbbVie employees and may hold AbbVie stock and/or stock options.

The design, study conduct, analysis, and financial support of the clinical trials were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the content.

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Resistance Analysis in the MAGELLAN-I Study (Part 2): Glecaprevir/Pibrentasvir Therapy in HCV-Infected Patients Who Had Failed Prior DAA Regimens Containing NS3/4A Protease and/or NS5A Inhibitors

SAT-204

Tami Pilot-Matias, Preethi Krishnan, Gretja Schnell, Rakesh Tripathi, Jill Beyer, Thomas Reisch, Michelle Irvin, Tatyana Dekhtyar, Teresa Ng, Yang Lei, Armen Asatryan, Federico Mensa, Christine Collins

AbbVie Inc., North Chicago, Illinois, United States

Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver, 19–23 April 2017, Amsterdam, the Netherlands

BACKGROUND

Next Generation Direct-acting Antivirals

In vitro:
- Synergistic antiviral activity
- High barrier to resistance
- Potent against common NS3 and NS5A polymorphisms

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P (100/40 mg) dosed once daily for a total dose of 300/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

Antiviral Activity of GLE and PIB

	Stable HCV Replicon EC_{50}, nM							
DAA	GT1a	GT1b	GT2a	GT2b	GT3a	GT4a	GT5a	GT6a
GLE	0.85	0.94	2.2	4.6	1.9	2.8	0.12*	0.86
PIB	0.0018	0.0043	0.0023	0.0019	0.0021	0.0019	0.0014	0.0028

*Transient replicon results.

- In vitro, GLE and PIB have each demonstrated potent antiviral activity against all major HCV genotypes

RESISTANCE PROFILES OF GLE AND PIB

- GLE is potent against common NS3 substitutions at positions 36, 43, 54, 55, 56, 80, 155, and 168
- Substitutions at NS3 position A156 confer resistance to GLE, but are associated with low viral fitness and are rarely detected clinically
- PIB is potent against common NS5A substitutions at positions 24, 28, 30, 31, 58, 92, and 93 that confer resistance to 1st/2nd generation NS5A inhibitors, including Y93H/N

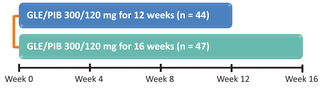
MAGELLAN-I (PART 1)

- In MAGELLAN-I (Part 1), 50 GT1-infected PI and/or NS5A inhibitor-experienced patients without cirrhosis were treated with GLE/PIB ± RBV
  - 92% SVR12 with a virologic failure rate of 4%
- Based on the results from MAGELLAN-I (Part 1), Part 2 of the study expanded the population to include those infected with GT1, 4, 5, or 6 with or without cirrhosis

MAGELLAN-I (PART 2) STUDY DESIGN

- MAGELLAN-I (Part 2) is an open-label, multicenter, randomized trial in DAA-experienced patients (PI, NS5A inhibitor, or both) with GT1, GT4, GT5*, or GT6* infection, without cirrhosis or with compensated cirrhosis

*The study was open to patients with GT5 or GT6, but none were enrolled.



MAGELLAN-I (Part 2) Key Demographics and Patient Characteristics

Characteristic	12-week Arm N = 44	16-week Arm N = 47
HCV RNA, median log_{10} IU/mL (range)	6.09 (4.71–7.20)	6.25 (4.73–7.12)
HCV subtype by phylogenetic analysis, n (%)		
1a	35 (79.5)	32 (68.1)
1b	8 (18.2)	10 (21.3)
1e	0	1 (2.1)
4r	1 (2.3)	2 (43)
Missing	0	2* (43)
Presence or absence of cirrhosis n (%)		
With cirrhosis	15 (34.1)	12 (25.5)
Without cirrhosis	29 (65.9)	35 (74.5)

* Based on LIPA 2.0 analysis, 1 GT1 and 1 GT4.

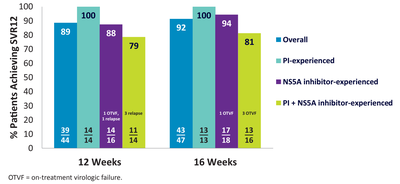
OBJECTIVES

- Resistance analysis of virus from HCV-infected DAA-experienced patients treated with G/P in MAGELLAN-I (Part 2)
  - Prevalence of baseline NS3 and NS5A amino acid substitutions
  - Impact of baseline substitutions on response to G/P
  - Characterization of treatment-emergent substitutions

METHODS

- Next Generation Sequencing (NGS)
  - HCV RNA was reverse-transcribed and amplified using RT-PCR and nested PCR for NS3/4A and NS5A followed by library preparation using the Nextera XT sample preparation kit
  - Paired end sequencing was conducted using the Illumina MiSeq platform
  - HCV subtype assignment
    - For each sample analyzed by NGS, a consensus sequence was generated for each target gene from the NGS nucleotide sequences, with an ambiguity setting of 0.25
    - Phylogenetic analysis was conducted using the full-length HCV NS3/4A and NS5A consensus nucleotide sequences in order to confirm the subtype assignment
  - Substitutions at baseline (NGS detection threshold of 15%) relative to subtype-specific reference sequence at the following amino acid positions for NS3/4A protease or NS5A inhibitor class were analyzed
    - NS3: 155, 156, 168
    - NS5A: 24, 28, 30, 31, 58, 92, 93
- In vitro studies
  - Resistance analyses were performed by introducing NS3 or NS5A substitutions into the wild-type replicons and testing their drug susceptibility in transient replicon assays

SVR12 Rate by DAA Class in Prior Therapy



OTVF = on-treatment virologic failure.

Prior DAA Regimen

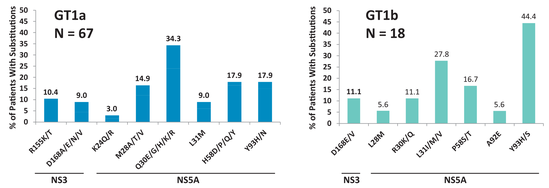
NS3/4A PI	NS5A Inhibitor	NS5B Inhibitor	Total Number of Patients Treated	
			12-week Arm	16-week Arm
	LDV	SOF	9	11
PTV	OBV	DSV	8	11
	DCV*		7	7
BOC*			4	7
TVR*			7	2
SMV*		± SOF	3	4
ASV	DCV	± BCV	3	2
SMV	DCV		1	1
Other DAA combinations not listed above			2	2

*Included pegIFN + RBV in some cases.
Table includes most recent DAA-containing regimen. Ten patients had previously failed 2 or more DAA-containing regimens; 70% achieved SVR12 in this study.
NS3/4A protease inhibitors (PIs): ASV = asunaprevir; BOC = boceprevir; PTV = paritaprevir; SMV = simeprevir; TVR = telaprevir.
NS5A inhibitors: DCV = daclatasvir; LDV = ledipasvir; OBV = ombitasvir.
NS5B polymerase inhibitors: BCV = beclabuvir; DSV = dasabuvir; SOF = sofosbuvir.

- The most common prior DAAs received were LDV/SOF or PTV/OBV/DSV

RESULTS

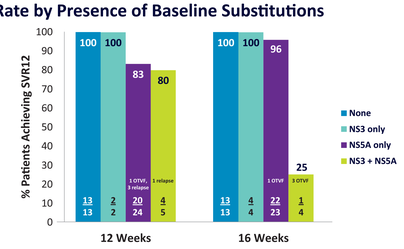
Baseline NS3 or NS5A Substitutions Present in GT1-Infected Patients



Analysis excludes 2 GT1-infected patients who did not have available sequence. GT4-infected subjects were excluded due to small numbers (N = 4).

- The most common amino acid substitutions at baseline were at NS5A amino acid positions Q30, H58, and Y93 in GT1a, and L31 and Y93 in GT1b
- 21/67 patients with GT1a infection had 2 or more NS5A substitutions
  - Combinations seen in more than 1 patient were at positions M28+Q30 (n = 5), Q30+Y93 (n = 5), Q30+L31 (n = 2), Q30+H58 (n = 2), and L31+H58 (n = 2)
- 7/18 patients with GT1b infection had 2 or more NS5A substitutions
  - Combinations seen in more than 1 patient were at positions L31+Y93 (n = 4)

SVR12 Rate by Presence of Baseline Substitutions



OTVF = on-treatment virologic failure. Analysis excluded 3 SVR-achieving patients in the 16-week arm who did not have available sequences (1 was PI only-experienced and 2 were NS5A inhibitor-only experienced). Substitutions at positions 155, 156, 168 in NS3 and 24, 28, 30, 31, 58, 92, 93 in NS5A relative to the subtype specific reference sequence were included in the analysis.

