Glecaprevir and Pibrentasvir for 12 Weeks for HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment

Fred Poordad[1], Franco Felizarta[2], Armen Asatryan[3], Mark S Sulkowski[4], Robert W Reindollar[5], Charles S Landis[6], Stuart C Gordon[7], Steven L Flamm[8], Michael W Fried[9], David E Bernstein[10], Chih-Wei Lin[3], Ran Liu[3], Sandra S Lovell[3], Teresa I Ng[3], Jens Kort[3], Federico J Mensa[3]

[1]Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas, USA; [2]Private Practice, Bakersfield, California, USA; [3]AbbVie Inc., North Chicago, Illinois, USA; [4]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [5]Piedmont Healthcare/Carolinas Center for Liver Disease, Statesville, North Carolina, USA; [6]Division of Gastroenterology, University of Washington, Seattle, Washington, USA; [7]Henry Ford Health System, Detroit, Michigan, USA; [8]Northwestern Feinberg School of Medicine, Chicago, Illinois, USA; [9]University of North Carolina, Chapel Hill, North Carolina, United States; [10]North Shore University Hospital, Manhasset, New York, United States

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AUTHOR E-MAILS
Fred Poordad: poordad@txliver.com
Franco Felizarta: ffelizarta@felizartamd.com
Mark S Sulkowski: msulkowski@jhmi.edu
Robert W Reindollar: robert.reindollar@piedmonthealthcare.com
Charles S Landis: clandis@medicine.washington.edu
Stuart C Gordon: sgordon3@hfhs.org
Steven L Flamm: s-flamm@northwestern.edu
Michael W Fried: michael_fried@med.unc.edu
David E Bernstein: dbernste@nshs.edu
Armen Asatryan: armen.asatryan@abbvie.com
Chih-Wei Lin: chih-wei.lin@abbvie.com
Ran Liu: ran.liu@abbvie.com
Sandra S Lovell: sandra.lovell@abbvie.com
Teresa I Ng: teresa.ng@abbvie.com
Jens Kort: jens.kort@abbvie.com
Federico J Mensa: federico.mensa@abbvie.com

CORRESPONDING AUTHOR:

Fred Poordad, MD
Texas Liver Institute
University of Texas Health Science Center
607 Camden St., Suite 101, San Antonio, TX 78215
Phone: +1 210.253.3426
E-mail: poordad@txliver.com

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ABBREVIATIONS

HCV, hepatitis C virus; GT, genotype; HCC, hepatocellular carcinoma; SVR, sustained virologic response; DAA, direct-acting antiviral; GLE, glecaprevir; NS, non-structural; EC_{50}, half-maximal effective concentration; PIB, pibrentasvir; RBV, ribavirin; SVR12, sustained virologic response at post-treatment week 12; ITT, intent-to-treat; mITT, modified intent-to-treat; CI, confidence interval; AE, adverse event; BMI, body-mass index.

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ABSTRACT

Although direct-acting antiviral (DAA) therapies for chronic hepatitis C virus (HCV) infection have demonstrated high rates of sustained virologic response, virologic failure may still occur, potentially leading to the emergence of viral resistance, which can decrease the effectiveness of subsequent treatment. Treatment options for patients who failed previous DAA-containing regimens, particularly those with NS5A inhibitors, are limited, and remain an area of unmet medical need. This phase 2, open-label study (MAGELLAN-1) evaluated the efficacy and safety of glecaprevir (GLE) + pibrentasvir (PIB) ± ribavirin (RBV) in HCV genotype 1-infected patients with prior virologic failure to HCV DAA-containing therapy. A total of 50 non-cirrhotic patients were randomized to three arms: 200 mg GLE + 80 mg PIB (Arm A), 300 mg GLE + 120 mg PIB with 800 mg once-daily RBV (Arm B), or 300 mg GLE + 120 mg PIB without RBV (Arm C). By intent-to-treat analysis, sustained virologic response at post-treatment week 12 (SVR12) was achieved in 100% (6/6, 95% CI 61 – 100), 95% (21/22, 95% CI 78 – 99), and 86% (19/22, 95% CI 67 – 95) of patients in Arms A, B, and C, respectively. Virologic failure occurred in no patients in Arm A, and 1 patient each in Arms B and C (two patients lost to follow-up in Arm C). The majority of adverse events were mild in severity; no serious adverse events related to study drug and no relevant laboratory abnormalities in alanine aminotransferase, total bilirubin, or hemoglobin, were observed. *Conclusion:* The combination of GLE and PIB was highly efficacious and well-tolerated in patients with HCV GT1 infection and prior failure to DAA-containing therapy; RBV coadministration did not improve efficacy.

Chronic infection with hepatitis C virus (HCV) genotype (GT) 1 is the most common among HCV GTs globally, accounting for approximately 46% of an estimated 185 million infections worldwide.(1, 2) Although the treatment landscape for HCV has rapidly evolved with highly effective and safe HCV treatments for patients with GT1 infection,(3, 4) as direct-acting antiviral (DAA) agents are used extensively, the number of patients with virologic failure to DAA regimens continues to grow.(5) Virologic failure to DAAs often results from baseline resistance-associated polymorphisms or resistance-associated substitutions that emerge during therapy.(4-8) Variants within the HCV non-structural (NS) protein 5A region substantially increase the risk of virologic failure for many DAA-containing regimens,(9, 10) and there are currently no treatments specifically indicated for either NS5A or NS5B inhibitor-experienced patients.

DAA treatment failure is a growing concern given the long-term persistence of NS5A resistance-associated variants(11, 12) and sub-optimal treatment response rates in patients with resistance-associated baseline polymorphisms or treatment-emergent substitutions.(9, 13, 14) Retreatment strategies using 24 weeks of ledipasvir/sofosbuvir have demonstrated a 60% sustained virologic response at post-treatment week 12 (SVR12) rate among patients with baseline NS5A polymorphisms, and 33% in patients with NS5A Y93H/N polymorphisms.(14) Similarly, the combination regimen of elbasvir and grazoprevir has reduced efficacy (70%) in GT1a-infected patients with baseline NS5A resistance-associated polymorphisms at elbasvir-specific positions (eg, M28, Q30, L31, Y93).(9, 15) In addition, the combination of sofosbuvir/velpatasvir has reduced potency to HCV GT1a NS5A variants at position Y93, including the common Y93H variant, which confers a 609-fold increase in EC_{50} to velpatasvir.(16) Therefore, treatments with a high barrier to viral resistance that maintain potency against viral variants, particularly for patients previously treated with HCV direct-acting antivirals (DAAs), are needed.

