Efficacy and Pharmacokinetics of Glecaprevir and Pibrentasvir With Concurrent Use of Acid-Reducing Agents in Patients With Chronic HCV Infection

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BACKGROUND & AIMS: **Proton pump inhibitors (PPIs) are commonly prescribed to treat acid-related disorders. Some direct-acting antiviral regimens for chronic hepatitis C virus (HCV) infection have reduced efficacy in patients taking concomitant acid-reducing agents, including PPIs, due to interactions between drugs. We analyzed data from 9 multicenter, phase 2 and 3 trials to determine the efficacy and pharmacokinetics of an HCV therapeutic regimen comprising glecaprevir and pibrentasvir (glecaprevir/pibrentasvir) in patients taking concomitant acid-reducing agents.**

METHODS: **We analyzed data from 2369 patients infected with HCV genotypes 1–6 and compensated liver disease treated with an all-oral regimen of glecaprevir/pibrentasvir for 8–16 weeks. We compared efficacy and pharmacokinetics among patients receiving at least 1 dose of an acid-reducing agent (a PPI, an H2 blocker, or antacid). High-dose PPI was defined as daily dose greater than 20 mg omeprazole dose equivalent. The objectives were to evaluate rate of sustained virologic response 12 weeks post-treatment (SVR12) and to assess steady-state glecaprevir and pibrentasvir exposures in patients on acid-reducing agents.**

RESULTS: **Of the 401 patients (17%) who reported use of acid-reducing agents, 263 took PPIs (11%; 109 patients took a high-dose PPI and 154 patients took a low-dose PPI). Rates of SVR12 were 97.0% among patients who used acid-reducing agents and 97.5% among those not using acid-reducing agents ($P = .6$). An SVR12 was achieved in 96.3% taking a high-dose PPI and 97.4% taking a low-dose PPI, with no virologic failures in those receiving a high-dose PPI ($P = .7$). Glecaprevir, but not pibrentasvir, bioavailability was affected; its exposure decreased by 41% in patients taking a high-dose PPI.**

CONCLUSIONS: **In an analysis of data from 9 clinical trials, we observed a high rate of SVR12 (approximately 97%) among patients treated with glecaprevir/pibrentasvir for HCV infection—even among patients taking concomitant ARA or high-dose PPI. This was despite decreased glecaprevir exposures in patients when on high-dose PPIs. ClinicalTrials.gov numbers, NCT02243280 (SURVEYOR-I), NCT02243293 (SURVEYOR-II), NCT02604017 (ENDURANCE-1), NCT02640482 (ENDURANCE-2), NCT02640157 (ENDURANCE-3), NCT02636595 (ENDURANCE-4), NCT02642432 (EXPEDITION-1), NCT02651194 (EXPEDITION-4), NCT02446717 (MAGELLAN-I).**

Keywords: DAA; ARA; Drug Interaction; Combination.

Abbreviations used in this paper: **AE, adverse event; ARA, acid-reducing agent; AUC, area under the curve; CI, confidence interval; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; IFN, interferon; ITT, intent-to-treat; LDV, ledipasvir; mITT, modified intent-to-treat; PK, pharmacokinetics; PPI, proton pump inhibitor; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12; VEL, velpatasvir.**

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Acid-reducing agents (ARAs), particularly proton pump inhibitors (PPIs), are among the most commonly prescribed medications in patients treated for chronic hepatitis C virus (HCV) infection.[1,2] Because ARAs cause gastric pH to become less acidic, many concomitant medications exhibit drug-drug interactions when taken with ARAs because of pH-dependent solubility issues, which in turn affect absorption and bioavailability of the concomitant medication.[3] Some of the currently available HCV direct-acting antivirals (DAA) exhibit this drug-drug interaction, leading to decreased DAA exposures and a resultant decrease in efficacy, particularly in patients with concurrent high-dose PPI use.

Because of these limitations, there was an unmet medical need for a pangenotypic DAA regimen that could be coadministered with ARAs, including high-dose PPIs. Because of pH-dependent solubility issues for ledipasvir (LDV) and velpatasvir (VEL), neither sofosbuvir (SOF)/LDV nor SOF/VEL are recommended with concurrent PPI use[4,5]; however, if medically necessary, SOF/VEL can be coadministered with a low-dose PPI when given 4 hours before the PPI.[5] SOF/VEL/voxilaprevir can be coadministered only with the low PPI dose.[6] Other SOF-containing regimens, including SOF/daclatasvir and SOF/simeprevir, can be used with ARAs without restrictions, but are only effective in certain patient populations.[7] For HCV genotypes 1 and 4 only, elbasvir/grazoprevir and ombitasvir/paritaprevir/ritonavir ± dasabuvir can be used in patients taking concomitant ARAs[8-10]; however, patients taking ombitasvir/paritaprevir/ritonavir ± dasabuvir should be monitored for decreased omeprazole efficacy because of a decrease in its exposure with ombitasvir/paritaprevir/ritonavir ± dasabuvir.[11]