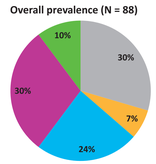
- Among patients in the NS5A only category with Y93H/N/S, 100% (17/17) achieved SVR12 across both study arms
- Lowest SVR12 rates were observed in the patients with substitutions in both NS3 and NS5A, although number of patients in this category was small in each arm

In Vitro Activity of GLE and PIB Against Substitutions Seen at Baseline in NS3 or NS5A

	GT1a		GT1b	
Target	Substitution(s)	Fold EC_{50} change	Substitution(s)	Fold EC_{50} change
NS3	R155K	0.5	D168E	0.9
	R155T	1.9	D168V	3.2
	D168A	4.0		
	D168E	1.3		
	D168N	0.4		
NS5A	K24R	0.3	L28M	1.0
	M28A	2.0	R30Q	0.5
	M28T	2.1	L31M	1.5
	M28V	1.8	L31V	0.8
	Q30E	2.4	P58S	1.2
	Q30G	1.3	A92E	0.5
	Q30H	1.0	Y93H	0.6
	Q30K	1.0	Y93S	0.4
	Q30R	1.7	L31M+Y93H	0.7
	L31M	1.1		
	H58D	1.1		
	H58P	0.6		
	Y93H	6.7		
	Y93N	7.1		
	M28T+Q30R	1.6		
	M28V+Q30R	1.1		
	Q30H+Y93H	17		
	Q30R+L31M	2.4		
	Q30R+H58D	108.0		
	M28T+Q30R+L31M	4.6		

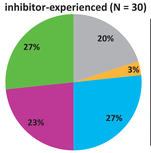
Prevalence of Baseline Substitutions and Impact on Outcome Based on Previous DAA Experience

Overall prevalence (N = 88)



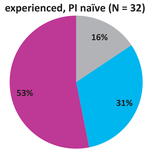
SVR12 % (n/N)	
12 weeks	16 weeks
100 (13/13)	100 (13/13)
100 (2/2)	100 (4/4)
80 (8/10)	100 (11/11)
86 (12/14)	92 (11/12)
80 (4/5)	25 (1/4)

Prevalence in PI + NS5A inhibitor-experienced (N = 30)



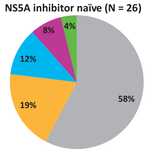
SVR12 % (n/N)	
12 weeks	16 weeks
100 (3/3)	100 (3/3)
—	100 (1/1)
60 (3/5)	100 (3/3)
100 (2/2)	100 (5/5)
75 (3/4)	25 (1/4)

Prevalence in NS5A inhibitor-experienced, PI naïve (N = 32)



SVR12 % (n/N)	
12 weeks	16 weeks
100 (1/1)	100 (4/4)
100 (4/4)	100 (6/6)
82 (9/11)	83 (5/6)

Prevalence in PI-experienced, NS5A inhibitor naïve (N = 26)



SVR12 % (n/N)	
12 weeks	16 weeks
100 (9/9)	100 (6/6)
100 (2/2)	100 (3/3)
100 (1/1)	100 (2/2)
100 (1/1)	100 (3/1)
100 (1/1)	—

Analysis excluded 3 SVR-achieving patients in the 16-week arm who did not have available sequences (1 was PI only-experienced and 2 were NS5A inhibitor only-experienced). Substitutions at positions 155, 156, 168 in NS3 and 24, 28, 30, 31, 58, 92, 93 in NS5A relative to the subtype specific reference sequence were included in the analysis.

- Patients who had no baseline substitutions or only had them in NS3 achieved 100% SVR12 regardless of previous treatment
- Most patients with NS5A inhibitor-experience had NS5A baseline substitutions, but that was not the case for PI-experienced patients and NS3 baseline substitutions
- The majority of patients with substitutions in NS5A had them at multiple positions, and the SVR12 rate was not substantially affected by multiple vs single NS5A substitutions
- Among patients with previous NS5A inhibitor experience (with or without PI) treated for 16 weeks, the SVR12 rate in patients with single target or no substitutions was 96% (27/28) whereas the SVR12 rate in the presence of substitutions in both NS3 and NS5A was 25% (1/4)

Profile of Patients Who Experienced Virologic Failure

Prior Treatment						NS3 substitutions[a,b]				NS5A substitutions[a,b]			
		Category				Baseline		VF		Baseline		VF	
GLE/PIB duration	DAAs[c]	PI	NS5Ai	HCV GT	Type of VF	Substitutions	Fold EC_{50} change	Substitutions	Fold EC_{50} change	Substitutions	Fold EC_{50} change	Substitutions	Fold EC_{50} change
12 Weeks	SOF+LDV	No	Yes	1a	OTVF	None	—	A156V	NV	Q30E/K	2.4	Q30K+Y93H	>1000
	SMV+SOF; SOF+LDV	Yes	Yes	1a	Relapse	V36M+R155K	0.7	V36M+R155K+A156T	NV	M28V+Q30R	1.1	M28G+Q30R	>1000
	DCV	No	Yes	1a	Relapse	None	—	None	—	Q30R+H58D	126	Q30R+H58D	126
	ASV+DCV+BCV	Yes	Yes	1a	Relapse	None	—	None	—	Q30G	1.3	P29R+Q30G	NV
	ASV+DCV	Yes	Yes	1b	Relapse	None	—	None	—	L28M, P32deletion	>1000	L28M+P32deletion	>1000
16 Weeks	TVR; SMV+SOF; SOF+LDV; PTV+OBV+DSV	Yes	Yes	1a	OTVF	Y56H+D168E	47	V36M+Y56H+D168E	127	K24Q+Y93H	6.7	K24R, K24Q+Q30K+Y93H	>1000
	SOF+LDV	No	Yes	1a	OTVF	None	—	A156V	NV	Q30R+L31M	3.0	Q30R+L31M+H58D	>1000
	DCV; PTV+OBV+DSV	Yes	Yes	1a	OTVF	Y56H+D168A	39	Y56H+A156G+D168A	NV	M28T/V, Q30R+L31M	4.6	NA	—
	PTV+OBV+DSV	Yes	Yes	1a	OTVF	Y56H, D168A	39	R155T+A156V+D168A	NV	Q30H+Y93H	17	M28A, Q30H+H58D+Y93H	>1000

NA = sequence not available; NV = not viable (replication efficiency <0.5%); NS5Ai = NS5A inhibitor; OTVF = on-treatment virologic failure; VF = virologic failure.
[a]For samples with multiple substitutions within a target, if individual substitutions were detected at ≥ 90% prevalence, they are considered to be linked and denoted by "+", whereas if one or more of the substitutions was detected at <90% prevalence, the variants are separated by a comma.
[b]Substitutions seen at positions 36, 56, 155, 156, 168 in NS3 and 24, 28, 30, 31, 32, 58, 92, 93 in NS5A are included.
[c]Each prior DAA regimen separated by semicolon.

- There were 8 GT1a and 1 GT1b patients who experienced virologic failure
- All 9 patients had substitutions in NS5A at baseline, and 4/9 also had substitutions in NS3
- Most patients had treatment-emergent substitutions in NS3 and NS5A at the time of failure, but no consistent substitution pattern was seen, either at baseline or at the time of failure

CONCLUSIONS

PI-EXPERIENCED PATIENTS (NS5A INHIBITOR-NAÏVE)

- No impact on efficacy with G/P; high SVR12 rates observed regardless of duration

NS5A INHIBITOR-EXPERIENCED PATIENTS (PI-NAÏVE)

- G/P for 16 weeks demonstrated high SVR12 rates regardless of the presence of single or multiple baseline NS5A substitutions
  - No need for NS5A resistance testing at baseline

PI AND NS5A INHIBITOR-EXPERIENCED PATIENTS

- Virologic failure was associated with presence of baseline substitutions in both NS3 and NS5A
  - G/P for 16 weeks demonstrated high SVR12 rates in patients without NS3 baseline substitutions

DISCLOSURES

All authors are employees of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

SUMMARY

- The presence of NS3 baseline substitutions alone had no impact on efficacy
- Among NS5A inhibitor-experienced patients and/or patients with NS5A substitutions at baseline, the 12-week regimen was associated with a higher rate of relapse than the 16-week regimen
- Among patients treated for 16 weeks, the presence of single or multiple NS5A baseline substitutions at positions 24, 28, 30, 31, 58, 92, 93 (in the absence of ones in NS3 at positions 155, 156, or 168) at baseline had no impact on efficacy:
  - SVR12 rate in NS5A inhibitor-experienced patients was 95% (19/20)
  - SVR12 rate in patients with NS5A substitutions was 96% (22/23)
- In patients experienced to both classes treated for 16 weeks:
  - Majority had baseline substitutions only in NS5A; just 25% (4/16) had both NS3 and NS5A substitutions
  - SVR12 rate in patients with both NS3 and NS5A baseline substitutions was 25% (1/4)
  - SVR12 rate in patients without substitutions in both NS3 and NS5A at baseline was 100% (12/12)