Current recommended retreatment strategies for patients with prior failure to NS3/4A protease inhibitor (PI)-containing DAA regimens include the NS5B nucleotide analog inhibitor sofosbuvir plus an NS5A inhibitor (ledipasvir, velpatasvir, or daclatasvir) for 12 weeks, or the combination of the NS3/4A PI grazoprevir plus the NS5A inhibitor elbasvir with RBV for 16 weeks.(16) Patients with baseline NS5A variants, either pre-existing or the result of treatment-emergence from prior exposure to an NS5A inhibitor, have proven more difficult to cure with approved DAA regimens; thus, longer treatment durations, addition of ribavirin (RBV), and the addition of a third or fourth DAA have been examined to maximize SVR12 rates.(14, 17-20)

Glecaprevir ([GLE]; formerly ABT-493; identified by AbbVie and Enanta) is an HCV NS3/4A PI that has potent pangenotypic antiviral activity. GLE does not inhibit human proteases, exhibits *in vitro* half-maximal effective concentration (EC_{50}) values ≤5 nanomolar across all major HCV GTs, and demonstrates <5-fold loss of activity against common GT1 variants at key resistance-associated positions of R155 and D168 to currently available NS3/4A PIs.(6, 21) Pibrentasvir ([PIB]; formerly ABT-530) is an HCV NS5A inhibitor with EC_{50} values ≤5 picomolar across all major HCV GTs; it maintains high potency against common NS5A resistance-associated variants, including GT1a Y93H (6.7-fold increase in EC_{50}; (22)), which has been associated with reduced susceptibility to other NS5A inhibitors, such as ledipasvir (3294-fold increase in EC_{50}), daclatasvir (1600-fold increase in EC_{50}), and velpatasvir (609-fold increase in EC_{50}).(23)

In Part 1 of the MAGELLAN-1 study, we evaluated the efficacy and safety of GLE + PIB for 12 weeks, with or without RBV, in patients with prior treatment failure to HCV regimens containing an NS5A inhibitor and/or NS3/4A PI with or without NS5B inhibitors. The impacts of baseline polymorphisms and RBV coadministration on SVR12 rates were also assessed.

METHODS

Study overview and regimens. The MAGELLAN-1 (NCT02446717) study was a phase 2, randomized, open-label, multicenter study that assessed the efficacy and safety of GLE + PIB in HCV GT1-infected patients with prior DAA treatment experience. Patients were initially randomized 1:1:1 into three arms (A, B, and C; **Figure 1**). Patients enrolled in Arm A were treated for 12 weeks with GLE (200 mg once-daily) + PIB (80 mg once-daily); however, a protocol amendment was implemented to halt enrollment (with 6 patients enrolled) to optimize doses of GLE and PIB for further development.(24) Subsequent to this protocol amendment, remaining enrolled patients were randomized 1:1 into Arms B or C for treatment with GLE (300 mg once-daily) + PIB (120 mg once-daily) with RBV (Arm B; 800 mg once-daily) or without RBV (Arm C) for 12 weeks. Patients were stratified by HCV subtype (1b or non-1b) and previous DAA class (NS5A inhibitor-experienced, NS3/4A PI-experienced but NS5A inhibitor-naïve, or other). For purpose of analysis, previous HCV treatment experience was deemed cumulative (ie, a patient exposed to NS3/4A PI and subsequently to NS5A inhibitor was considered NS5A and NS3/4A PI experienced). All patients signed informed consent, and the study was conducted in accordance with its protocol (designed and sponsored by AbbVie), the Good Clinical Practice Guidelines, and the ethics set forth by the Declaration of Helsinki, with independent ethics committee or institutional review board approval for all study sites.

Patient population, criteria and study design. Patients were non-cirrhotic adults, 18 – 70 years, with chronic HCV GT1 infection and treatment-experienced with a prior DAA-containing regimen. Patients must have completed past DAA treatment at least 1 month prior to screening visit, with the outcome of prior HCV treatment being either on-treatment virologic failure or post-treatment relapse. Plasma samples for HCV genotyping were collected at screening and assessed with the Versant® HCV Genotype Inno LiPA Assay, version 2.0 or higher. The absence of cirrhosis (METAVIR score ≤3, Ishak score ≤4) was

determined by one of the following: liver biopsy within 24 months prior to (or during) screening, transient elastography (Fibroscan) result of <12.5 kPa within 6 months prior to (or during) screening, or a screening FibroTest score of ≤0.48 with an aspartate aminotransferase to platelet ratio index (APRI) <1. Patients co-infected with hepatitis B virus, human immunodeficiency virus, or more than one HCV GT at screening were excluded. Key eligibility criteria and definitions of prior treatment responses are provided in the **Supporting Information**.

Efficacy, virologic, and safety assessments. Plasma samples for HCV RNA measurements were collected at screening, treatment days 1 and 3, weeks 1, 2, 4, 6, 8, 10, and 12 (or early discontinuation), and post-treatment weeks 2, 4, 8, 12, and 24 (or early discontinuation) and assessed via COBAS® AmpliPrep/ COBAS® TaqMan HCV Quantitative Test, v2.0. The primary efficacy endpoint was the percentage of patients who achieved SVR12 (HCV RNA <15 IU/mL) in the intent-to-treat (ITT) population, defined as all randomized patients that received at least 1 dose of study drug. A modified ITT (mITT) analysis was also conducted excluding all non-virologic failures (ie, patients lost to follow-up or early discontinuation). Two-sided confidence intervals (CI) were determined at a significance level of 0.05 using the Wilson score method for binomial proportions. Statistical summaries were performed using SAS® software, version 9.3.

Viral sequences from the baseline plasma sample for each patient were analyzed by next generation sequencing (Illumina MiSeq®) to identify NS3 or NS5A polymorphisms at detection thresholds of 2% and 15%. For patients who had virologic failure within the study, the first samples with HCV RNA ≥1,000 IU/mL collected at or after the time of virologic failure were also analyzed by next generation sequencing at the same thresholds. Sequences were compared to the corresponding baseline and reference sequences to identify amino acid substitutions that could be associated with resistance to components of the therapy. For HCV resistance analysis, a polymorphism was defined as a baseline

amino acid difference relative to the appropriate subtype-specific reference sequence; despite DAA experienced patients having had prior HCV antiviral therapy, a patient's baseline amino acid variants in this study were considered polymorphisms, since the patient's HCV amino acid sequences prior to all previous therapies are unknown. A substitution was defined as a treatment-emergent amino acid sequence different from the patient's baseline viral sequence. An amino acid variant was considered an amino acid change due to a baseline polymorphism or treatment-emergent substitution. Detailed information on the collection of plasma samples, HCV RNA measurement, virologic-failure criteria, and amino acid variants included in resistance analysis are available in the **Supporting Information**.

Safety assessments were based on the safety population (same as ITT population). Safety and tolerability assessments were conducted at screening and throughout the study, and included monitoring vital signs, physical examinations, adverse events (AEs) and clinical chemistry and hematology tests. Adverse events were recorded up to 30 days post treatment.

