

2018

Glecaprevir/Pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure

F. Poordad

S. Pol

A. Asatryan

M. Buti

D. Shaw

See next page for additional authors

Follow this and additional works at: <https://academicworks.medicine.hofstra.edu/publications>



Part of the [Hepatology Commons](#)

Recommended Citation

Poordad F, Pol S, Asatryan A, Buti M, Shaw D, Hezode C, Felizarta F, Reindollar RW, Bernstein DE, Mensa FJ, . Glecaprevir/Pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. . 2018 Jan 01; 67(4):Article 4335 [p.]. Available from: <https://academicworks.medicine.hofstra.edu/publications/4335>. Free full text article.

This Article is brought to you for free and open access by Donald and Barbara Zucker School of Medicine Academic Works. It has been accepted for inclusion in Journal Articles by an authorized administrator of Donald and Barbara Zucker School of Medicine Academic Works. For more information, please contact academicworks@hofstra.edu.

Authors

F. Poordad, S. Pol, A. Asatryan, M. Buti, D. Shaw, C. Hezode, F. Felizarta, R. W. Reindollar, D. E. Bernstein, F. J. Mensa, and +10 additional authors

Glecaprevir/Pibrentasvir in Patients With Hepatitis C Virus Genotype 1 or 4 and Past Direct-Acting Antiviral Treatment Failure

Fred Poordad,¹ Stanislas Pol,² Armen Asatryan,³ Maria Buti,⁴ David Shaw,⁵ Christophe Hézode,⁶ Franco Felizarta,⁷ Robert W. Reindollar,⁸ Stuart C. Gordon,⁹ Stephen Pianko,¹⁰ Michael W. Fried,¹¹ David E. Bernstein,¹² Joel Gallant,¹³ Chih-Wei Lin,³ Yang Lei,³ Teresa I. Ng,³ Preethi Krishnan,³ Sarah Kopecky-Bromberg,³ Jens Kort,³ and Federico J. Mensa³

Patients with hepatitis C virus (HCV) who have virological failure (VF) after treatment containing a nonstructural protein 5A (NS5A) inhibitor have limited retreatment options. MAGELLAN-1 Part 2 was a randomized, open-label, phase 3 study to evaluate the efficacy and safety of ribavirin (RBV)-free glecaprevir and pibrentasvir (G/P; 300 mg/120 mg) in patients with chronic HCV and past VF on at least one NS3/4A protease and/or NS5A inhibitor-containing therapy. Patients with compensated liver disease, with or without cirrhosis, and HCV genotype (GT) 1, 4, 5, or 6 were randomized 1:1 to receive 12 or 16 weeks of G/P. The primary endpoint was sustained virological response (SVR) at 12 weeks posttreatment (SVR12). Among 91 patients treated, 87 had GT1 and 4 had GT4 infection. SVR12 was achieved by 89% (39 of 44) and 91% (43 of 47) of patients who received 12 and 16 weeks of G/P, respectively. Virological relapse occurred in 9% (4 of 44) of patients treated with 12 weeks of G/P; there were no relapses with 16 weeks of treatment. Past treatment history with one class of inhibitor (protease or NS5A) had no impact on SVR12, whereas past treatment with both classes of inhibitors was associated with lower SVR12 rate. The most common adverse event (AE) was headache ($\geq 10\%$ of patients), and there were no serious AEs assessed as related to study drugs or AEs leading to discontinuation. *Conclusion:* Sixteen weeks of G/P treatment achieved a high SVR12 rate in patients with HCV GT1 infection and past failure to regimens containing either NS5A inhibitors or NS3 protease inhibitors. (HEPATOLOGY 2018;67:1253-1260)

Most currently available direct-acting antiviral (DAA) treatment regimens for chronic infection with hepatitis C virus (HCV) include nonstructural protein 5A (NS5A) inhibitors and are highly effective. However, patients that have virological failure (VF) with NS5A inhibitor-containing regimens commonly develop resistance-associated substitutions (RASs) that decrease the efficacy of subsequent retreatment.⁽¹⁻³⁾ Additionally, in contrast to treatment-emergent substitutions in NS3, which disappear within the first year posttreatment, RASs in NS5A

can persist for several years.^(4,5) Therefore, effective retreatment of patients who have had VF on NS5A inhibitor-containing regimens has been challenging, and retreatment options for this population are currently limited.^(6,7) Addition of ribavirin (RBV) and/or extended treatment durations using combinations of three to four DAAs have been strategies utilized to provide retreatment options for patients^(2,8-12); however, clinical data from large studies are not available for most of these regimens, and sustained virological response (SVR) rates have generally been suboptimal. Recently,

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; CI, confidence interval; DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; EC₅₀, half-maximal effective concentration; GLE, glecaprevir; G/P, glecaprevir and pibrentasvir; GT, genotype; HCV, hepatitis C virus; kPa, kilopascals; LDV, ledipasvir; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NS5A, nonstructural protein 5A; OBV, ombitasvir; PI, protease inhibitor; PIB, pibrentasvir; PTV/r, ritonavir boosted paritaprevir; RASs, resistance-associated substitutions; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; SVR12, sustained virological response at posttreatment week 12; TE, transient elastography; VEL, velpatasvir; VF, virological failure.