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Safety and Efficacy of Glecaprevir/Pibrentasvir in Adults With Chronic Hepatitis C Virus Infection Genotype 1–6 as a Function of Chronic Kidney Disease Stage

SAT-273

Stanislas Pol[1], Paul Pockros[2], David Pugatch[3], Norbert Bräu[4], Charles Landis[5], Ira Jacobson[6], Magdy Elkhashab[7], Joe Sasadeusz[8], Albert Tran[9], Yiran Hu[3], Matthew Kosloski[3], Federico J Mensa[3]

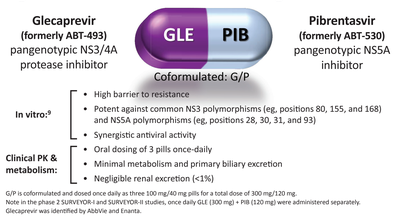
[1]Groupe Hospitalier Cochin-Saint Vincent De Paul, Paris, France; [2]Division of Gastroenterology/Hepatology, Scripps Clinic, La Jolla, California, United States; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]James J Peters VA Medical Center, Bronx, New York, United States; [5]Division of Gastroenterology, University of Washington, Seattle, Washington, United States; [6]Mount Sinai Beth Israel, New York, New York, United States ; [7]Toronto Liver Centre, Toronto, Ontario, Canada; [8]Royal Melbourne Hospital, Melbourne, Australia; [9]University Hospital of Nice, Digestive Centre, Nice, F-06202, Cedex 3, France

Presented at the 52nd Annual Meeting of the European Association for the Study of the Liver, 19–23 April 2017, Amsterdam, the Netherlands

INTRODUCTION

- Patients with chronic kidney disease (CKD) have an increased prevalence of chronic hepatitis C virus (HCV) infection[1]
- HCV infection is associated with an increased risk of CKD progression[2,3] and mortality from renal disease[4,5]
- Glecaprevir (GLE, formerly ABT-493), an NS3/4A protease inhibitor, and pibrentasvir (PIB, formerly ABT-530), an NS5A inhibitor, are direct-acting antivirals (DAAs) being developed as a once-daily, ribavirin (RBV)-free, fixed-dose combination regimen (G/P) to treat genotype (GT) 1–6 chronic HCV infection in patients with any degree of renal impairment, including those with end-stage renal disease **(Figure 1)**
- GLE and PIB both undergo minimal metabolism and negligible renal excretion, which makes them potentially suitable for the treatment of patients with renal disease[6]
- Phase 1 pharmacokinetic (PK) studies demonstrated that no dose modification is required in patients with any degree of CKD, including those on haemodialysis[7,8]
- Here, we report results of an integrated analysis of efficacy, safety, and PK of 2238 NS5A inhibitor-naive patients in phase 2 or 3 studies
- In phase 3 studies, patients were treated with a fixed-dose combination of G/P, whereas patients in phase 2 studies (ie, SURVEYOR-I [parts 1 and 2] and SURVEYOR-II) were treated with separately formulated tablets. The total daily dose for both formulations was 300 mg/120 mg and will be collectively referred to as G/P

Figure 1. Next Generation Direct-acting Antivirals



G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Note in the phase 2 SURVEYOR-I and SURVEYOR-II studies, once daily GLE (300 mg) + PIB (120 mg) were administered separately.
Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVES

- To describe the efficacy, safety, and PK properties of G/P in patients treated for 8, 12, or 16 weeks across eight phase 2 or 3 studies, including all major HCV GTs, without or with compensated cirrhosis, as a function of CKD stage

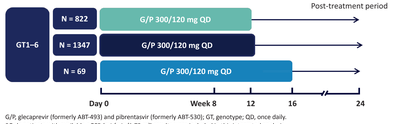
METHODS

- Eight global, multicentre, open-label or double blind and placebo controlled phase 2 and 3 clinical trials with available estimated glomerular filtration rate (eGFR mL/min/1.73 m^2) results were included in this analysis:
  - ENDURANCE-I (NCT02604017): phase 3, randomised study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT1 infection
  - ENDURANCE-II (NCT02640482): phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT2 Infection
  - ENDURANCE-III (NCT02640157): phase 3, randomised, active-controlled study to compare efficacy and safety of G/P to sofosbuvir (SOF) co-administered with daclatasvir in adults with chronic HCV GT3 infection (Foster GR et al. EASL 2017, Oral presentation number: GS-006)
  - ENDURANCE-IV (NCT02636595): phase 3, single-arm study to evaluate the efficacy and safety of G/P in adults with chronic HCV GT4, GT5, or GT6 infection
  - EXPEDITION-I (NCT02642432): phase 3, single-arm study to evaluate the efficacy and safety of ABT-493/ABT-530 in adults with chronic HCV GT1, GT2, GT4, GT5, or GT6 infection and compensated cirrhosis (Forns X et al. EASL 2017, Oral presentation number: GS-005)
  - EXPEDITION-IV (NCT02651194): phase 3, single-arm study to evaluate the efficacy and safety of G/P in renally-impaired adults with chronic HCV GT1–6 infection

METHODS (CONTINUED)

  - SURVEYOR-I (NCT02243280): phase 2 study to evaluate the efficacy, safety, and PK of co-administration of GLE and PIB ± RBV in subjects with HCV GT1, GT4, GT5, or GT6. Patients who received RBV were excluded from this integrated analysis
  - SURVEYOR-II (NCT02243293): phase 2, randomised study to evaluate the efficacy, safety, and PK of co-administration of GLE and PIB ± RBV in subjects with chronic HCV GT2–6 infection. Patients who received RBV were excluded from this integrated analysis
- Patients were stratified by CKD stage, defined by eGFR (mL/min/1.73 m^2) according to the Modification of Diet in Renal Disease (MDRD) equation[10] measured at baseline:
  - CKD stage 1 = eGFR ≥90 (normal renal function)
  - CKD stage 2 = eGFR ≥60–<90 (mild renal impairment)
  - CKD stage 3 = eGFR ≥30–<60 (moderate renal impairment)
  - CKD stage 4 = eGFR ≥15–<30 (severe renal impairment)
  - CKD stage 5 = eGFR <15 (severe renal impairment or on dialysis)
- Patients were assigned to treatment arms of 8-, 12-, or 16-week duration, as defined in the study protocols **(Figure 2)**

Figure 2. Phase 2 and 3 Multicentre Studies of GT1–6 HCV-infected Patients*



G/P, glecaprevir (formerly ABT-493) and pibrentasvir (formerly ABT-530); GT, genotype; QD, once daily.
*Only patients with available eGFR (mL/min/1.73 m^2) results were included in this integrated analysis.

KEY ELIGIBILITY CRITERIA

- Eligible patients in studies ENDURANCE-I, ENDURANCE-II, ENDURANCE-III, ENDURANCE-IV, EXPEDITION-I, EXPEDITION-IV, SURVEYOR-I, and SURVEYOR-II had chronic HCV GT1–6 infection at screening, did not have co-infection with >1 HCV GT and were documented as without cirrhosis or with compensated cirrhosis
- Patients enrolled included those who were treatment-naive or treatment-experienced with prior pegylated interferon (pegIFN)/RBV or SOF + RBV ± pegIFN. Patients were ≥18 years of age, without HIV (except ENDURANCE-I) or HBV co-infection
- Patients enrolled in phase 3 studies were required to have platelets ≥60 000 cells per mm^3 or ≥90 000 cells per mm^3 in those with compensated cirrhosis and without cirrhosis, respectively (with the exception of ≥40 000 cells per mm^3 in EXPEDITION-IV). Patients enrolled in phase 2 studies were required to have platelets ≥120 000 cells per mm^3 for patients without cirrhosis or ≥90 000 cells per mm^3 for patients with compensated cirrhosis
- Patients were eligible for enrolment if they had:
  - Direct bilirubin ≤ upper limit of normal (ULN 0.4 mg/dL) and albumin >3.3 g/dL in patients without cirrhosis in phase 3 studies and in SURVEYOR-I and SURVEYOR-II (which included both cirrhotic and non-cirrhotic patients)
  - Total bilirubin <3.0 mg/dL and albumin >2.8 g/dL in patients with compensated cirrhosis in phase 3 studies and in EXPEDITION-IV (which included both cirrhotic and non-cirrhotic patients)
  - An international normalised ratio <2.3
- Eligible patients had creatinine clearance of ≥50 mL/min (except EXPEDITION-IV)
- Eligible patients for EXPEDITION-IV were documented at screening to have eGFR by MDRD <30 mL/min/1.73 m^2
  - Stage 4 CKD: eGFR 15–29 mL/min/1.73 m^2
  - Stage 5 CKD: eGFR <15 mL/min/1.73 m^2 or haemodialysis dependent

STUDY ASSESSMENTS

- Percentage of patients with SVR12 (HCV RNA < LLOQ* 12 weeks after the last dose of study drug)
- Adverse events (AEs) and clinical laboratory parameters were monitored throughout the treatment and immediate post-treatment periods (within 30 days after treatment completion)
- Safety analyses included pooled AEs and laboratory data from all patients who received at least 1 dose of study medications in the studies specified
- PK exposures in patients were estimated using population PK analyses

*Phase 3 studies: Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0. HCV RNA ≤ 15 IU/mL (LLOQ), phase 2 studies Roche COBAS TaqMan® real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 HCV RNA <25 IU/mL (LLOQ).