RESULTS

A total of 91 patients with HCV GT1 were screened within the United States; 50 were randomized and received at least one dose of study drug. Patients not randomized due to abnormal laboratory values had elevated alanine aminotransferase, aspartate aminotransferase, direct bilirubin, or low platelet count. Among randomized patients, 82% were male, 34% reported black race, and 84% had GT1a infection (**Table 1**). The majority of patients (66%) had prior treatment failure to regimens containing multiple DAAs; 50% had been previously treated with an NS5A inhibitor, 84% with an NS3/4A PI, and 54% with an NS5B polymerase inhibitor. Of 27 patients with NS5B polymerase inhibitor exposure, 56% had prior treatment with a nucleotide analog inhibitor, 33% with non-nucleoside inhibitors, and 11% had exposure to both. The most common prior DAA-containing regimens were boceprevir plus pegIFN/RBV (n = 10), telaprevir plus pegIFN/RBV (n = 8), ledipasvir/sofosbuvir (n = 8), and simeprevir plus sofosbuvir with or without RBV (n = 8) (**Supporting Table 1**). Overall, 21/50 patients had prior failure to NS3/4A PI + pegIFN/RBV; 5 of those 21 patients were also experienced with NS5A- or NS5B-inhibitors within the IFN-containing regimen or within other regimens. The type of prior DAA-experience (NS3/4A PI only or NS5A inhibitor only or both) was well balanced across treatment groups (**Table 1**). Next generation sequencing identified baseline polymorphisms in NS3 and/or NS5A in 86% (43/50) patients at a detection threshold of 2%, and in 80% (40/50) patients at a threshold of 15%. At a 15% detection threshold, the majority of patients had at least one baseline polymorphism across all treatment groups; although no patients in Arm A had polymorphisms in both NS3 and NS5A targets, 27%(6/22) and 41% (9/22) had polymorphisms in both targets in Arms B and C, respectively (**Table 1**). In addition, baseline NS5A polymorphisms were detected in 50% (3/6), 50% (11/22), and 55% (12/22) of patients in Arms A, B and C, respectively, at a detection threshold of 15%. Although a detection threshold of 15% is commonly accepted as clinically relevant, lower thresholds of detection give greater

insight into amino acid changes that may emerge in the majority of the population after prior therapy with DAA-containing regimens. At a more sensitive 2% detection threshold, the most common polymorphisms in NS3 were at amino acid positions Q80 (n = 23), R155 (n = 4), D168 (n = 4), and I/V170 (n = 4) and those for NS5A were at positions Q30 (n = 14), Y93 (n = 8), L31 (n = 7), M28 (n = 6), Q54 (n = 6), H/P58 (n = 5); baseline amino acid polymorphisms detected at a threshold of 2% are shown in **Supporting Table 2** and the prevalence of specific polymorphisms detected at both 2% and 15% is summarized in **Supporting Table 3**.

Overall, by intent-to-treat (ITT) analysis, SVR12 was achieved in 92% (46/50, 95% CI 81 – 97) of patients treated with GLE + PIB with or without RBV for 12 weeks. In the halted Arm A, in which patients received the lower dose of 200 mg GLE and 80 mg PIB, 100% (6/6, 95% CI 61 – 100) of patients achieved SVR12. In Arm B (300 mg GLE + 120 mg PIB + 800 mg RBV for 12 weeks) SVR12 was achieved in 95% (21/22, 95% CI 78 – 99) of patients, and among patients in Arm C (300 mg GLE + 120 mg PIB for 12 weeks), 86% (19/22, 95% CI 67 – 95) of patients achieved SVR12 (**Figure 2**). The rates of virologic failure were identical (1/22, 5%) with or without administration of RBV (Arm B vs Arm C). The two patients in Arm C that did not achieve SVR12 were lost to follow-up; however, both patients had undetectable HCV RNA at post-treatment week 8. By mITT analysis, excluding patients that failed to achieve SVR12 due to non-virologic reasons, SVR12 rates were 100%, 95%, and 95% for Arms A, B, and C, respectively.

Two confirmed virologic failures were observed; both patients were compliant and had on-treatment drug levels of GLE and PIB that were consistent with those observed in other patients (**Table 3**). The patient in Arm C (300 mg GLE + 120 mg PIB), had on-treatment HCV breakthrough at week 8; using a 2% detection threshold, this patient had baseline polymorphisms in both NS3 (Y56H and D168A/T) and NS5A (M28V, Q30R, and H58C). At the time of virologic failure, this patient had treatment-emergent substitutions of V36M in NS3, and M28G in NS5A. Of note, although GLE and PIB levels in this patient

were within expected therapeutic ranges, the patient had Crohn's disease, was receiving immunosuppressive therapy, and had a prior ileocolectomy. The other patient who had virologic failure was a post-treatment week 4 relapse in Arm B (300 mg GLE + 120 mg PIB + 800 mg RBV) and had baseline NS5A polymorphisms L31M and H58D, with no polymorphisms in NS3. At the time of relapse, this patient had treatment-emergent substitutions of A156V in NS3 and Q30R in NS5A. Overall, in patients with baseline polymorphisms in NS3 only, NS5A only, or both NS3 and NS5A at a 15% detection threshold, SVR12 rates were 100% (14/14), 91% (10/11), and 93% (14/15), respectively; SVR12 was achieved by 100% (10/10) of patients with no baseline polymorphisms in NS3 or NS5A.

Adverse events were mostly mild in severity and reported in 84% of patients. Adverse events occurring in ≥10% of patients were headache, fatigue, nausea and insomnia (**Table 2**); such events were more common in the RBV-containing arm. Two treatment-emergent serious adverse events were reported, neither of which were deemed related to study drug by the investigator (fractured femur and breast cancer). No patient prematurely discontinued treatment due to adverse events. Clinical chemistry and hematology revealed no significant on-treatment abnormalities in alanine aminotransferase ([ALT]; >3 × ULN), aspartate aminotransferase ([AST]; >3 × ULN), hemoglobin (<10 g/dL), or total bilirubin (>3 × ULN).

DISCUSSION

The once-daily regimen of glecaprevir and pibrentasvir was well-tolerated with no serious adverse events related to study drug, no discontinuations due to adverse events, and no relevant laboratory abnormalities. It also resulted in high rates of SVR with or without coadministration of RBV in patients with HCV GT1 infection and prior DAA therapy experience. Overall, the DAA-experienced population in the MAGELLAN-1 study had broad representation of baseline NS3 and NS5A polymorphisms, including polymorphisms at key NS5A positions M28, Q30, L31, H58 and Y93 that confer resistance to earlier generation NS5A inhibitors. Additionally, all eight patients previously treated with ledipasvir/sofosbuvir achieved SVR12 despite the presence of the NS5A resistance-associated Y93H/N polymorphism in five patients and multiple NS5A polymorphisms in four patients. This confirms *in vitro* data suggesting that variants at the Y93 position are susceptible to pibrentasvir,(22) and suggests glecaprevir plus pibrentasvir is an effective treatment for those with a baseline polymorphism or treatment-emergent substitution at this position. Furthermore, 14 of 15 (93%) patients who failed a prior dual (NS3/4A PI plus NS5A inhibitor) or triple (NS3/4A PI plus NS5A inhibitor plus NS5B polymerase inhibitor) DAA regimen achieved SVR12.

The addition of RBV to the GLE + PIB regimen had no apparent impact on response, as the rates of virologic failure were identical in Arms B and Arm C by mITT analysis. All 5 patients who modified RBV dose achieved SVR12, similar to findings with other DAA regimens.(25-27) However, this study did not have a large enough sample size for sufficient statistical power to confirm the impact of RBV on SVR. The patient with virologic relapse in the RBV-containing arm had prior treatment with two different therapeutic regimens: daclatasvir alone, and telaprevir plus pegylated interferon with RBV. This patient had L31M and H58D in NS5A at baseline; at the time of virologic failure at post-treatment week 4, a Q30R substitution emerged in this patient in addition to L31M and H58D from baseline. The one other

patient in this study with a baseline H58D mutation in NS5A also had baseline M28V and Q30R polymorphisms (instead of L31M) in the same target, with an additional Q80K polymorphism in NS3, and this patient achieved SVR12. The patient with virologic breakthrough was on immunosuppressive therapy for Crohn's disease and had prior ileocolectomy; it is unclear whether this contributed to virologic failure. This patient had three NS5A baseline polymorphisms (M28V, Q30R, and H58C), and NS3 baseline polymorphisms at amino acid positions Y56 and D168 that were maintained until virologic failure. While three other patients with baseline D168 polymorphisms achieved SVR12, this was the only patient with a baseline Y56 polymorphism. The NS3 V36M and NS5A M28G substitutions emerged in this patient after virologic failure. Both patients that experienced virologic failure were reported as compliant and had drug exposures similar to other patients.