Received September 14, 2017; accepted November 14, 2017.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29671/suppinfo.

the three DAA fixed-dose combination of sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir demonstrated an overall 96% SVR12 rate in patients with past NS5A inhibitor experience.^(13,14) However, the use of SOF may not be suitable for important subpopulations, such as those with advanced renal disease.⁽¹⁵⁾ Therefore, effective retreatment options using RBV-free DAA combinations without SOF, which retain antiviral activity against common NS5A RASs, are needed.

Glecaprevir (GLE) is an HCV NS3/4A protease inhibitor (PI), and pibrentasvir (PIB) is an NS5A inhibitor. They have been coformulated (G/P) in clinical trials for the treatment of all six major HCV genotypes. GLE has demonstrated *in vitro* half-maximal effective concentration (EC₅₀) values ≤5 nanomolar across all major HCV genotypes (GTs), and has <5-fold loss of activity against most GT1 RASs (such as those at positions 36, 56, 80, 155, and 156) that may

be selected during treatment with currently available NS3/4A PIs.^(16,17) PIB has EC₅₀ values ≤5 picomolar across all major HCV GTs and has demonstrated minimal loss in potency against known NS5A RASs (such as those at positions 24, 28, 30, 31, 58, 92, and 93), including GT1a Y93H (6.7-fold increase in EC₅₀),⁽¹⁸⁾ which substantially reduces susceptibility to other NS5A inhibitors, such as VEL (609-fold increase in EC₅₀), ledipasvir (LDV; 3,294-fold increase in EC₅₀), and daclatasvir (DCV; 1,600-fold increase in EC₅₀).⁽¹⁹⁾ This suggests that G/P could provide an effective retreatment regimen, including for patients with past experience with NS5A inhibitor-containing regimens.

MAGELLAN-1 Part 1 was a phase 2 dose-ranging study that evaluated the efficacy and safety of GLE and PIB for 12 weeks, with or without RBV, in GT1-infected patients with past treatment failure on DAA

Copyright © 2017 The Authors. Hepatology published by Wiley Periodicals, Inc. on behalf of American Association for the Study of Liver Diseases. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.29671

Potential conflict of interest: Dr. Poordad consults for, advises for, is on the speakers' bureau for, and received grants from Gilead, Merck, GlaxoSmithKline, and Vertex. He consults for, advises for, and received grants from AbbVie, Achillion, Anadys, Biolex, Boehringer Ingelheim, Bristol-Myers Squibb, GlobeImmune, Idenix, and Novartis. He consults for and advises for Tibotec/Janssen and Theravance. He is on the speakers' bureau for and received grants from Genentech. He is on the speakers' bureau for Kadmon, Onyx/Bayer for, and Salix. He received grants from Idera, Intercept, Janssen, Medarex, Medtronic, Santaris, Scynexis, and ZymoGenetics. Prof. Pol is on the speakers' bureau for and received grants from Bristol-Myers Squibb, Gilead, Roche, AbbVie, and MSD. He is on the speakers' bureau for Boehringer Ingelheim and Janssen. Dr. Bernstein consults for and is on the speakers' bureau for AbbVie. Dr. Reindollar advises for and is on the speakers' bureau for AbbVie and Gilead. Dr. Fried consults for and received grants from AbbVie, Bristol-Myers Squibb, and Merck. He received grants from Gilead. He owns stock in Target PharmaSolutions. Dr. Pianko advises for, is on the speakers' bureau for, and received grants from AbbVie, Gilead, and MSD. Dr. Hezode consults for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and MSD. Dr. Felizarta is on the speakers' bureau for and received grants from AbbVie, Gilead, Janssen, and Merck. Dr. Gallant advises for, received grants from, and is employed by Gilead. He advises for and received grants from Bristol-Myers Squibb, Merck, ViiV, and GlaxoSmithKline. He advises for Thera-technologies. He received grants from AbbVie, Janssen, and Sangamo. Dr. Buti consults for and is on the speakers' bureau for Gilead, AbbVie, and MSD. Dr. Gordon advises for and received grants from AbbVie, Bristol-Myers Squibb, Intercept, Gilead, and Merck. He advises for CVS Caremark. He received grants from Conatus, CymaBay, and Exalenz. He received royalties from UpToDate. Dr. Kort is employed by and owns stock in AbbVie. Dr. Ng is employed by and owns stock in AbbVie. Dr. Lin is employed by and owns stock in AbbVie. Dr. Asatryan is employed by and owns stock in AbbVie. Dr. Mensa is employed by and owns stock in AbbVie. Dr. Krishnan is employed by and owns stock in AbbVie. Dr. Lei is employed by and owns stock in AbbVie. Dr. Kopecky-Bromberg owns stock in AbbVie.