RESULTS

PATIENTS

- A total of 2238 patients were enrolled from 26 countries and included in this integrated PK, efficacy, and safety analysis
- Baseline demographic and clinical characteristics stratified by CKD stage, as defined by eGFR, are shown in **Table 1**
- The highest proportion of patients were HCV GT1, treatment-naive, non-cirrhotic and CKD stage 1 (normal renal function), or 2 (mild renal impairment)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	CKD 1 n = 1054	CKD 2 n = 1045	CKD 3 n = 36	CKD 4–5 n = 103	Total N = 2238
Male, n (%)	624 (59)	506 (48)	14 (39)	79 (77)	1223 (55)
Age, median (range), years	50 (19–88)	56 (25–84)	60 (29–75)	57 (28–83)	54 (19–88)
Race, n (%)					
White	836 (80%)	872 (83)	29 (81)	64 (62)	1801 (81)
Black or African American	53 (5)	39 (4)	3 (8)	24 (23)	119 (5)
Asian	143 (14)	114 (11)	3 (8)	9 (9)	269 (12)
BMI, median (range), kg/m^2	25 (17–49)	26 (18–66)	29 (18–41)	26 (18–45)	26 (17–66)
HCV genotype, n (%)					
1	399 (38)	421 (40)	15 (42)	54 (52)	889 (40)
2	195 (19)	239 (23)	12 (33)	16 (16)	462 (21)
3	329 (31)	285 (27)	7 (19)	11 (11)	632 (28)
4	89 (8)	66 (6)	0	20 (19)	175 (8)
5	11 (1)	19 (2)	1 (3)	1 (1)	32 (1)
6	31 (3)	15 (1)	1 (3)	1 (1)	48 (2)
Treatment-naive, n (%)	786 (75)	757 (72)	25 (69)	60 (58)	1628 (73)
Treatment-experienced, n (%)	268 (25)	288 (28)	11 (31)	43 (42)	610 (27)
Cirrhosis status					
Yes	129 (12)	115 (11)	8 (22)	20 (19)	272 (12)
No	925 (88)	930 (89)	28 (78)	83 (81)	1966 (88)
Baseline HCV RNA level, $\log_{10}$ IU/mL, median (range)	6.2 (1–8)	6.2 (1–8)	6.3 (4–8)	5.9 (3–8)	6.2 (1–8)
Baseline eGFR, mL/min/1.73 m^2, median (range)	103 (90–204)	82 (60–90)	56 (38–60)	8 (4–28)	89 (4–204)

CKD stages are defined by eGFR (mL/min/1.73 m^2); CKD stage 1 = eGFR ≥90 (normal renal function), CKD stage 2 = eGFR ≥60–<90 (mild renal impairment), CKD stage 3 = eGFR ≥30–<60 (moderate renal impairment), and CKD stage 4–5 = eGFR <30 (severe renal impairment). CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

EFFICACY

- High SVR12 rates were achieved irrespective of baseline CKD stage **(Figure 3A)**, and HCV genotype **(Figure 3B)**

Figure 3A. Percentage of Patients Achieving SVR12 (ITT) by Baseline eGFR (mL/min/1.73m^2)

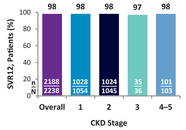
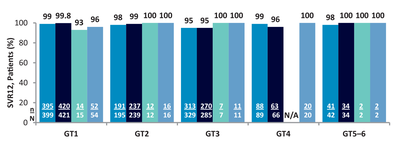


Figure 3B. Percentage of Patients Achieving SVR12 (ITT) by Baseline eGFR (mL/min/1.73m^2) and HCV Genotype



- High SVR12 rates were achieved across all CKD stages irrespective of baseline characteristics, including treatment duration, cirrhosis status, and prior HCV treatment **(Table 2)**

Table 2. Percentage of Patients Achieving SVR12 (ITT) Stratified by Baseline CKD Stage

Characteristic, n (%)	CKD 1 n = 1054	CKD 2 n = 1045	CKD 3 n = 36	CKD 4–5 n = 103	Total N = 2238
Baseline HCV RNA level					
≥6 000 000 IU/mL	207/220 (94)	238/248 (96)	12/12 (100)	8/8 (100)	465/488 (95)
<6 000 000 IU/mL	821/834 (98)	786/797 (99)	23/24 (96)	93/95 (98)	1723/1750 (99)
Treatment duration					
8 weeks	378/392 (96)	407/413 (99)	16/17 (94)	0	801/822 (97)
12 weeks	622/633 (98)	581/593 (98)	18/18 (100)	101/103 (98)	1322/1347 (98)
16 weeks	28/29 (97)	36/39 (92)	1/1 (100)	0	65/69 (94)
Treatment-naive, n (%)	764/786 (97)	746/757 (99)	24/25 (96)	58/60 (97)	1592/1628 (98)
Treatment-experienced, n (%)	264/268 (99)	278/288 (97)	11/11 (100)	43/43 (100)	596/610 (98)
Cirrhosis status					
Yes	127/129 (98)	112/115 (97)	8/8 (100)	18/20 (90)	265/272 (97)
No	901/925 (97)	912/930 (98)	27/28 (96)	83/83 (100)	1923/1966 (98)
IL28B					
CC	361/372 (97)	325/332 (98)	15/15 (100)	24/24 (100)	725/743 (98)
non-CC	666/681 (98)	699/713 (98)	20/21 (95)	77/79 (98)	1462/1494 (98)
Missing	1/1 (100)	N/A	N/A	N/A	1/1 (100)
Presence of polymorphisms					
NS5A	176/183 (96)	177/184 (96)	5/5 (100)	17/17 (100)	375/389 (96)
NS3	15/17 (88)	17/17 (100)	1/1 (100)	1/1 (100)	34/36 (94)
Haemodialysis					
Yes	N/A	N/A	N/A	83/85 (98)	83/85 (98)
No	1028/1054 (98)	1024/1045 (98)	35/36 (97)	18/18 (100)	2105/2153 (98)

CKD stages are defined by eGFR (mL/min/1.73m^2); CKD stage 1 = eGFR ≥90 (normal renal function), CKD stage 2 = eGFR ≥60–<90 (mild renal impairment), CKD stage 3 = eGFR ≥30–<60 (moderate renal impairment), and CKD stage 4–5 = eGFR <30 (severe renal impairment). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; N/A = not applicable.

SAFETY

- In total, 1507/2238 (67%) patients reported experiencing at least 1 AE **(Table 3)**
- The type and frequency of AEs observed across CKD stages 1–5 were broadly similar and the majority of events were mild or moderate in severity, with only 3% (70/2238) of all patients experiencing a serious adverse event (SAE)
- The number of patients 25/103 (24%) who experienced SAEs was larger amongst those with CKD stage 4–5; however, none was considered drug-related
- The most commonly reported AEs occurring in ≥10% of patients in any CKD stage group were nausea, fatigue, headache, nasopharyngitis, vomiting, and pruritus (reported at higher rate in the CKD stage 4–5 subjects) **(Table 3)**
- Only 1 patient experienced a DAA-related SAE (transient ischaemic attack) judged to be DAA-related by the investigator; the patient discontinued treatment on Day 12 and did not achieve SVR12. The AE subsequently resolved; but, a second transient ischaemic attack occurred following discontinuation
- Overall rates of AEs leading to discontinuation of study drug were low (12/2238; 0.5%); 5/2238 (0.2%) patients discontinued study drugs due to AEs assessed as being possibly related to DAA treatment
- 6/2238 (0.3%) patients died across all CKD stages. All deaths were considered not related to the study drug