No clinically significant laboratory abnormalities were reported in hemoglobin levels, including in the RBV-containing arm. Furthermore, no clinically significant chemistry values were observed, including on-treatment elevations in total bilirubin or ALT >3 times the upper limit of normal after ALT normalization or nadir. Although no serious adverse events related to study drug were reported in either arm, the addition of RBV did not reduce the rate of virologic failure, but did increase the rate of adverse events. One potential limitation of this study was that RBV coadministration was 800 mg daily, regardless of patient weight, ie, below the conventional 1000 or 1200 mg weight-based RBV dosing. Because of this, it is unclear whether weight-based RBV coadministration could have increased the efficacy in Arm B. By corollary, it is also likely that a conventional weight-based RBV dose would have resulted in a further increased rate of adverse events for these patients when compared with that seen with the lower dose of RBV in Arm B, as increasing side effects with higher RBV dose is well-documented.(28) However, regardless of comparison between treatment arms, the low rate of virologic failure in the RBV-sparing arm suggests that the response rate is already near maximal and the addition of RBV may not impact

this. The patient population enrolled here is considered inherently difficult to cure, owing to increased prevalence of baseline resistance-associated polymorphisms likely stemming from prior DAA-failure.(29-33) As such, additional study is required in this diverse patient population to further confirm efficacy of the regimen in GT1 patients with prior failure to DAA therapy, including patients with prior exposure to DAA-containing therapies and concomitant cirrhosis, which were excluded here.

In summary, the combination of glecaprevir and pibrentasvir showed potent antiviral activity, regardless of the presence of one or more baseline resistance-associated polymorphisms, and irrespective of previous DAA-containing treatment regimens, resulting in high SVR12 rates in non-cirrhotic patients with HCV GT1 infection. This suggests the combination of GLE and PIB is highly effective in this population which, currently, has limited treatment options. Based on these findings, larger and more diverse patient groups are being evaluated in phase 3 studies to confirm the safety and efficacy of the RBV-free co-formulation of GLE/PIB (300 mg/120 mg) in all six major HCV GTs, including patients with prior DAA-experience and compensated cirrhosis.

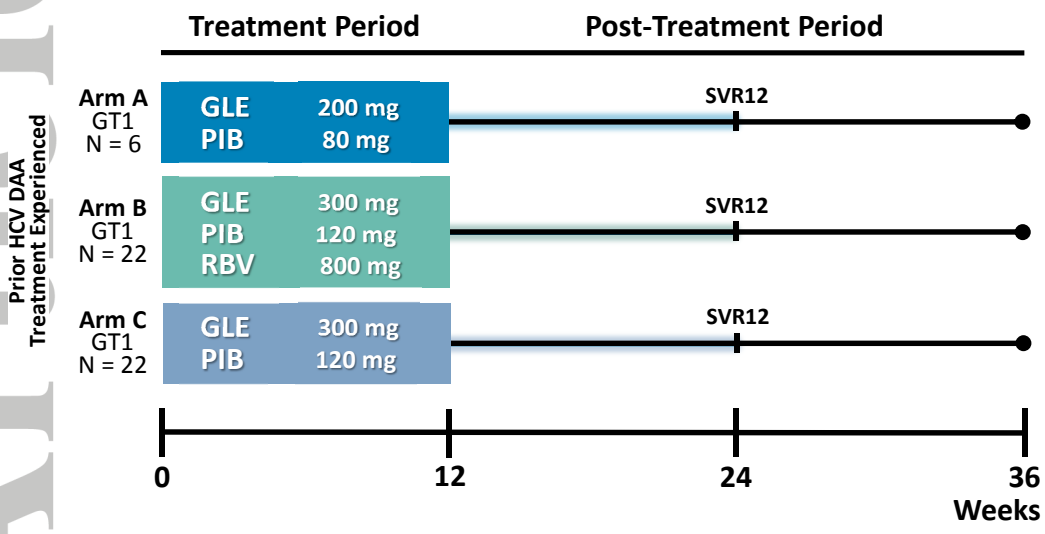

Figure 1. MAGELLAN-1, Part 1, Clinical Trial Design Schematic. In part 1 of the MAGELLAN-1 study, patients were randomized 1:1:1 into three treatment arms, stratified by HCV subtype (1b or non-1b) and previous DAA classification (NS5A inhibitor-experienced, NS3/4A PI-experienced but NS5A inhibitor-naïve, or other). Enrollment in Arm A was halted via protocol amendment after 6 patients were randomized to that arm (see methods). In total, 50 patients were enrolled to receive GLE + PIB ± RBV, once-daily, for 12 weeks. The primary endpoint was the proportion of patients with SVR12. DAA, direct-acting antiviral; GLE, glecaprevir; GT, genotype; PIB, pibrentasvir; RBV, ribavirin; SVR12, sustained virologic response at post treatment week 12.

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Arm A GLE+PIB (200 mg + 80 mg) n=6	Arm B GLE+PIB (300 mg + 120 mg) + RBV (800 mg) n=22	Arm C GLE+PIB (300 mg + 120 mg) n=22
Male, n (%)	3 (50)	20 (91)	18 (82)
Black race[a], n (%)	2 (33)	5 (23)	10 (45)
Age, median years (range)	59 (39 – 61)	56 (39 – 64)	59 (46 – 70)
HCV subtype, n (%)			
1a	4 (67)	20 (91)	18 (82)
1b	2 (33)	2 (9)	4 (18)
Treatment experience by DAA class, n (%)			
NS5A-experienced/PI-naïve	0	4 (18)	4 (18)
NS5A-naïve/PI-experienced	3 (50)	11 (50)	11 (50)
NS5A-experienced/PI-experienced	3 (50)	7 (32)	7 (32)
BMI, median kg/m^2 (range)	27 (25 – 37)	28 (22 – 34)	28 (19 – 37)
IL28B non-CC genotype, n (%)	4 (67)	16 (73)	19 (86)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.1 (5.6 – 6.7)	6.7 (5.0 – 7.3)	6.6 (5.5 – 7.2)
HCV RNA ≥6,000,000 IU/mL, n (%)	0	11 (50)	10 (46)
Baseline fibrosis stage, n (%)			
F0-F1	4 (67)	17 (77)	11 (50)
F2	1 (17)	0	6 (27)
F3	1 (17)	5 (23)	5 (23)
Baseline polymorphisms, n (%)			
Any polymorphism (NS3 or NS5A)	5 (83)	18 (82)	17 (77)
NS3 only[b]	2 (33)	7 (32)	5 (23)
NS5A only[b]	3 (50)	5 (23)	3 (14)
Both NS3 and NS5A	0	6 (27)	9 (41)

BMI, body-mass index; DAA, direct-acting antiviral; HCV, hepatitis C virus; *IL28B*, interleukin 28B; NS, non-structural; SD, standard deviation; GLE, glecaprevir; PIB, pibrentasvir