ARTICLE INFORMATION:

From the ¹The Texas Liver Institute, University of Texas Health, San Antonio, TX; ²Groupe Hospitalier Cochin-Saint Vincent De Paul, Paris, France; ³AbbVie Inc., North Chicago, IL; ⁴Vall d'Hebron University Hospital and CiBERHED del Instituto Carlos III, Barcelona, Spain; ⁵Royal Adelaide Hospital, Adelaide, Australia; ⁶Hôpital Henri Mondor, Université Paris-Est, Créteil, France; ⁷Private Practice, Bakersfield, CA; ⁸Piedmont Healthcare/Carolinas Center for Liver Disease, Statesville, NC; ⁹Henry Ford Health System, Detroit, MI; ¹⁰Monash Health and Monash University, Caulfield South, Victoria, Australia; ¹¹University of North Carolina, Chapel Hill, NC; ¹²North Shore University Hospital, Manhasset, NY; and ¹³Southwest CARE Center, Santa Fe, NM.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Fred Poordad, M.D.
Texas Liver Institute, University of Texas Health
607 Camden Street
Suite 101

San Antonio, TX 78215
E-mail: poordad@txliver.com
Tel: +1-210-253-3426

regimens containing an NS5A inhibitor and/or NS3/4A PI with or without NS5B inhibitors. The modified intent-to-treat (modified intent-to-treat analysis excludes patients that failed because of nonvirological reasons) sustained virological response (SVR) at 12 weeks posttreatment (SVR12) rate was 95%, regardless of RBV coadministration, and was not affected by past treatment regimen or presence of baseline RASs.⁽²⁰⁾

In this study, MAGELLAN-1 Part 2, the efficacy and safety of RBV-free G/P for 12 or 16 weeks was planned to be evaluated in patients with chronic HCV GT1, 4, 5, or 6 infection, including those with compensated cirrhosis, and past treatment failure on NS3/4A protease and/or NS5A inhibitor-containing regimens.

Patients and Methods

STUDY OVERSIGHT

All patients signed informed consent, and the study was conducted in accord with the International Conference on Harmonization guidelines and the ethics set forth by the Declaration of Helsinki.

STUDY DESIGN

MAGELLAN-1 (NCT02446717) Part 2 was a randomized, open-label, multicenter, phase 3 study that assessed the efficacy and safety of G/P in patients with chronic HCV GT1 or GT4 infection, including those with compensated cirrhosis, who had past failure on at least one NS3/4A protease and/or NS5A inhibitor-based regimen. The trial design schematic is shown in Fig. 1, and a flow diagram showing patient recruitment and enrollment is depicted in Supporting Fig. S1. Patients were randomized 1:1 to receive either 12 or 16 weeks of all-oral coformulated G/P (without RBV; GLE was discovered by AbbVie and Enanta). G/P was dosed as 3 pills (100 mg/40 mg each) for a total dose of 300 mg/120 mg once-daily.

PATIENT POPULATION

Patients were screened at 31 sites in Australia, France, Spain, the United Kingdom, and the United States (including Puerto Rico). Patients at least 18 years old (no upper limit) were eligible if they had chronic HCV GT1, 4, 5, or 6 infection with HCV RNA >1,000 IU/mL at screening. HCV genotype and subtype were assessed with the Versant HCV Genotype Inno LiPA Assay, version 2.0 or higher, or

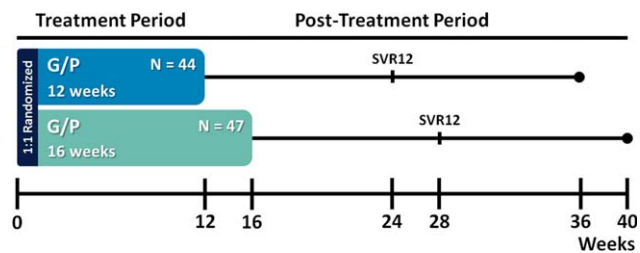


FIG. 1. MAGELLAN-1, Part 2 study design. Patients were randomized 1:1 and stratified by HCV GT (1 or 4) and past treatment experience (NS5A inhibitor-naïve or -experienced) to receive either 12 or 16 weeks of once-daily G/P (300 mg/120 mg). All patients had past VF, virological failure to at least one HCV treatment regimen containing an approved NS3/4A protease and/or NS5A inhibitor allowed by study protocol. Patients were followed for 24 weeks posttreatment to monitor safety and SVR.