Table 3. Summary of Adverse Events

Event	CKD 1 n = 1054	CKD 2 n = 1045	CKD 3 n = 36	CKD 4–5 n = 103	Total N = 2238
Any AE, n (%)	712 (68)	698 (67)	23 (64)	74 (72)	1507 (67)
AEs occurring in ≥10% of patients, n (%)					
Nausea	111 (11)	78 (8)	7 (19)	12 (12)	208 (9)
Fatigue	154 (15)	158 (15)	4 (11)	15 (15)	331 (15)
Headache	204 (19)	174 (17)	4 (11)	9 (9)	391 (18)
Nasopharyngitis	58 (6)	39 (4)	4 (11)	2 (2)	103 (5)
Vomiting	20 (2)	21 (2)	4 (11)	7 (7)	52 (2)
Pruritus	35 (3)	61 (6)	2 (6)	21 (20)	119 (5)
Any SAE	25 (2)	17 (2)	3 (8)	25 (24)	70 (3)
DAA-related SAE	0	1 (<0.1)	0	0	1 (<0.1)
Any AE leading to discontinuation of study drug	4 (0.4)	3 (0.3)	1 (3)	4 (4)	12 (0.5)
Any fatal AE	1 (<0.1)	0	1 (3)	1 (1)	3 (0.1)
Death*†	3 (0.3)	1 (<0.1)	1 (3)	1 (1)	6 (0.3)

*All deaths were considered not related to the study drug; †Causes of death: CKD stage 1 (n = 3) pneumonia, accidental overdose, alcohol poisoning and toxicity to various agents; CKD stage 2 (n = 1) cerebral haemorrhage; CKD stage 3 (n = 1) adenocarcinoma; CKD stage 4–5 (n = 1) cerebral haemorrhage.
AE, adverse event; CKD, chronic kidney disease; DAA, direct-acting antiviral; SAE, serious adverse event.

LABORATORY ABNORMALITIES

- Grade ≥3 laboratory abnormalities from baseline were infrequent **(Table 4)**
- Two (<0.1%) patients experienced grade 3 elevations in alanine aminotransferase (ALT) from baseline; >5 × ULN; both patients had CKD stage 2
  - Across the phase 2 and 3 studies, 4 (<0.1%) patients experienced a post-nadir grade 3 in ALT (>5 × ULN). All 4 patients were non-cirrhotic and elevations were considered not clinically relevant or most likely associated with etiologies unrelated to study drug (passage of gallstone)
- There were no cases consistent with drug-induced liver injury
- Nine (0.4%) patients experienced grade 3 (>3.0 × ULN) elevations of total bilirubin; most had indirect predominance without associated ALT increase, at isolated visits in patients with indirect hyperbilirubinaemia at baseline (Gilbert's syndrome)

Table 4. Summary of Laboratory Abnormalities

Laboratory Abnormalities, n (%)	CKD 1 n/N (%)	CKD 2 n/N (%)	CKD 3 n/N (%)	CKD 4–5 n/N (%)	Total n/N (%)
ALT ≥grade 3 (>5 × ULN)*	0/1052	2/1045 (0.2)	0/36	0/103	2/2236 (<0.1)
Total bilirubin ≥grade 3 (>3 × ULN)*	5/1052 (0.5)	3/1045 (0.3)	0/36	1/103 (1)	9/2236 (0.4)

ALT, alanine aminotransferase; CKD, chronic kidney disease; ULN, upper limit of normal.
*Increased grade from baseline result.

MEAN CHANGE IN eGFR

- The mean change assessment excluded patients on haemodialysis
- Overall, the mean change in eGFR (mL/min/1.73m^2) from baseline to final post-treatment visit was -2.54 ± 12.74. Renal function appeared to slightly improve in patients with CKD stage 3 (7.73 ± 9.49) **(Table 5)**

Table 5. Mean Change in eGFR (mL/min/1.73m^2) From Baseline to Final Post-Treatment Visit by CKD Stage*

Event	CKD 1 n = 920	CKD 2 n = 905	CKD 3 n = 31	CKD 4–5 n = 18	Total N = 1874
Mean change in eGFR (mL/min/1.73m^2) from baseline to final post-treatment visit	-6.02 ± 14.13	0.62 ± 10.21	7.73 ± 9.49	-0.82 ± 2.29	-2.54 ± 12.74

GFR from creatinine adjusted for BSA (mL/min/1.73m^2).
*Mean change assessment excludes patients on haemodialysis.
BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

PHARMACOKINETIC DATA

- Exposures of GLE and PIB were higher in patients with more advanced CKD; however, maximum increases in geometric mean AUC$_{24,ss}$ were <2-fold and were not clinically relevant **(Table 6)**

Table 6. Summary of Individual Estimated Steady-state Exposures for GLE and PIB by CKD Stage, Geometric Mean (Mean, CV %)

		GLE AUC$_{24,ss}$ ng*h/mL		PIB AUC$_{24,ss}$ ng*h/mL	
CKD Stage	N*	Geometric Mean (Mean, %CV)	Central Value Ratio (90% Confidence Interval) vs CKD Stage 1	Geometric Mean (Mean, %CV)	Central Value Ratio (90% Confidence Interval) vs CKD Stage 1
1	1050	5120 (9040, 189)	—	1390 (1590, 58)	—
2	1042	5490 (9290, 158)	1.07 (1.00 to 1.15)	1510 (1720, 56)	1.08 (1.04 to 1.12)
3–4	48	8320 (16600, 156)	1.63 (1.29 to 2.06)	1540 (1870, 65)	1.11 (0.98 to 1.25)
5	91	9490 (18200, 175)	1.85 (1.56 to 2.20)	2090 (2580, 76)	1.50 (1.37 to 1.65)

*Plasma samples for pharmacokinetic analysis were unavailable in N = 4 CKD stage 1 patients and N = 3 CKD stage 2 patients.
AUC$_{24,ss}$, steady-state area under concentration-time curve over the dosing interval; CKD, chronic kidney disease; CV, coefficient of variation; GLE, glecaprevir; PIB, pibrentasvir.

CONCLUSIONS

- In HCV GT1–6 infected patients treated in phase 2 and 3 clinical studies, once daily RBV-free, G/P 300/120 mg achieved high SVR12 rates and was well tolerated regardless of any degree of renal impairment
- Majority of AEs were mild or moderate in severity. SAEs considered drug-related were rare (<0.1%) and none occurred among patients with CKD stage 4 or 5
- The type and frequency of AEs observed across CKD stages 1–5 were broadly similar with the exception of pruritus which occurred at a higher frequency in the patients with CKD stages 4–5 which is consistent with the high background rates of pruritus in this population[11,12]
- Post-baseline grade ≥3 laboratory abnormalities were infrequent and there were no cases consistent with drug-induced liver injury
- This integrated analysis demonstrates that renal function does not impact on the very high efficacy and favorable safety profile of G/P

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DISCLOSURES

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High SVR Rates With Eight and Twelve Weeks of Pangenotypic Glecaprevir/Pibrentasvir: Integrated Efficacy Analysis of Genotype 1–6 Patients Without Cirrhosis

SAT-233

Massimo Puoti[1], Graham R Foster[2], Stanley Wang[3], David Mutimer[4], Edward Gane[5], Christophe Moreno[6], Ting Tsung Chang[7], Sam Lee[8], Rui Marinho[9], Jean-Francois DuFour[10], Stanislas Pol[11], Christophe Hezode[12], Stuart C Gordon[13], Simone I Strasser[14], Paul J Thuluvath[15], Ran Liu[3], Tami Pilot-Matias[3], Federico Mensa[3]

[1]AO Ospedale Niguarda Ca Granda, Milan, Italy; [2]Queen Mary University of London, Barts Health, London, United Kingdom; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]Queen Elizabeth Hospital and NIHR Liver Biomedical Research Unit, Birmingham, United Kingdom; [5]University of Auckland, Auckland, New Zealand; [6]CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; [7]National Cheng Kung University Hospital, Tainan City, Taiwan; [8]University of Calgary, Calgary, Alberta, Canada; [9]Hospital S. Maria, Medical School of Lisbon, Portugal; [10]Hepatology, University Clinic for Visceral Surgery and Medicine, Bern University Hospital, Switzerland; [11]Groupe Hospitalier Cochin-Saint Vincent De Paul, Paris, France; [12]Hôpital Henri Mondor, AP-HP, Université Paris-Est, Créteil, France; [13]Henry Ford Health System, Detroit, Michigan, United States; [14]Royal Prince Alfred Hospital, Sydney, Australia; [15]Mercy Medical Center & University of Maryland School of Medicine, Baltimore, Maryland, United States

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INTRODUCTION

- In seven phase 2 or 3 clinical trials, treatment with the all-oral, interferon- and ribavirin-free glecaprevir and pibrentasvir combination regimen achieved SVR12 (HCV RNA <lower limit of quantification 12 weeks post-treatment) rates of 93–100% across all 6 major HCV genotypes (GTs)[1–5]