Polymorphisms were detected at a 15% detection threshold with next generation sequencing

[a] Race was self-reported

[b] 'Only' indicates total number of patients with baseline polymorphisms within the indicated target, and none in the other target

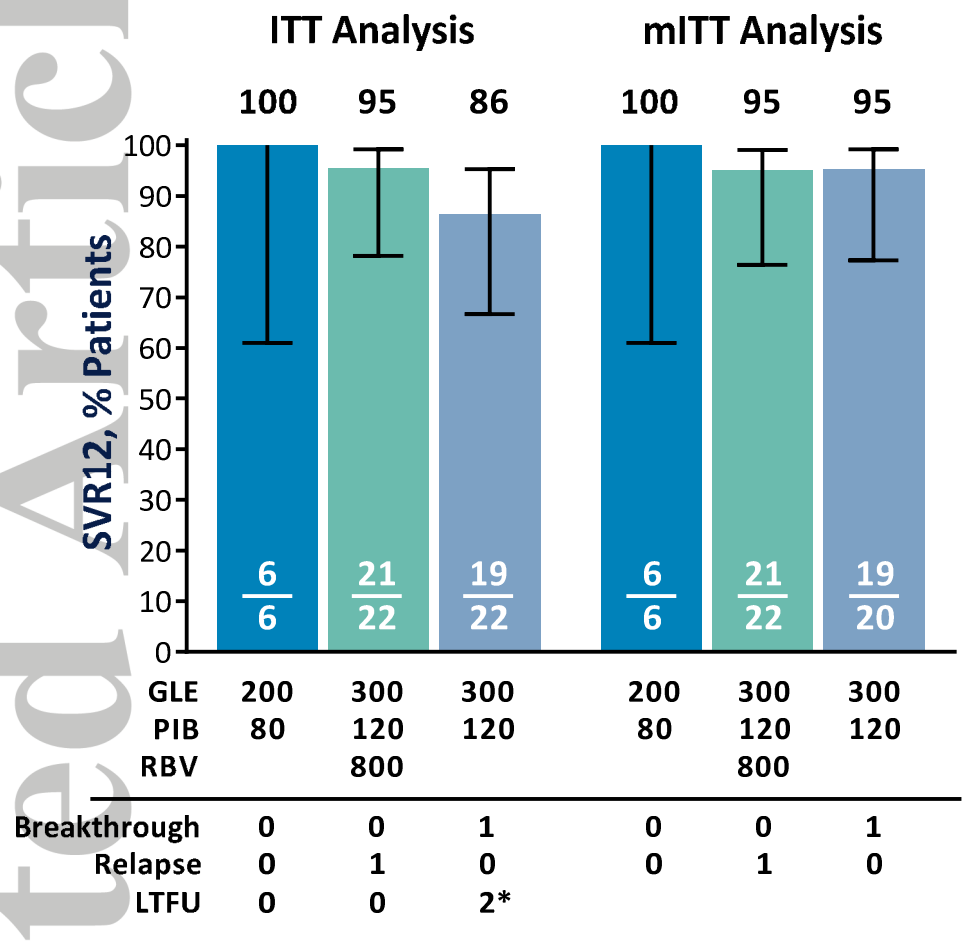

Figure 2. Sustained Virologic Response in the ITT and mITT Populations. Individual SVR12 rates for Arm A (blue), Arm B (green) and Arm C (grey-blue) are shown for the ITT population and mITT. The ITT population was all patients that received at least one dose of study drug (n = 50), while the mITT population excluded all patients that did not achieve SVR due to reasons other than virologic failure. Whiskers represent the 95% confidence interval using the Wilson score method. *Both patients lost to follow-up had non-detectable HCV RNA at post-treatment week 8. ITT, intent-to-treat; mITT, modified intent-to-treat; SVR12, sustained virologic response at post-treatment week 12; RBV, ribavirin; LTFU, lost-to-follow-up; GLE, glecaprevir; PIB, pibrentasvir

Table 2. Adverse Events and Laboratory Abnormalities

Event, n (%)	GLE + PIB (200 mg + 80 mg) n=6	GLE + PIB (300 mg + 80 mg) + RBV (800 mg) n=22	GLE + PIB (300 mg + 120 mg) n=22
Adverse Events			
Any AE	5 (83.3)	19 (86.4)	18 (81.8)
Serious AE	1 (16.7)[a]	1 (4.5)[b]	0
Discontinuation due to AE	0	0	0
Common AEs[c]			
Headache	1 (16.7)	5 (22.7)	8 (36.4)
Fatigue	1 (16.7)	8 (36.4)	4 (18.2)
Nausea	1 (16.7)	6 (27.3)	3 (13.6)
Insomnia	0	6 (27.3)	0

RBV, ribavirin; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; Serious AEs were defined as events resulting in hospitalization or prolongation of hospitalization, persistent or clinically-significant disability or incapacity, or death or that was life-threatening or required medical or surgical intervention to prevent a serious outcome

[a] Breast cancer

[b] Fractured femur

[c] Occuring in >10% of all patients

Table 3. Characteristics of Patients with Virologic Breakthrough or Relapse

Sub-genotype	Prior Treatment	12 week Treatment	Reason for non-response	Timepoint sequenced	NS3 Variants[a]	NS5A Variants[a]
1a	DCV; TVR + PR	GLE + PIB + RBV 300 mg + 120 mg + 800 mg	Relapse[b]	Baseline	None	L31M, H58D (26%)
				PTW4	A156V (91%)	Q30R, L31M, H58D
1a	OBV + PTV/RTV + DSV +RBV	GLE + PIB 300 mg + 120 mg	Breakthrough	Baseline	Y56H (5%), D168A/T (94%/3%)	M28V (3%), Q30R (98%), H58C (99%)
				Week 8	V36M (6%), Y56H, D168A	M28G, Q30R (99%), H58C

[a]Variants due to baseline polymorphisms or treatment-emergent substitutions

[b]This patient had Crohn's disease, was on immunosuppressant therapy, and had prior ileocolectomy

Variants were detected at a 2% detection threshold with next generation sequencing. Only variants with prevalence ≥2% are listed; variants with prevalence >99% within a patient's viral population do not have the prevalence (%) listed

DCV, daclatasvir; DSV, dasabuvir; GLE, glecaprevir; OBV, ombitasvir; PIB, pibrentasvir; PR, pegylated interferon plus ribavirin; PTV/RTV, ritonavir-boosted paritaprevir; PTW, post-treatment week; RBV, ribavirin; TVR, telaprevir

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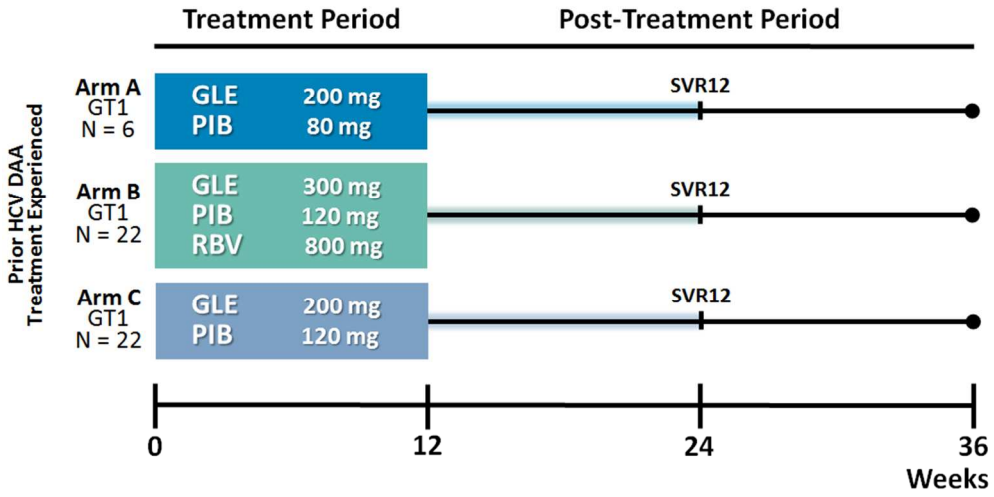