Glecaprevir (a potent pangenotypic NS3/4A protease inhibitor identified by AbbVie and Enanta) and pibrentasvir (a potent pangenotypic NS5A inhibitor), coformulated as G/P, is an efficacious and safe ribavirin-free DAA regimen approved for the treatment of chronic HCV infection in patients with HCV genotypes 1–6 and compensated liver disease, including patients coinfected with human immunodeficiency virus or patients with severe renal impairment including those on dialysis.[12-19] Overall, ≥97% of patients achieved sustained virologic response at post-treatment week 12 (SVR12) with low rates of discontinuation caused by an adverse event (AE) and DAA-related serious AEs.[20] A dedicated phase 1 drug-drug interaction study evaluated the pharmacokinetics (PK) of G/P when administered with multiple dose regimens of omeprazole.[21,22] In that study, G/P was administered with food at least 1 hour after fasted dosing of omeprazole to maximize potential interactions. For glecaprevir, area under the plasma concentration-time curve (AUC) was decreased by 29% when coadministered with daily omeprazole, 20 mg, and by up to 51% with daily omeprazole, 40 mg, whereas pibrentasvir exposure was unaffected by PPI regimens.[21] Subsequent analysis of exposure-efficacy relationships determined that attainment of SVR12 was independent of glecaprevir plasma concentration in the patient population, suggesting that glecaprevir levels are well above the therapeutic threshold.[22] However, pibrentasvir plasma levels were an independent predictor of SVR12.

Here, we present an integrated analysis of 9 phase 2 and 3 studies aimed at evaluating the impact of concomitant ARA usage on efficacy and PK of G/P.

What You Need to Know

Background

Some direct-acting antiviral regimens for treating chronic hepatitis C virus have reduced efficacy in patients taking concomitant acid-reducing agents including proton pump inhibitors due to drug-drug interactions.

Findings

In its registrational program, glecaprevir/pibrentasvir exhibited high SVR12 rates even in patients receiving concomitant acid-reducing agents including high-dose proton pump inhibitors despite modest decreases in glecaprevir exposures seen in patients when on high-dose proton pump inhibitors.

Implications for patient care

Glecaprevir/pibrentasvir is a recently approved, pangenotypic direct acting antiviral regimen suitable for patients taking concomitant acid-reducing agents, including high-dose proton pump inhibitors.

Methods

Analysis Set

Data from 9 phase 2 and 3 clinical trials assessing the efficacy and safety of G/P (SURVEYOR-I and –II; MAGELLAN-I; ENDURANCE-1, 2, 3, and 4; and EXPEDITION-1 and -4) were pooled.[12-19] Patients received glecaprevir, 300 mg, and pibrentasvir, 120 mg, coadministered (phase 2) or coformulated G/P (300 mg/120 mg; phase 3) dosed orally as a 3-pill once daily regimen taken with food for 8, 12, or 16 weeks based on HCV genotype, cirrhosis status, and prior HCV treatment experience. Patients reporting at least 1 ARA dose during G/P treatment were classified into mutually exclusive groups based on the most potent ARA taken during treatment. For this classification, PPIs were considered more potent than H_2 blockers, which were considered more potent than antacids. Patients taking concomitant PPIs were further stratified by total daily PPI dosing regimen into mutually exclusive groups of patients taking either low-dose or high-dose PPI. Low-dose PPI regimens were defined as up to omeprazole, 20 mg, dexlansoprazole, 60 mg, esomeprazole, 20 mg, ilaprazole,

10 mg, lansoprazole, 30 mg, pantoprazole, 20 mg, or rabeprazole, 20 mg total daily dosing. If a subject received at least 1 daily dose of high-dose PPI, they were classified as a high-dose PPI user. All authors had access to the study data, and reviewed and approved the final manuscript for submission.