Next Generation Direct-acting Antivirals

Glecaprevir (formerly ABT-493) pangenotypic NS3/4A protease inhibitor

Pibrentasvir (formerly ABT-530) pangenotypic NS5A inhibitor

In vitro:[6]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Synergistic antiviral activity

Clinical PK & metabolism:
- Oral dosing of 3 pills once-daily
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVE

Conduct an integrated efficacy analysis of treatment for 8 or 12 weeks in non-cirrhotic patients with GT1-6 infection, and determine whether any baseline factors impact achievement of SVR12

METHODS

- Data was pooled from arms of the SURVEYOR-I and -II, and EXPEDITION-4 and ENDURANCE 1, 2, 3, and 4 studies, in which patients received treatment with GLE 300 mg + PIB 120 mg or coformulated G/P (300 mg/120 mg) without ribavirin (RBV) for either 8 or 12 weeks

KEY ELIGIBILITY CRITERIA

- Adults with chronic HCV GT 1, 2, 3, 4, 5 or 6 infection (HCV RNA >1000 IU/mL)
- Age ≥18 years and BMI ≥18 kg/m^2
- HCV treatment-naïve or treatment-experienced with interferon (IFN) or pegylated IFN (pegIFN) ± RBV, or sofosbuvir (SOF) plus RBV ± pegIFN
- Absence of cirrhosis based on liver biopsy, transient elastography (Fibroscan®), or serum biomarkers (Fibrotest®) and APRI
- No prior HCV treatment experience with a DAA other than SOF
- Absence of co-infection with hepatitis B virus

ENDPOINTS AND ANALYSES

Primary Efficacy Endpoint
The proportion of patients with SVR12, conducted in the ITT (intention-to-treat) and mITT (modified ITT) populations*

Secondary Efficacy Endpoints
The proportion of patients with on-treatment virologic failure and post-treatment relapse, conducted in the ITT population

Subgroup Analyses
- Over 20 continuous and categorical baseline variables were included in the analysis
- Multivariate stepwise logistic regression was performed to identify factors associated with reduced SVR12 rates
- Conducted in mITT population

Safety Assessments
Adverse events (AEs) and laboratory abnormalities were assessed in ITT population

*ITT population includes all patients that received at least 1 dose of study drug, mITT population excludes patients with non-virologic failures.

RESULTS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	8-Week G/P N = 828	12-Week G/P N = 1076
Male, n (%)	424 (51)	584 (54)
Race, n (%)		
White	688 (83)	825 (77)
Asian	81 (10)	163 (15)
Black	41 (5)	61 (6)
Age, median (range), years	53 (19 – 84)	53 (20 – 83)
BMI, median (range), kg/m^2	25.6 (17.3 – 65.7)	25.3 (17.4 – 54.1)
Genotype, n (%)		
1	387 (47)	401 (37)
Subtype 1a	178 (21)	168 (16)
Subtype 1b	208 (25)	230 (21)
Other	1 (0.1)	3 (0.3)
2	197 (24)	234 (22)
3	186 (22)	270 (25)
4	46 (6)	112 (10)
5	2 (0.2)	28 (3)
6	10 (1)	31 (3)
IL28B non-CC genotype, n (%)	534 (64)	723 (67)
HCV treatment-naïve, n (%)	657 (79)	801 (74)
HCV treatment-experienced, n (%)*	171 (21)	275 (26)
IFN-based	164 (96)	266 (97)
SOF-based	7 (4)	9 (3)
HCV RNA, median (range), $\log_{10}$ IU/mL	6.2 (0.7 – 7.6)	6.2 (2.5 – 7.8)
Baseline HCV RNA level, IU/mL, n (%)		
<1000000	338 (41)	446 (41)
≥1000000	490 (59)	630 (59)
<6000000	623 (75)	850 (79)
≥6000000	205 (25)	226 (21)
Fibrosis stage, n/N (%)†		
F0–F1	678/825 (82)	870/1075 (81)
F2	56/825 (7)	87/1075 (8)
F3	91/825 (11)	118/1075 (11)
HIV-1 co-infected, n (%)	15 (2)	18 (2)
Concomitant PPI use, n (%)	61 (7)	125 (12)
On stable opiate substitution, n (%)	62 (7)	63 (6)
>80% treatment compliant, n (%)	735 (89)	979 (91)
APRI, n (%)		
<1	686 (83)	881 (82)
≥1	142 (17)	195 (18)
Fibroscan, n/N (%)†		
<9.6 kPa	501/579 (87)	703/801 (88)
≥9.6 kPa	78/579 (13)	98/801 (12)
Fibrotest n/N (%)†		
<0.59	279/347 (80)	292/367 (80)
≥0.59	68/347 (20)	75/367 (20)

G/P, glecaprevir/pibrentasvir; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; SOF, sofosbuvir; PPI, proton pump inhibitor; APRI, aspartate aminotransferase to platelet ratio.
*IFN-based: IFN or pegIFN ± RBV; SOF-based: SOF + RBV ± pegIFN; SOF + RBV ± pegIFN patients counted as SOF-experienced only.
†N adjusted for patients missing data.
‡N adjusted for patients with fibrosis status assessed by FibroScan or Fibrotest.

- Patient baseline demographics and disease characteristics were similar across the 8 and 12 week treatment arms

Figure 1. Efficacy of 8- vs 12-week G/P

Figure 1a. SVR12, ITT Population

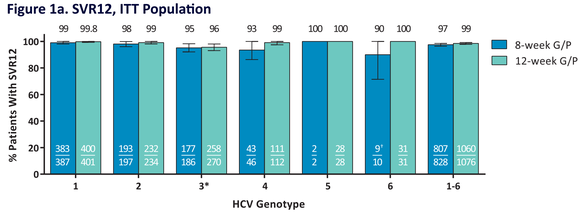
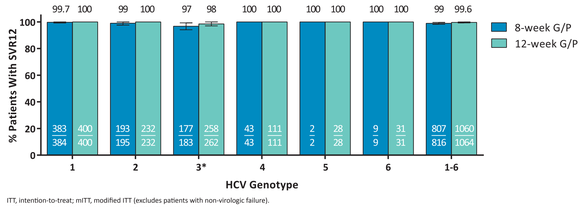


Figure 1b. SVR12, mITT Population



ITT, intention-to-treat; mITT, modified ITT (excludes patients with non-virologic failure).
*GT3 patients included in this analysis were treatment-naïve only.
†Patient missing SVR12 data returned after post-treatment Week 12 visit and has achieved HCV RNA <lower limit of quantification.

- Across all genotypes, G/P for 8 weeks yielded high SVR12 rates comparable to those following 12-week treatment, with no virologic failures in patients with GT 4–6 infection

Table 2. Reasons for Non-Response, Pooled

Reasons for Non-Response, n (%)	8-week G/P N = 828	12-week G/P N = 1076
Breakthrough	2 (0.2)*	1 (<0.1)†
Relapse	7 (0.9)‡	3 (0.3)‡
Non-virologic failure		
Discontinuation	5 (0.6)	6 (0.6)
Missing data	7 (0.8)	6 (0.6)

*1 GT1, 1 GT3. †1 GT3. ‡2 GT2, 5 GT3. ¶3 GT3.

- Less than 1% of patients had virologic failure, and the relapse rate was similarly low (<1%) in both the 8 and 12 week treatment arms

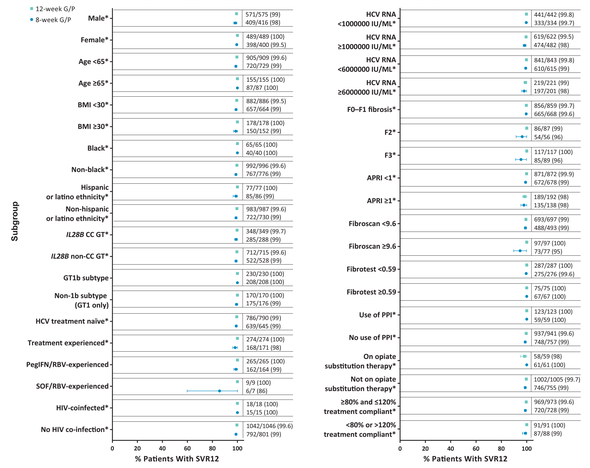
Table 3. SVR12 by Presence of Baseline Polymorphisms at a Key Subset of Positions*