Figure 1. MAGELLAN-1, Part 1, Clinical Trial Design Schematic. In part 1 of the MAGELLAN-1 study, patients were randomized 1:1:1 into three treatment arms, stratified by HCV subtype (1b or non-1b) and previous DAA classification (NS5A inhibitor-experienced, NS3/4A PI-experienced but NS5A inhibitor-naïve, or other). Enrollment in Arm A was halted via protocol amendment after 6 patients were randomized to that arm (see methods). In total, 50 patients were enrolled to receive GLE + PIB ± RBV, once-daily, for 12 weeks. The primary endpoint was the proportion of patients with SVR12. DAA, direct-acting antiviral; GLE, glecaprevir; GT, genotype; PIB, pibrentasvir; RBV, ribavirin; SVR12, sustained virologic response at post treatment week 12.

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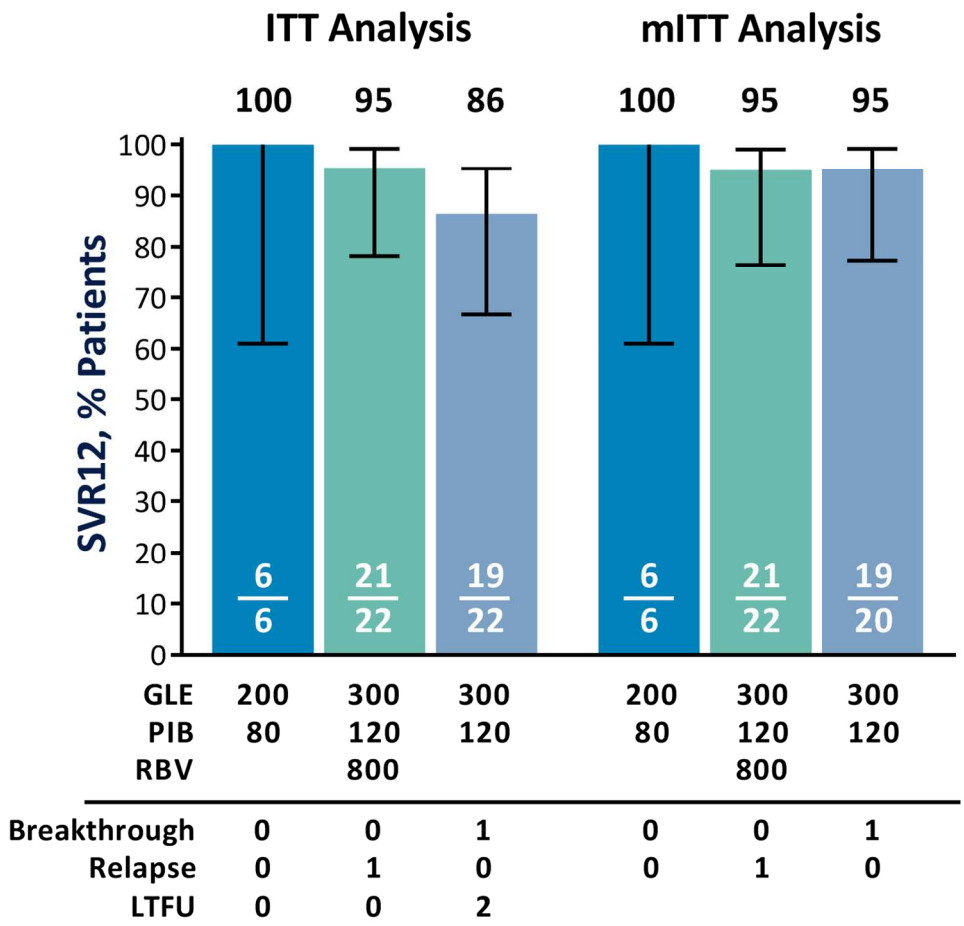

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Online Supporting Information

Glecaprevir and Pibrentasvir for 12 Weeks in Patients with Chronic HCV Genotype 1 Infection and Prior Direct-acting Antiviral Treatment

Fred Poordad, Franco Felizarta, Armen Asatryan, Mark S Sulkowski, Robert W Reindollar, Charles S Landis, Stuart C Gordon, Steven L Flamm, Michael W Fried, David E Bernstein, Chih-Wei Lin, Ran Liu, Sandra S Lovell, Teresa I Ng, Jens Kort, Federico J Mensa

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ABT-493 was identified by AbbVie and Enanta Pharmaceuticals.

Study Investigators

Humberto Aguilar, David Bernstein, Franco Felizarta, Steven Flamm, Michael Fried, Stuart Gordon, Sinikka Green, Daniel Jackson, Kris Kowdley, Jacob Lalezari, Charles Landis, Godson Oguchi, Fred Poordad, Robert Reindollar, Mark Sulkowski, Peter Varunok, Ziad Younes.

Key Eligibility Criteria

Inclusion

- Male or female between 18 and 70 years of age
- Screening laboratory result indicating HCV genotype 1 infection
- Chronic HCV infection defined as one of the following:
    - Positive for anti-HCV Ab or HCV RNA at least 6 months before screening, and positive for HCV RNA and anti-HCV Ab at the time of screening; or
    - Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed prior to enrollment with evidence of chronic HCV infection); or
    - Positive for anti-HCV Ab and HCV RNA at the time of Screening with abnormal alanine aminotransferase (ALT) levels for at least 6 months before screening
- History of previous direct-acting antiviral-containing treatment (which was either approved at the time of treatment, or if investigational, then approval of AbbVie must be obtained; examples of investigational therapies in Part 1 include, but are not limited to, DCV + SMV, DCV + SOF, ASV + DCV, SOF + SMV, OBV + PTV/r for chronic HCV genotype 1 infection, with treatment outcome as either on-treatment virologic failure or
- post-treatment relapse, defined as:
    - On-Treatment Failure: The patient will be considered to have experienced on-treatment failure of the prior direct-acting antiviral-containing treatment regimen if a) the patient did not achieve unquantifiable HCV RNA prior to or by the planned end of the direct-acting antiviral-containing therapy (including those with on-treatment virologic breakthrough after achieving unquantifiable HCV RNA), or if b) the patient was documented to have met futility criteria as defined in the product label (e.g., for TVR or BOC containing regimens); or
    - Post-Treatment Relapse: The patient will be considered to have experienced post-treatment relapse if the HCV RNA was < LLOQ at the planned end of the prior direct-acting antiviral-containing treatment regimen, but was confirmed to be quantifiable after the end-of-treatment
- Treatment must have been completed at least 1 month prior to Screening Visit
- Body Mass Index (BMI) is from ≥18 to <38 kg/m^2 at the time of screening. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m)
- All patients must be documented as non-cirrhotic defined as meeting the criteria described in the Cirrhosis Determination section of the Supplementary Appendix
- HCV RNA >10,000 IU/mL at screening