Patients

Inclusion and exclusion criteria were largely the same for all clinical trials with differences noted in the Supplementary Appendix and Supplementary Table 1. Patients were at least 18 years of age and positive for anti-HCV antibody with a plasma HCV RNA viral load $\geq$1000 IU/mL in Phase 3 trials or $\geq$10,000 IU/mL in Phase 2 trials at screening visit. Patients without cirrhosis or with compensated cirrhosis were either HCV treatment-naive or had prior treatment experience with interferon (IFN)/pegIFN $\pm$ ribavirin or SOF $\pm$ ribavirin $\pm$IFN/pegIFN. Additionally, 1 study (MAGELLAN-I) included patients who had failed a prior treatment with NS5A inhibitors and/or NS3/4A protease inhibitors. Absence or presence of cirrhosis was confirmed through either liver biopsy, FibroScan score, or screening Fibrotest and aspartate aminotransferase to platelet ratio index as outlined in the Supplementary Appendix. EXPEDITION-1 exclusively studied G/P in patients with compensated cirrhosis and HCV genotypes 1, 2, 4, 5, and 6. EXPEDITION-4 exclusively studied G/P in patients with severe renal impairment (estimated glomerular filtration rate $<$30 mL/min/1.73 m^2) infected with HCV genotypes 1–6 and with compensated liver disease. All other studies excluded patients whose estimated creatinine clearance was $<$50 mL/min. Patients were excluded from all studies if they were positive for hepatitis B surface antigen at screening. Only ENDURANCE-1 enrolled patients with HIV infection. All patients provided written informed consent. Studies were designed and conducted in accordance with the Good Clinical Practice guidelines, Declaration of Helsinki, and applicable local regulation, with approval from independent ethics committees or institutional review boards at all study sites.

Assessments

HCV genotype was determined using the Versant HCV Genotype Inno LiPA Assay, version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY), and confirmed by phylogenetic analysis of viral sequences. Plasma HCV RNA was quantified by polymerase chain reaction for assessing baseline viral load and SVR12; assay details are described in the Supplementary Appendix. Safety was evaluated through physical examinations, laboratory testing, and monitoring of AEs. Study investigators assessed AEs and determined relatedness to study drug. G/P plasma concentrations were measured using a validated assay method by the Drug Analysis Department at AbbVie.[23]

End Points

The primary endpoint for these studies was the rate of SVR12 (HCV RNA less than lower limit of quantification) in the intent-to-treat (ITT) population, which included all patients who received at least 1 dose of study drug. Secondary endpoints included the number of on-treatment virologic failures and relapses. Additional endpoints included PK evaluation of G/P exposure in patients on ARAs, and safety including AEs and study drug discontinuations.

Statistical Analysis

The number and percentage of patients in the ITT population achieving SVR12 on each ARA and different PPI doses were summarized with 2-sided 95% confidence intervals (CIs) calculated using the Wilson score method. Statistical analyses compared ITT SVR12 rates as outlined in the Results section using Fisher exact test. Further analyses of SVR12 used a modified ITT (mITT) population that excluded subjects who did not achieve SVR_{12} for reasons other than virologic failure (eg, patients who discontinued early or were lost to follow-up).

Nonlinear mixed effect models were developed in NONMEM 7.3 to characterize the population PK of G/P.[23] Intrinsic and extrinsic covariates that potentially cause variability in PK were tested at $\alpha = 0.001$ significance level, based on the likelihood ratio test. Use of PPI at any dose (high-dose and low-dose), high-dose PPI, and ARA drugs other than PPI (including H_2-blockers and antacids) were tested as covariates in the model, and their impact on bioavailability of G/P were evaluated in the population PK analyses. Exposure data from population PK analyses are expressed as AUC for patients. The AUC values were estimated based on the projected individual concentration-time profiles over the dosing interval using the PK models and individual PK parameter estimates.

Results

Baseline Patient Demographics and Characteristics

This analysis included 2369 patients with chronic HCV genotypes 1–6 from phase 2 and 3 clinical trials who were treated with G/P for either 8, 12, or 16 weeks following enrollment between October 7, 2014, and May 13, 2016 (Supplementary Figure 1). Overall, the analysis included 401 (17%) patients concurrently taking an ARA, among whom 263 (11%), 84 (4%), and 54 (2%) were classified as taking PPIs, H_2 blockers, or antacids, respectively. Table 1 delineates the baseline and disease characteristics of patients in each ARA category with PPI