Sequence	8-week G/P: Patients with Polymorphisms (ITT), n (%) N = 783†	8-week G/P: mITT SVR12 n/N (%; 95% CI) N = 772‡	12-week G/P: Patients with Polymorphisms (ITT), n (%) N = 1013†	12-week G/P: mITT SVR12 n/N (%; 95% CI) N = 1001‡
NS3 alone	6 (0.8)	6/6 (100; 100–100)	14 (1)	14/14 (100; 100–100)
NS5A alone	122 (16)	119/122 (98; 94.8–100)	184 (18)	182/183 (99; 98.4–100)
Both NS3 and NS5A	3 (0.4)	2/3 (67; 13.3–100)	6 (0.6)	5/6 (83; 53.5–100)
None	652 (83)	636/641 (99; 98.5–99.9)	809 (80)	796/798 (99.7; 99.4–100)

mITT, modified ITT population, which excludes patients with non-virologic failure.
*Baseline polymorphisms relative to subtype specific reference sequence detected at 15% next generation sequencing threshold in samples that had sequences available for both targets (N) at a key subset of amino acid positions:
NS3: 155, 156, 168.
NS5A: 28, 30, 31, 93, or H58D, E62A in GT1a; 31 or 93 in GT1b, 24, 28, 30, 92, 93 in GT2; 24, 28, 30, 31, 58, 93 in GT3; 24, 28, 30, 31, 93 in GT4; 24, 28, 30, 31, 58, 92, 93 in GT5-6.
†N adjusted for patients missing data.
‡N adjusted for patients missing data and excludes those with non-virologic failure.

- Pooled resistance analysis of HCV patients receiving G/P (300 mg/120 mg) in Phase 2 and 3 clinical trials is being presented Friday, April 21st, poster FRI-205

Figure 2. SVR12 by Subgroup, mITT Population, n/N (%)



2-sided 95% confidence intervals are shown.
*Indicates variable that was included in the logistic regression analysis (also included in logistic regression: presence of baseline polymorphisms at a key subset of positions, treatment duration, and HCV genotype).

LOGISTIC REGRESSION ANALYSIS

- A multivariate stepwise logistic regression analysis revealed that neither treatment duration (8-week or 12-week) nor genotype (1–6) was associated with achievement of SVR12
- Presence of baseline polymorphisms in key NS3 positions (155, 156, or 168) or in NS5A had no impact on SVR12
- Presence of baseline polymorphisms in key NS3 positions (155, 156, or 168) combined with NS5A polymorphisms had a statistically significant impact on SVR12 (odds ratio = 0.017 [95% CI 0.003–0.098], *P*-value <.0001)
  - Since all patients in this analysis were NS5A inhibitor/PI-naïve, less than 1% (9/1773) had polymorphisms in those key NS3 positions combined with NS5A polymorphisms
  - Most achieved SVR12 (78%; 7/9)
  - This observation may be relevant for patients with prior treatment experience with both NS5A and protease inhibitors

Table 4. Overview of Adverse Events and Laboratory Abnormalities

Event, n (%)	8-week G/P N = 828	12-week G/P N = 1076
Any AE	524 (63)	733 (68)
Serious AE	12 (1)	27 (3)
DAA-related serious AE	0	1 (<0.1)
AE leading to D/C	1 (0.1)	9 (0.8)
DAA-related AE leading to D/C	0	3 (0.3)
Laboratory Abnormalities, n/N (%)		
ALT, grade ≥3 (>5 × ULN)	0	1/1075 (<0.1)*
Total bilirubin, grade ≥3 (>3 × ULN)	4/827 (0.5)†	2/1075 (0.2)†

AE, adverse event; DAA, direct-acting antiviral; D/C, discontinuation; ALT, alanine aminotransferase.
*Grade 3 ALT elevation associated with grade 2 bilirubin and grade 3 AST and alkaline phosphatase elevations at Week 12 in the context of cholelithiasis (multiple gallstones); patient achieved SVR12.
†All patients had bilirubin elevations at baseline; the grade 3 elevations were primarily indirect, with no associated post-nadir ALT elevations by grade.

- G/P was well-tolerated regardless of treatment duration
- An in-depth safety analysis of G/P in patients without cirrhosis is being presented Friday, April 21st, poster FRI-238

CONCLUSIONS

- 8 and 12 weeks of G/P demonstrated high SVR12 rates (≥97%) in patients with HCV GT 1–6 infection without cirrhosis and was well-tolerated
  - G/P was highly efficacious regardless of baseline host and viral factors, including HCV RNA, fibrosis stage, prior treatment experience, HIV-1 co-infection and NS5A polymorphisms
  - The relapse rate was similarly low (<1%) for the 8- and 12-week treatment durations
- Eight weeks of the pangenotypic G/P regimen is the optimal treatment duration for the majority of chronic HCV-infected patients without cirrhosis, currently the most prevalent subpopulation

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abbvie

Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients Co-infected With Hepatitis C Virus and Human Immunodeficiency Virus-1: The EXPEDITION-2 Study

Juergen Rockstroh[1], Karine Lacombe[2], Rolando M Viani[3], Chloe Orkin[4], David Wyles[5], Annie Luetkemeyer[6], Ruth Soto-Malave[7], Robert Flisiak[8], Sanjay Bhagani[9], Kenneth E Sherman[10], Tatiana Shimonova[11], Peter Ruane[12], Joseph Sasadeusz[13], Jihad Slim[14], Zhenzhen Zhang[3], Teresa I Ng[3], Abhishek Gulati[3], Nancy S Shulman[3], Roger Trinh[3], Mark Sulkowski[15]

[1]Universitätsklinikum Bonn, Bonn, Germany; [2]Inserm UMR-S1136, Université Pierre et Marie Curie, Hôpital Saint-Antoine, APHP, Paris; [3]AbbVie Inc., North Chicago, Illinois, United States; [4]The Royal London Hospital, London, United Kingdom; [5]Denver Health Medical Center, Denver, Colorado, United States; [6]Zuckerberg San Francisco General, San Francisco, California, United States; [7]Innovative Care P.S.C., Bayamon, Puerto Rico; [8]Klinika Chorób Zakaźnych i Hepatologii UM w Białymstoku, Białystok, Poland; [9]Royal Free London Foundation Trust, London, United Kingdom; [10]University of Cincinnati, Cincinnati, Ohio, United States; [11]State Budgetary Healthcare Institution Infectious Clinical Hospital #2 of Moscow City Healthcare Department, Moscow, Russia; [12]Ruane Medical & Liver Health Institute, Los Angeles, California, United States; [13]Royal Melbourne Hospital, Parkville, Victoria, Australia; [14]St. Michael's Medical Center, Newark, New Jersey, United States; [15]Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

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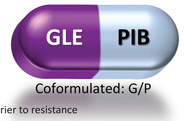
INTRODUCTION

- In phase 2 and 3 studies, patients with hepatitis C virus (HCV) genotype (GT) 1–6 infection without cirrhosis achieved sustained virologic response (HCV RNA <lower limit of quantification [LLOQ]) 12 weeks post-treatment (SVR12) rates of 93–100% following treatment with the all-oral, once-daily, interferon- and ribavirin-free, pangenotypic glecaprevir/pibrentasvir (G/P) regimen[1–4]
- 100% (33/33) of HCV GT1/HIV-1 co-infected patients without cirrhosis achieved SVR12 following 8- or 12- week treatment with G/P[1]

Next Generation Direct-acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor



Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:[5]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31, and 93)
- Synergistic antiviral activity

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

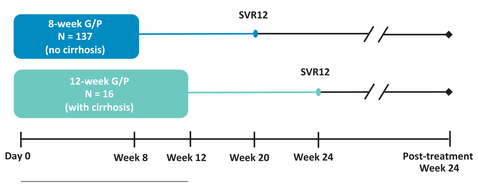
G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg. Glecaprevir was identified by AbbVie and Enanta.

OBJECTIVE

- EXPEDITION-2 is a phase 3, multicenter global study evaluating 8- or 12-week treatment with G/P in HCV/HIV-1 co-infected adults without or with compensated cirrhosis, respectively

MATERIALS AND METHODS

STUDY DESIGN



- Patients were enrolled in Australia, Belarus, France, Germany, Poland, Puerto Rico, Russian Federation, United Kingdom and United States

KEY INCLUSION CRITERIA

- ≥18 years of age and with BMI ≥18 kg/m^2
- Chronic HCV infection with GT 1, 2, 3, 4, 5, or 6 (HCV RNA ≥1000 IU/mL) and a positive test result for anti-HIV-1 antibody
- HCV treatment-naïve or treatment-experienced with interferon (IFN), pegIFN ± ribavirin (RBV), or sofosbuvir (SOF) + RBV ± pegIFN
  - All GT3 patients must be treatment-naïve

MATERIALS AND METHODS (CONTINUED)

- Antiretroviral therapy (ART) naïve with CD4+ count ≥500 cells/mm^3 or ≥29% *or*
- On a stable ART regimen for at least 8 weeks prior to screening, with CD4+ count ≥200 cells/mm^3 or ≥14%, and plasma HIV-1 RNA <LLOQ:

Allowed ART Anchor Agents (all patients)	Raltegravir (RAL) BID
	Dolutegravir (DTG) QD or BID
	Rilpivirine (RPV) QD
Allowed ART Regimens (patients without cirrhosis)	Elvitegravir/cobicistat (EVG/COBI) QD
	Darunavir (DRV) + ritonavir (r) QD
	DRV/COBI QD
	Lopinavir/r BID
Allowed N(t)RTI Backbone (all patients)	Tenofovir disoproxil fumarate (TDF)
	Tenofovir alafenamide (TAF)
	Abacavir (ABC)
	Emtricitabine (FTC)
	Lamivudine (3TC)

ART, antiretroviral therapy; BID, twice-daily; QD, once-daily; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor.