Key Eligibility Criteria Continued

Exclusion

- Absence of a positive test result at screening for hepatitis B surface antigen (HBsAg) and anti-human immunodeficiency virus antibody (HIV Ab)
- HCV genotype performed during screening indicating co-infection with more than one HCV genotype
- Screening laboratory analyses showing any of the following abnormal laboratory results:
    - ALT >5 × ULN
    - AST >5 × ULN
    - Calculated creatinine clearance of <50 mL/min
    - Albumin <LLN
    - INR >1.5
    - Hemoglobin <LLN
    - Platelets <120,000 cells per mm3
    - ANC <1500 cells/µL (<1200 cells/µL for patients of black race or patients of African descent who are black)
- History of solid organ transplant
- Discontinuation of the prior direct-acting antiviral treatment regimen for reasons other than virologic failure (eg, non-adherence and/or the occurrence of an adverse event)

Cirrhosis Determination

Patients must have been documented as having no cirrhosis defined as meeting one of the following criteria (per local standard):

- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR Score of ≤3, Batts-Ludwig, Knodell (Histologic Activity Index; Fibrosis component), IASL, Scheuer, or Laennec fibrosis score of ≤3, Ishak (modified Knodell) fibrosis score of ≤ 4; or
- A FibroScan score of <12.5 kPa within 6 months prior to Screening or during the Screening Period; or
    - Patients with indeterminate FibroScan score (12.5 ≤ score <14.6) must have qualifying liver biopsy.
- A screening FibroTest score of ≤ 0.48 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) <1;
    - Patients with non-qualifying/conflicting FibroTest and APRI results (e.g., FibroTest ≤0.48, but APRI ≥1) must have a qualifying liver FibroScan or biopsy.

HCV RNA Measurement

Plasma HCV RNA levels were determined for each collected sample using the COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0. The lower limit of detection and lower limit of quantification for this assay are both 15 IU/mL.

Virologic Stopping and Futility Criteria

Patients were required to stop treatment with study drugs if they met any of the following criteria:

- Confirmed increase from nadir in HCV RNA, defined as 2 consecutive HCV RNA measurements (>1 $\log_{10}$ IU/mL above nadir) at any time point during treatment
- Confirmed quantifiable HCV RNA level at any point after an unquantifiable level.

Resistance-associated Variant Definition

All variants at the following resistance-associated amino acid positions for NS3/4A protease inhibitor class were included in the analysis:

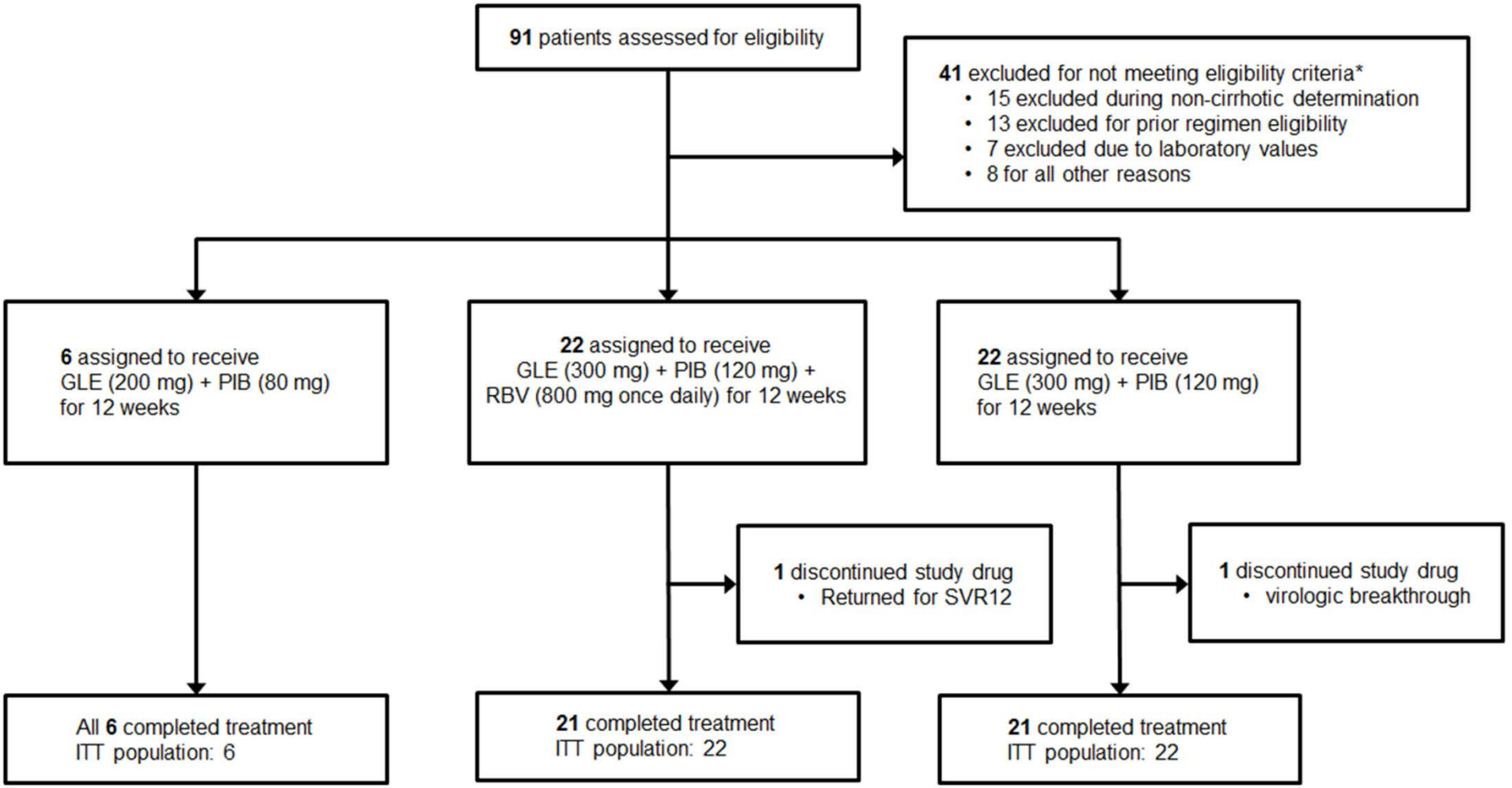
GT1a: 36, 43, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, and 170.

GT1b: 36, 54, 55, 56, 80, 107, 122, 155, 156, 158, 168, 170, and 175.

All variants at the following resistance-associated amino acid positions for NS5A inhibitor class were included in the analysis:

GT1a: 24, 28, 29, 30, 31, 32, 58, 62, 92, and 93.

GT1b: 24, 28, 29, 30, 31, 32, 54, 58, 62, 92, and Y93.