Sanger sequencing of the NS5B region if indeterminate initially by LiPA. Patients had to have past VF failure to an approved DAA-containing regimen that included an NS5A inhibitor (limited to DCV, LDV, or ombitasvir [OBV]) and/or NS3/4A PI (limited to paritaprevir, simeprevir [SIM], asunaprevir, telaprevir, or boceprevir). NS5B inhibitors (SOF or dasabuvir [DSV]) could have been present in any past treatment regimen, and patients could have had failure to multiple past regimens. Patients with sequential exposures to multiple regimens (i.e., PI-containing regimen followed by an NS5A inhibitor-containing regimen) were considered to have past experience to both. Median time since patients' last previous VF is reported in the Supporting Information. Patients could have compensated cirrhosis (Child-Pugh score of 6 or less) or no cirrhosis. Absence of cirrhosis (e.g., METAVIR score ≤ 3 , Ishak score ≤ 4) was determined by liver biopsy within 24 months before (or during) screening, transient elastography (TE; FibroScan) score of <12.5 kilopascals (kPa) within 6 months before (or during) screening, or a screening FibroTest score of ≤ 0.48 and an aspartate aminotransferase (AST) to platelet ratio index (APRI) <1. Presence of cirrhosis was determined by past histological diagnosis of cirrhosis on liver biopsy (e.g., METAVIR [or equivalent] score of >3 [including 3/4], Ishak score of >4), past TE (FibroScan) score of ≥ 14.6 kPa, or a screening FibroTest score of ≥ 0.75 and an APRI >2. Patients with indeterminate FibroScan were required to have liver biopsy and indeterminate FibroTest or conflicting FibroTest, and APRI scores were required to have TE

or liver biopsy to determine cirrhosis status. Complete inclusion and exclusion criteria are included in [Supporting Table S1](#).

ASSESSMENT OF EFFICACY, SAFETY, AND VIROLOGICAL RESISTANCE

The primary endpoint was the percentage of patients who achieved SVR at 12 weeks after the last dose of study drug (SVR12 defined as HCV RNA below the lower limit of quantification [LLOQ; 15 IU/mL]). Secondary endpoints included the percentage of patients with on-treatment VF and relapse. Plasma samples were collected at screening, days 1 and 3, weeks 1 and 2, 4, 6, 8, 10, 12, and 16 (only for patients treated for 16 weeks), and at post-treatment weeks 2, 4, 8, 12, and 24. In the event of premature discontinuation, a plasma sample was taken at the time of discontinuation. Plasma HCV-RNA levels were determined using the Roche (Basel, Switzerland) AmpliPrep COBAS TaqMan real-time reverse transcriptase PCR assay v2.0 with a high pure system. The lower limit of detection (LLOD) and LLOQ of HCV RNA for this assay were both 15 IU/mL.

Safety analyses were conducted on adverse events (AEs), vital signs, physical examinations, electrocardiograms, and laboratory tests and included all patients receiving at least 1 dose of study drug. Treatment-emergent AEs were collected from study drug initiation until 30 days after study drug discontinuation. Each AE was classified using the MedDRA version 19.0 system organ class and preferred term, and, subsequently, causality of each AE with respect to study drugs was determined by the study physician. Changes from baseline in laboratory tests and vital sign measurements were also assessed.

Next-generation sequencing was used with a 15% detection threshold to identify the presence of baseline substitutions in NS3 and NS5A relative to subtype-specific reference sequences. The amino acid positions included in the analysis of baseline substitutions were 36, 56 (GT1a only), 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A. Positions known to commonly harbor polymorphisms that do not confer significant *in vitro* resistance to GLE or PIB (e.g., Q80 in NS3) were not included in the analysis in order to focus analysis on relevant resistance positions. Treatment-emergent substitutions in NS3 and NS5A were analyzed for patients who had VF.

STATISTICAL ANALYSES

The study did not test a formal hypothesis. The percentage of patients who achieved SVR12 in each arm was summarized with a two-sided 95% confidence interval (CI) using the Wilson score method for binomial proportions. The difference in SVR12 rates between treatment arms was analyzed using the stratum-adjusted Mantel-Haenszel proportion with a continuity correction for variance, adjusted for each randomization stratum. Statistical analyses were performed using SAS software.

Results

BASELINE PATIENT DEMOGRAPHICS

A total of 122 patients were screened between January 12, 2016 and March 14, 2016; 31 patients failed screening, and 91 with HCV GT1 (n = 87) or GT4 (n = 4) infection were enrolled and treated. No patients with GT5 or GT6 infection were enrolled. Patients were randomized (1:1): 44 patients received 12 weeks of G/P and 47 were treated for 16 weeks. Demographics across the two treatment arms were generally well balanced. A majority of patients were male (70%), white race (76%), and had subtype 1a HCV (74%); 30% (27 of 91) of patients had compensated cirrhosis (34% and 26% of patients in the 12- and 16-week arms, respectively). In both the 12- and 16-week treatment arms, approximately one third of patients had past experience with an NS3/4A PI alone, an NS5A inhibitor alone, or both (Table 1). Nineteen (21%) patients had previously taken SOF + LDV (NS5A inhibitor-only experienced) as their only past treatment. Twenty (22%) patients had past treatment with more than one course of DAA-containing regimen.