- Absence or presence of cirrhosis documented by liver biopsy or:

	Without Cirrhosis	With Cirrhosis
Transient elastography (Fibroscan) *or*	<12.5 kPa	≥12.5 kPa
Serum biomarkers (FibroTest) *and* APRI	≤0.48 + <1	≥0.75 + >2

For discordant cases, cirrhosis status was dictated by FibroScan results.

KEY EXCLUSION CRITERIA

- Co-infection with HBV (HBsAg positive) or more than 1 HCV genotype
- GT3 infection with prior HCV treatment experience
- Abnormal laboratory values including: ALT or AST >10 × ULN, albumin <3.0 g/dL, CrCl <50 mL/min, platelets <60 000 cells/mm^3 (with cirrhosis) or <90 000 cells/mm^3 (without cirrhosis)

ENDPOINTS AND ASSESSMENTS

Primary Efficacy Endpoint
The proportion of total patients with SVR12 in the ITT population
- Efficacy comparison to 96% SVR12 rate of historical standard of care (SOF + ledipasvir or grazoprevir/elbasvir) with the lower confidence bound of the 2-sided 95% confidence interval for SVR12 of >90%

Secondary Efficacy Endpoints
The proportion of patients in the ITT population with on-treatment virologic failure and post-treatment relapse

Safety Assessments
Adverse events (AEs) and laboratory abnormalities were assessed in the ITT population

Additional Assessments
Next generation sequencing was performed on samples from patients with virologic failure to identify baseline polymorphisms and treatment-emergent substitutions in NS3 and NS5A using a 15% detection threshold

ITT, intention to treat; includes all patients who received at least 1 dose of study drug.

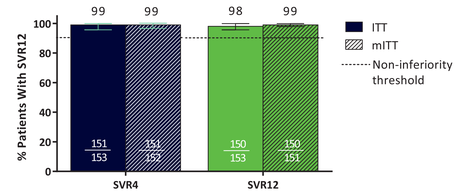
RESULTS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
Male, n (%)	113 (83)	15 (94)
Age, median (range), years	45 (23–74)	50 (35–62)
BMI, median (range), kg/m^2	25.0 (18.1–40.6)	27.6 (21.6–38.2)
Race, n (%)*		
White	106 (77)	15 (94)
Black	24 (18)	1 (6)
Genotype, n (%)†		
1	84 (61)	10 (63)
Subtype 1a	66 (48)	5 (31)
Subtype 1b	18 (13)	5 (31)
2‡	12 (9)	1 (6)
3‡	22 (16)	4 (25)
4‡	16 (12)	1 (6)
5‡	0	0
6‡	3 (2)	0
HCV RNA, median (range), $\log_{10}$ IU/mL§	6.2 (4.0–7.4)	6.1 (4.4–7.0)
HCV treatment-naïve, n (%)	111 (81)	14 (87)
HCV treatment-experienced, n (%)	26 (19)	2 (13)
IFN-based	23 (17)	2 (13)
SOF-based	3 (2)	0
Fibrosis Stage, n (%)		
F0–F1	120 (88)	0
F2	2 (1)	0
F3	15 (11)	0
F4	0	16 (100)
CD4+ cell count, median (range), cells/mm^3	588 (154–2103)	545 (222–1806)
No antiretroviral therapy, n (%)	9/137 (7)	0
Anchor ARV Agent, n (%)		
Raltegravir	39 (29)	6 (38)
Dolutegravir	62 (45)	5 (31)
Rilpivirine	27 (20)	5 (31)
Elvitegravir/cobi	1 (1)	0
Darunavir/r	0	0
Lopinavir/r	0	0
N(t)RTI backbone agent, n (%)		
Tenofovir disoproxil fumarate	74 (54)	13 (81)
Tenofovir alafenamide	6 (4)	0
Abacavir	49 (36)	3 (19)
Concomitant PPI use, n (%)	11 (8)	1 (6)
IDU within 12 months, n (%)	12 (9)	1 (6)
IDU >12 months prior to screening, n (%)	62 (45)	10 (63)
On opiate substitution therapy, n (%)	11 (8)	2 (13)

BMI, body mass index; IFN, interferon; SOF, sofosbuvir; ARV, antiretroviral; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; PPI, proton pump inhibitor; IDU, injection drug use.
*Race was self-reported.
†Genotype determined by the Versant HCV Genotype Inno-LiPA Assay v2.0.
‡The following subtypes were reported: GT2a/2c, GT2b; GT3a; GT4a/4c/4d; GT6c-l; GT6xa.
§HCV RNA quantified by Roche COBAS Amplirep/TaqMan v2.0.

Figure 1. Efficacy of G/P



	SVR4	SVR12
Breakthrough	1	1
Relapse	0	0
Missing Data	0	1*
Discontinued	1	1

mITT, modified ITT population, which excludes patients with non-virologic failure.
*One patient achieved SVR4 but was lost to follow-up due to homelessness and did not return for PTW12 visit

- The SVR12 rate was 100% (136/136) in patients without cirrhosis treated for 8 weeks
- The SVR12 rate in the mITT population of patients with cirrhosis treated for 12 weeks was 93% (14/15)
  - One patient with GT3a infection and cirrhosis had on-treatment virologic failure at treatment Week 8:
    - NS3: no polymorphisms at baseline; Y56H at failure
    - NS5A: A30V at baseline; S24F and M28K (not A30V) at failure

Table 3. Adverse Events and Laboratory Abnormalities

Event, n (%)	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
Any AE	86 (63)	8 (50)
Serious AE	3 (2)*	1 (6)†
DAA-related serious AE	0	0
AE leading to discontinuation	0	1 (6)†
AEs occurring in ≥5% of overall patients		
Fatigue	18 (13)	0
Nausea	12 (9)	1 (6)
Headache	12 (9)	0
Nasopharyngitis	12 (9)	0
Laboratory Abnormalities‡		
ALT, grade ≥3 (>5 × ULN)	0	0
AST, grade ≥3 (>5 × ULN)	0	0
Total bilirubin, grade ≥3 (>3 × ULN)	1 (0.7)	0

AE, adverse event; DAA, direct-acting antiviral; ALT, alanine aminotransferase; AST, aspartate aminotransferase. *Upper GI hemorrhage, obliterating arteriopathy, and urolithiasis in 1 patient each, all unrelated to G/P. †One patient with cerebrovascular accident and cerebral hemorrhage, both unrelated to G/P. ‡Grade must be more extreme than baseline.

- One GT2-infected patient with cirrhosis experienced serious AEs unrelated to G/P of cerebrovascular accident and cerebral hemorrhage on Day 23 that led to discontinuation of study drug; the patient did not achieve SVR12
- One patient had a Grade 3 total bilirubin elevation on Day 10 that continued through Day 31; levels normalized by Day 59 without treatment interruption
- No patients met pre-specified criteria for failure to maintain HIV RNA suppression during the Treatment Period

CONCLUSIONS

- An overall SVR12 rate of 98% with no relapses was achieved in HCV/HIV-1 co-infected patients without or with cirrhosis following 8 or 12 weeks of G/P, respectively
  - Achievement of SVR12 was not impacted by high baseline viral load, cirrhosis status, or any other baseline factor
  - Non-inferiority to historical standard of care was achieved
- G/P was well tolerated and exhibited a similar safety profile in HCV/HIV-1 co-infected patients with or without cirrhosis; serious adverse events, clinically significant laboratory abnormalities, and treatment discontinuations were rare
- In HCV/HIV-1 co-infected patients without cirrhosis, 8-week G/P yielded a 99.3% SVR12 rate, with no virologic failures
  - These results suggest that the G/P regimen could be the first 8-week pangenotypic treatment option for HCV/HIV-1 co-infected patients without cirrhosis

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