*Total not equal to 41 because some patients were not eligible based on more than one inclusion/exclusion criterion

Supporting Table 1. Prior HCV DAA Regimens and Baseline Polymorphisms of Enrolled Patients

Arm	Patient ID	HCV SubGT	Reported Previous DAA Regimen	NS3 Polymorphisms	NS5A Polymorphisms
A	1	1a	BOC + PR	Q80L	None
A	2	1a	SAM + SMV + TMC-647055 + RTV	None	M28V, Q30H
A	3	1a	SOF + SMV	Q80K (3%), I170V (6%)	None
A	4	1a	SOF + SMV	Q80K	None
B	5	1a	BOC + PR	Q80K	None
B	6	1a	BOC + PR	Q80K	None
B	7	1a	BOC + PR	I170V	None
B	8	1a	BOC + PR	Q80K, S122G	None
B	9	1a	BOC + PR; SOF + SMV + RBV; OBV + PTV/RTV + DSV + RBV	V55I (13%), Q80K (98%), D168V (95%)	M28T (2%), Q30R (99%)
B	**10**	**1a**	**DCV; TVR + PR**	**None**	**L31M, H58D (26%)**
B	11	1a	OBV + PTV/RTV + DSV	Q80K	Q30R (96%)
B	12	1a	OBV + PTV/RTV + DSV + RBV	Q80K	M28T (3%), Q30R (72%)
B	13	1a	RDV + DBV + FDV	R155K (11%)	M28T (99%), Q30H/R (72%/27%)
B	14	1a	RDV + DBV + FDV + RBV	None	Q30L, L31V (73%), Y93H
B	15	1a	RDV + DBV + FDV + RBV	None	K24N (8%), Q30K (14%)
B	16	1a	SMV + PR	Q80K	None
B	17	1a	SOF + LDV	Q80K	Y93N
B	18	1a	SOF + LDV	Q80K	None
B	19	1a	SOF + LDV	None	Q30H, Y93H
B	20	1a	SOF + LDV	None	Y93N
B	21	1a	SOF + SMV	Q80K	None
B	22	1a	SOF + SMV + RBV	None	None
B	23	1a	TVR + PR	None	None
B	24	1a	TVR + PR	None	None
C	25	1a	ASV + DCV + BCV	Q80K	Q30E/G (31%/4%), E62V (8%)
C	26	1a	ASV + DCV + PR	Q80K	L31M (31%), H58P
C	27	1a	BOC + PR	I170V (10%)	None

C	28	1a	BOC + PR	Q80K	None
C	29	1a	BOC + PR	None	None
C	30	1a	DCV + PR	R155K	Q30T (4%)
C	**31**	**1a**	**OBV + PTV/RTV + DSV + RBV**	**Y56H (5%), D168A/T (94%/3%)**	**M28V (3%), Q30R (98%), H58C (99%)**
C	32	1a	RDV + DBV + FDV	S122G	None
C	33	1a	SOF + LDV	Q80K	L31M
C	34	1a	SOF + LDV	Q80K	Q30H (62%), Y93H (61%)
C	35	1a	SOF + SMV	Q80K, R155K (10%)	None
C	36	1a	SOF + SMV	None	None
C	37	1a	SVP + ODV	Q80R (20%)	E62V (77%), Y93N
C	38	1a	TVR + PR	Q80K	None
C	39	1a	TVR + PR	None	None
C	40	1a	TVR + PR	None	None
C	41	1a	TVR + VX-222 + PR; SOF + LDV	V36M (30%), T54S, Q80K	K24R, Q30R
C	42	1a	VDV + LDV + RBV	Q80K	K24R (98%), M28V (9%), Q30R (9%), H58D (3%)
A	43	1b	SAM + SMV	None	L31M, Q54H
A	44	1b	SAM + SMV	None	L31M, Q54H
B	45	1b	BOC + PR	V170I (58%)	Q54H, Y93H (37%)
B	46	1b	SOF + SMV	R155Q (5%), D168V (16%)	P58S (99%)
C	47	1b	PTV/RTV + DSV + RBV	D168E (90%)	Q54H, A92T (97%)
C	48	1b	SOF + LDV	None	L31I, Y93H
C	49	1b	TVR + PR	None	Q54T
C	50	1b	TVR + PR; SOF + PR	None	Q54H

Polymorphisms were detected at a 2% detection threshold with next generation sequencing; only polymorphisms with prevalence ≥2% are listed; polymorphisms with prevalence >99% within a patient's viral population do not have the prevalence (%) listed. Patients in **BOLD** had virologic failure

DAA, direct-acting antiviral; PR, peginterferon plus ribavirin; RBV, ribavirin; RTV, ritonavir

NS3/4A protease inhibitors: ASV, asunaprevir; BOC, boceprevir; FDV, faldaprevir; PTV, paritaprevir; SMV, simeprevir; SVP, sovaprevir; TVR, telaprevir; VDV, vedroprevir

NS5A inhibitors: DCV, daclatasvir; LDV, ledipasvir; OBV, ombitasvir; ODV, odalasvir; RDV, ravidasvir; SAM, samatasvir

NS5B polymerase inhibitors: BCV, beclabuvir; DSV, dasabuvir; DBV, deleobuvir; SOF, sofosbuvir; VX-222; TMC-647055

Supporting Table 2. Baseline Resistance-associated Polymorphisms

Polymorphisms, n (%)	**Arm A** GLE+PIB (200 mg + 80 mg) n=6	**Arm B** GLE+PIB (300 mg + 120 mg) + RBV (800 mg) n=22	**Arm C** GLE+PIB (300 mg + 120 mg) n=22
Any Polymorphism (NS3 or NS5A)	6 (100)	19 (86)	18 (82)
NS3 only	3 (50)	7 (33)	5 (23)
NS5A only	3 (50)	5 (23)	3 (14)
Both NS3 and NS5A	0	7 (33)	10 (45)

Polymorphisms were detected at a 2% detection threshold with next generation sequencing
'Only' indicates total number of patients with baseline polymorphisms within the indicated target, and none in the other target
GLE, glecaprevir; PIB, pibrentasvir; RBV, ribavirin

Supporting Table 3. Baseline NS3 and NS5A Amino Acid Polymorphisms

	2% NGS Detection Threshold	15% NGS Detection Threshold
NS3 Polymorphisms	**n (%)**	**n (%)**
Q80K/L/R	23 (46)	22 (44)
R155K/Q	4 (8)	1 (2)
D168A/E/T/V	4 (8)	4 (8)
I170V (GT1a)	3 (7)[a]	1 (2)[a]
S122G	2 (4)	2 (4)
V36M	1 (2)	1 (2)
T54S	1 (2)	1 (2)
V55I	1 (2)	0
Y56H	1 (2)	0
NS5A Polymorphisms	**n (%)**	**n (%)**
Q30E/G/H/K/L/R/T	14 (28)	11 (22)
Y93H/N	8 (16)	8 (16)
L31I/M/V	7 (14)	7 (14)
M28T/V	6 (12)	2 (4)
Q54H/T (GT1b)	6 (75)[b]	6 (75)[b]
H58C/D/P (GT1a)	4 (10)[a]	3 (7)[a]
K24N/R	3 (6)	2 (4)
E62V	2 (4)	1 (2)
P58S (GT1b)	1 (13)[b]	1 (13)[b]

GT, genotype; DAA, direct-acting antiviral; NGS, next generation sequencing

Total number of GT1 patients: 50; total number of GT1a patients: 42; total number of GT1b patients: 8

[a]Percentage relative to the total number of GT1a patients

[b]Percentage relative to the total number of GT1b patients