Across both treatment arms, 30% of patients had no baseline substitutions in either NS3 or NS5A, whereas 66% (29 of 44) and 61% (27 of 44) had substitution(s) in NS5A in the 12- and 16-week treatment arms, respectively (Table 1). Seventeen percent (15 of 88) of patients had substitutions in NS3 at baseline. Baseline substitutions in both NS3 and NS5A had similar prevalence in the 12- and 16-week treatment arms. In patients with past experience with only NS5A inhibitors (NS3/4A PI-naïve), 84% (27 of 32) had baseline substitutions in NS5A; none of the patients had baseline NS3 substitutions. In contrast, 27% (8 of 30) of

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristic	12 Weeks N = 44	16 Weeks N = 47
Male, n (%)	31 (70)	33 (70)
White race, n (%)	34 (77)	35 (75)
Black race, n (%)	9 (20)	11 (23)
Age, median years (range)	57 (22-67)	56 (36-70)
BMI, median kg/m ² (range)	28 (21-41)	29 (20-52)
<i>IL28B</i> non-CC genotype, n (%)	38 (86)	42 (89)
HCV RNA, median log ₁₀ IU/mL (range)	6.1 (4.7-7.2)	6.3 (4.7-7.1)
Compensated cirrhosis, n (%)	15 (34)	12 (26)
HCV subtype*, n (%)		
1a	35 (80)	32 (71)
1b	8 (18)	11 (23)
1c	—	1 (2)
4	1 (2)	3 (6)
Previous DAA regimen class [†] , n (%)		
NS3/4A PI only (NS5A inhibitor-naïve)	14 (32)	13 (28)
NS5A inhibitor only (PI-naïve)	16 (36)	18 (38)
N3/4A PI + NS5A inhibitor	14 (32)	16 (34)
Past DAA treatment response, n (%)		
On-treatment failure	14 (32)	13 (28)
Virological relapse	30 (68)	34 (72)
Time since last treatment, median (range) months	19 (2-94)	10 (3-61)
Presence of key baseline substitutions [‡] , n (%)		
None	13 (30)	13 (30)
NS3 only	2 (5)	4 (9)
NS5A only	24 (55)	23 (52)
NS3 + NS5A	5 (11)	4 (9)

*Genotype and subtype determined by the Versant HCV Genotype Inno LiPA Assay, version 2.0 or higher, or Sanger sequencing of NS5B if LiPA result was indeterminate.

[†]SOF (NS5B inhibitor) could be included in any previous treatment regimen.

[‡]Sequencing data were available in 44 patients in each arm; percentages are based on N = 44; substitutions detected by next-generation sequencing using 15% detection threshold at positions 36, 56 (GT1a only), 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A. Abbreviation: BMI, body mass index.

patients with past experience with both classes of inhibitors had baseline substitutions in both NS3 and NS5A, whereas 3% (1 of 30) and 50% (15 of 30) of those patients had baseline substitutions in NS3 or NS5A alone, respectively. Detailed information on prevalence of baseline substitutions is shown in [Supporting Tables S2 and S3](#).

EFFICACY

Patients treated with 12 weeks of G/P had an SVR12 rate of 89% (39 of 44; 95% CI, 76-95), with one on-treatment VF and four relapses, whereas those treated for 16 weeks had an SVR12 rate of 91% (43 of 47; 95% CI, 80-97), with four on-treatment VFs (Table 2). All 4 patients with GT4 infection achieved SVR12; details for the 9 GT1 patients that had VF (four relapses and five on-treatment failures) are shown in [Supporting Table S4](#). Of the 5 patients with on-treatment failure, all 5 ended their past treatment within 1 year of initiating G/P, with a median time since last treatment of 4.6 (range, 2.6-8.7) months.

Median time from past treatment failure to retreatment with G/P for the entire enrolled population was 17 (range, 2.2-94) months, whereas those with relapse had a median time since last treatment of 26 (range, 5.7-60) months.

Patients with past treatment experience with only NS3/4A PIs (NS5A inhibitor-naïve) had 100% SVR12 regardless of treatment duration. For patients with past experience with only NS5A inhibitors, SVR12 rates were 88% (14 of 16; 95% CI, 64-97) and 94% (17 of 18; 95% CI, 74-99) for 12 and 16 weeks of treatment, respectively. For patients with past experience with both classes of inhibitors (NS3/4A and NS5A), SVR12 rates were 79% (11 of 14; 95% CI, 52-92) and 81% (13 of 16; 95% CI, 57-93) in those treated for 12 and 16 weeks, respectively. Three of six patients with past experience to both classes of inhibitors that did not achieve SVR12 had on-treatment VF.

Patients with no baseline substitutions in either NS3 or NS5A, or with substitutions in NS3 alone, had a 100% SVR12 rate. Patients with baseline substitutions in NS5A alone had SVR12 rates of 83% (20 of

TABLE 2. SVR and Efficacy Outcomes

Event, n/N (%, CI*)	12 Weeks N = 44	16 Weeks N = 47
Overall SVR12	39/44 (89; 76-95)	43/47 (91; 80-97)
On-treatment VF	1/44 (2)	4/47 (9)
Virological relapse	4/44 (9)	0/47
Past DAA class		
NS3/4A PI only	14/14 (100; 79-100)	13/13 (100; 77-100)
NS5A inhibitor only	14/16 (88; 64-97)	17/18 (94; 74-99)
NS3/4A PI + NS5A inhibitor	11/14 (79; 52-92)	13/16 (81; 57-93)
Past DAA regimen		
SOF/LDV	8/9 (89)	9/10 (90)
SOF + SIM	—	3/3 (100)
OBV/PTV/r ± DSV ± RBV	5/5 (100)	5/6 (83)
Other DAA [†] + pegIFN/RBV	16/17 (94)	16/16 (100)
Multiple past regimens	4/5 (80)	4/6 (67)
Other [‡]	6/8 (75)	6/6 (100)
Baseline substitutions [§]		
None	13/13 (100; 77-100)	13/13 (100; 77-100)
NS3 only	2/2 (100)	4/4 (100)
NS5A only	20 /24 (83; 64-93)	22 [¶] /23 (96; 79-99)
NS3 + NS5A	4 [#] /5 (80)	1 ^{**} /4 (25)

*CI calculated at 95% with the normal approximation to the binomial distribution.

[†]Includes DCV, telaprevir, or boceprevir.

[‡]Any other combination of DAA regimens allowed by study protocol.

[§]Sequencing data were available in 44 patients in each arm; substitutions detected by next-generation sequencing using 15% detection threshold at positions 36, 56 (GT1a only), 155, 156, and 168 in NS3, and 24, 28, 30, 31, 58, 92, and 93 in NS5A.

^{||}Three relapses and one on-treatment failure.

[¶]One on-treatment failure.

[#]One relapse.

^{**}Three on-treatment failures.

Abbreviation: pegIFN/RBV, pegylated interferon plus ribavirin.

24; 95% CI, 64-93) and 96% (22 of 23; 95% CI, 79-99) with 12 and 16 weeks of G/P treatment, respectively. Among these patients, three of four VFs in the 12-week arm were relapses; there were no relapses in patients treated for 16 weeks (Table 2). Of those patients with baseline substitutions in both NS3 and NS5A, three of nine (33%) had on-treatment VF in the 16-week arm of G/P treatment. These 3 patients all failed their last previous treatment regimen within 9 months of starting G/P. Furthermore, all 3 of these patients had past experience with NS5A, NS5B, and PIs, including OBV/paritaprevir/ritonavir and DSV (OBV/PTV/r [ritonavir boosted paritaprevir] + DSV) with or without additional regimens (Supporting Table S4). SVR12 rates by all past DAA regimens are listed in Table 2.

SAFETY, AEs, AND LABORATORY ABNORMALITIES

The majority of AEs were classified as mild (65%), and no patient prematurely discontinued study drug because of AEs (Table 3). There were three treatment-

emergent serious AEs reported in the study: a gastrointestinal viral infection, back pain, and wound infection; none were assessed by the study investigators as related to the study drugs. Headache was the only AE reported in $\geq 10\%$ of patients. There were no clinically significant alanine aminotransferase (ALT), AST, or bilirubin elevations in the study (Table 3). Safety was comparable between those with and without cirrhosis. Three patients experienced non-treatment-emergent AEs of hepatocellular carcinoma, all detected during the posttreatment period (37, 71, and 105 days after last treatment), and all considered not related to the study drugs by investigators.

Discussion

In this study, RBV-free coformulated G/P for 16 weeks was safe and demonstrated 100% and 94% SVR12 rates, with no virological relapses, in patients with past failure to NS3/4A PI only- and NS5A inhibitor only-containing regimens, respectively. Those with past experience with both of these classes of inhibitors had a lower SVR12 rate.

TABLE 3. AEs and Laboratory Abnormalities*

Event, n (%)	12 Weeks N = 44	16 Weeks N = 47
Adverse events		
Any AE	33 (75)	32 (68)
Grade 1 (mild) AE, n/N (%)	24/33 (73)	18/32 (56)
Serious AE [†]	1 (2)	2 (4)
Serious AE related to study drugs	0	0
AEs leading to study drug discontinuation	0	0
AEs occurring in ≥ 10% of patients		
Headache	6 (14)	11 (23)
Laboratory abnormalities		
ALT [‡] , Grade ≥3 (>5 × ULN)	0	0
AST [‡] , Grade ≥3 (>5 × ULN)	0	0
Total bilirubin, Grade ≥3 (>3 × ULN)	0	0
Hemoglobin, Grade ≥3 (<8 g/dL)	0	0

*Grades as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

[†]Serious AEs included gastrointestinal viral infection, back pain, and wound infection.

[‡]Postnadir increase in grade to Grade ≥3.

NS5A inhibitor-naïve patients with past failure with NS3/4A PI-containing regimens (i.e., boceprevir, telaprevir, and SIM) had 100% SVR12 rate, regardless of treatment duration. The median time from past treatment failure to retreatment with G/P in the enrolled population was 17 months, and the majority of patients had no substitutions in NS3 at baseline. This is consistent with the observation that RASs in NS3 selected by past PI therapy are generally undetectable within 1 year posttreatment,⁽²¹⁾ making successful retreatment of this patient population more likely over time.

Patients with past failure to NS5A inhibitor-containing regimens (but PI-naïve) had a 94% (17 of 18) SVR12 rate after 16 weeks of G/P treatment, compared to 88% (14 of 16) when treated for 12 weeks. Consistent with these results, patients with baseline substitutions in NS5A alone had a 96% (22 of 23) SVR12 rate when treated for 16 weeks, compared to 83% (20 of 24) when treated for 12 weeks. Among those with chronic HCV GT1 infection and past failure with NS5A inhibitor-containing regimens, the lack of virological relapses in patients treated for 16 weeks (compared with one relapse in the 12-week treatment arm), indicates that a 16-week duration may be required to minimize virological relapse. With only 4 GT4-infected patients enrolled in this study, all whom achieved SVR12, the optimal treatment duration could not be identified in this population.

The presence of NS5A substitutions at baseline was observed in the majority of patients with past NS5A inhibitor experience (50 of 64; 78%); however, there was no consistent pattern of substitutions associated

with VF to G/P. Treatment failure in this study was generally associated with the presence of baseline NS5A substitutions in conjunction with NS3 substitutions. All 3 patients that had on-treatment VF after past exposure to both NS3/4A and NS5A classes of inhibitors and had detectable combinations of Y56H and D168A/E substitutions in NS3 at baseline, in addition to substitutions in NS5A. All 3 patients were randomized to the 16-week treatment arm, had past failure to OBV/PTV/r ± DSV with or without additional regimens, and had recent failure on their previous course of DAA therapy (within 9 months of enrollment). These factors explain the presence of multiple baseline NS3 substitutions that decrease susceptibility to GLE in these patients.⁽²²⁾ Thus, these data suggest that patients with past experience to OBV/PTV/r ± DSV ± RBV, or those with multiple past courses of therapy that included NS3/4A protease and NS5A classes of inhibitors, may have an increased rate of VF.

One limitation of this study was the small number of GT4 patients available for enrollment, which prevented a robust assessment of efficacy in this genotype. Another limitation was the lack of patients with failure to more recently approved DAA regimens, such as elbasvir/grazoprevir and SOF/VEL; these regimens were approved after study initiation. However, SOF/LDV- or DCV-containing regimens are currently the most commonly prescribed HCV treatment regimens for patients with GT1 infection; 27% and 24% of patients enrolled in this study were SOF/LDV- and DCV-experienced, respectively. Another limitation was the small number of patients enrolled with compensated cirrhosis. Finally, few patients were enrolled with past failure to both an NS3/4A PI and NS5A inhibitor, because these patients are less common given the high efficacy of current generation regimens. In this study, patients with past experience to both classes of DAAs had lower SVR12 rates, at 79% and 81% after 12 or 16 weeks of G/P treatment, respectively. In contrast, 30 of 31 (97%) patients with past experience to either NS3/4A protease or NS5A inhibitor DAA classes achieved SVR12 after 16 weeks of G/P treatment.

In this study, the RBV-free combination of G/P was safe and well tolerated, regardless of treatment duration (12 or 16 weeks), and there were no AEs that led to study drug discontinuation. Furthermore, G/P demonstrated a low rate of serious AEs (none of which were assessed as related to study drugs), and there were no clinically relevant elevations in ALT, AST, or total bilirubin.

In summary, patients with NS3/4A PI experience alone had a 100% SVR12 rate regardless of 12- or 16-week treatment duration, whereas 16-week treatment duration may be required for patients with NS5A inhibitor experience alone (94% SVR12 with no virological relapses). Those with past experience with both of these DAA classes had lower SVR12 rates. Overall, RBV-free G/P demonstrated high SVR12 rates in patients with past failure with approved NS3/4A PIs or NS5A inhibitors.

Acknowledgments: AbbVie and the authors express their gratitude to the patients who participated in this study, and their families. They also thank all of the participating study investigators and coordinators, particularly Traci Baker, of AbbVie. Medical writing was provided by Ryan J Bourgo, Ph.D., of AbbVie.

REFERENCES

- Jacobson IM, Asante-Appiah E, Wong P, Black TA, Howe AY, Wahl J, et al. Prevalence and impact of baseline NS5A resistance-associated variants (RAVs) on the efficacy of elbasvir/grazoprevir (EBR/GZR) against GT1a infection. *HEPATOLOGY* 2015;62(Suppl 6):1393A-1394A.
- Lawitz E, Flamm S, Yang JC, Pang PS, Zhu Y, Svarovskaia E, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. *J Hepatol* 2015;62(Suppl 2):S192.
- Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naïve cirrhotic and noncirrhotic patients with chronic HCV genotype 1, 4, or 6 infection: a randomized trial. *Ann Intern Med* 2015;163:1-13.
- Dvory-Sobol H, Wyles D, Ouyang W, Chodavarapu K, McNally J, Cheng W, et al. Long-term persistence of HCV NS5A variants after treatment with NS5A inhibitor ledipasvir. *J Hepatol* 2015;62(Suppl 2):S221.
- Krishnan P, Tripathi R, Schnell G, Reisch T, Beyer J, Dekhtyar T, et al. Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A, and NS5B with paritaprevir/r-, ombitasvir-, and dasabuvir-based regimens. *J Hepatol* 2015; 62(Suppl 2):S220.
- AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. 2017. <http://www.hcvguidelines.org>. Accessed July 16, 2017.
- European Association for the Study of the Liver. Electronic address eee. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017;66:153-194.
- Buti M, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, et al. Grazoprevir, Elbasvir, and Ribavirin for Chronic Hepatitis C Virus Genotype 1 Infection After Failure of Pegylated Interferon and Ribavirin With an Earlier-Generation Protease Inhibitor: Final 24-Week Results From C-SALVAGE. *Clin Infect Dis* 2016;62:32-36.
- Gane E, Shiffman ML, Etkorn K, Morelli G, Stedman CA, Davis MN, et al. Sofosbuvir/Velpatasvir in combination with

ribavirin for 24 weeks is effective retreatment for patients who failed prior NS5A containing DAA regimens: results of the GS-US-342-1553 study. *J Hepatol* 2016;64(Suppl 2):S147-S148.

- Lawitz E, Poordad F, Gutierrez JA, Wells JT, Landaverde CE, Reiling JR, et al. C-SWIFT Retreatment (Part B): 12 Weeks of Elbasvir/Grazoprevir with Sofosbuvir and Ribavirin Successfully Treated G1-Infected Subjects who Failed Short-Duration All-Oral Therapy. Paper presented at The Liver Meeting 2015: American Association for the Study of Liver Diseases (AASLD) 2015, November 13-17, San Francisco, CA.
- Poordad F, Bennett M, Sepe TE, Cohen E, Reindollar RW, Everson GT, et al. QUARTZ-I: Retreatment of HCV Genotype 1 DAA-failures With Ombitasvir/Paritaprevir/r, Dasabuvir, and Sofosbuvir. Paper presented at The Liver Meeting 2015: American Association for the Study of Liver Diseases (AASLD) 2015, November 13-17, San Francisco, CA.
- Hezode C, Fourati S, Chevaliez S, Scoazec G, Soulier A, Varaut A, et al. Sofosbuvir-Daclatasvir-Simeprevir Plus Ribavirin in Direct-Acting Antiviral-Experienced Patients With Hepatitis C. *Clin Infect Dis* 2017;64:1615-1618.
- VOSEVI (sofosbuvir/velpatasvir/voxilaprevir) [package insert]. Foster City, CA: Gilead Sciences; 2017.
- Bouliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017;376:2134-2146.
- SOVALDI (sofosbuvir) tablets [package insert]. Foster City, CA: Gilead Sciences. Revised on November 2017.
- Ahmed A, Felmlee DJ. Mechanisms of Hepatitis C Viral Resistance to Direct Acting Antivirals. *Viruses* 2015;7:6716-6729.
- Ng TI, Krishnan P, Pilot-Matias T, Kati W, Schnell G, Beyer J, et al. ABT-493, a potent HCV NS3/4A protease inhibitor with broad genotype coverage. 2014. <http://www.croiconference.org/sites/default/files/posters/636.pdf>. Accessed July 25, 2016.
- Ng TI, Krishnan P, Pilot-Matias T, Kati W, Schnell G, Beyer J, et al. In vitro antiviral activity and resistance profile of the next generation hepatitis C virus NS5A inhibitor pibrentasvir. *Antimicrob Agents Chemother* 2017;61. pii: e02558-16. doi: 10.1128/AAC.02558-16. Print 2017 May.
- Gao M. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. *Curr Opin Virol* 2013;3:514-520.
- Poordad F, Felizarta F, Asatryan A, Sulkowski MS, Reindollar RW, Landis CS, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *HEPATOLOGY* 2017;66:389-397.
- Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology* 2014;146:1176-1192.
- Pilot-Matias T, Krishnan P, Schnell G, Tripathi R, Beyer J, Reisch T, et al. 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). Paper presented at International Liver Congress (EASL) 2017, April 19-23, Amsterdam, The Netherlands.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29671/supinfo.