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	PPI use n = 263		H2 blocker use n = 84	Antacid use n = 54	No acid- reducing drugs n = 1968
	High-dose[a] n = 109	Low-dose[a] n = 154			
Male, n (%)	54 (50)	93 (60)	44 (52)	32 (59)	1095 (56)
Race, n (%)					
White	92 (84)	131 (85)	62 (74)	44 (81)	1569 (80)
Black or African American	14 (13)	12 (8)	8 (10)	3 (6)	112 (6)
Asian	1 (<1)	9 (6)	12 (14)	4 (7)	246 (13)
Other	2 (2)	2 (1)	2 (2)	3 (6)	41 (2)[b]
Age, median (range), *y*	56 (30–79)	56 (27–82)	56.5 (33–72)	58.5 (19–83)	54 (19–88)
BMI, median (range), kg/m^2	28.1 (17.4–55.4)	26.9 (18.5–54.1)	27.3 (18.5–43.1)	25.2 (19.1–34.4)	25.7 (17.3–65.7)
Treatment-naive, n (%)	80 (73)	98 (64)	53 (63)	34 (63)	1375 (70)
Treatment-experienced, n (%)					
IFN/RBV	18 (17)	40 (26)	17 (20)	16 (30)	455 (23)
SOF/RBV	4 (4)	4 (3)	7 (8)	0	55 (3)
PI and/or NS5A	7 (6)	12 (8)	7 (8)	4 (7)	83 (4)
HCV RNA ≥1,000,000 IU/mL, n (%)	65 (60)	86 (56)	49 (58)	30 (56)	1177 (60)
HCV genotype, n (%)[c]					
1	47 (43)	82 (53)	33 (39)	17 (31)	819 (42)
Subtype 1a	28 (26)	42 (27)	18 (21)	11 (20)	387 (20)
Subtype 1b	19 (17)	39 (25)	15 (18)	6 (11)	426 (22)
Other	0	1 (<1)	0	0	6 (<1)
2	34 (31)	27 (18)	14 (17)	9 (17)	382 (19)
3	19 (17)	27 (18)	34 (40)	17 (31)	546 (28)
4	8 (7)	14 (9)	3 (4)	8 (15)	149 (8)
5	1 (<1)	3 (2)	0	2 (4)	26 (1)
6	0	1 (<1)	0	1 (2)	46 (2)
Fibrosis stage, n (%)					
F0–F1	58 (53)	84 (55)	50 (60)	37 (69)	1422 (72)
F2	9 (8)	15 (10)	8 (10)	0	133 (7)
F3	14 (13)	25 (16)	7 (8)	8 (15)	191 (10)
F4	28 (26)	30 (19)	19 (23)	9 (17)	217 (11)
Missing	0	0	0	0	5

BMI, body mass index; HCV, hepatitis C virus; IFN, interferon; PI, protease inhibitor; PPI, proton pump inhibitor; RBV, ribavirin; SOF, sofosbuvir.
[a]PPI use was subdivided into low- or high-dose PPI as defined by daily dose-equivalent of omeprazole where patients receiving at least 1 dose of greater than a 20-mg omeprazole equivalent were classified as high-dose PPI users.
[b]Includes 3 patients with missing values for race.
[c]HCV genotype and subtype from phylogenetic analysis or central laboratory if phylogenetic result was not available.

use subdivided into those taking high- or low-dose PPI. Overall, patients taking concomitant ARAs were older, had higher body mass index, and more frequently had F4 fibrosis, but were otherwise similar to patients taking no ARAs. Although patients receiving 1 dose of ARA were included in this analysis, concomitant use of each ARA occurred throughout most G/P treatment (Table 2).

Efficacy Outcomes

Overall SVR12 rates in the ITT population were 97.5% (1918/1968; 95% CI, 96.7–98.1) in patients not concurrently taking ARAs compared with 97.0% (389/401; 95% CI, 94.8–98.3) in patients taking ARA (Fisher exact test, $P = .6$). Among the patients taking an ARA, SVR12 rates were 97.0% (255/263; 95% CI, 94.1–98.5), 98.8% (83/84; 95% CI, 93.6–99.8), and 94.4% (51/54; 95% CI, 84.9–98.1) in patients taking PPIs, H_2 blockers, or antacids, respectively (Figure 1*A*). The mITT SVR12 rates were 98.5% (1918/1947; 95% CI, 97.9–99.0) in patients not taking any ARAs compared with 99.6% (255/256; 95% CI, 97.8–99.9), 98.8% (83/84; 95% CI, 93.6–99.8), and 96.2% (51/53; 95% CI, 87.2–99.0) in patients taking PPIs, H_2 blockers, or antacids, respectively (Figure 1*A*). SVR12 rates stratified by genotype are reported in Figures 1*B* and 1*C*.

Table 2. Mean Duration of G/P Treatment and Concomitant Acid-Reducing Drug Use

Group	Concurrent ARA and G/P duration mean (range), d	G/P treatment duration mean (range), d
PPI use (n =263)	65.2 (1–114)	78.9 (27–114)
High-dose PPI (n = 109)	61.4 (1–112)	77.2 (27–113)
Low-dose PPI (n = 154)	67.9 (1–114)	80.1 (36–114)
H_2 blocker use (n = 84)	67.8 (1–115)	79.4 (46–115)
Antacid use (n = 54)	59.4 (1–112)	78.0 (5–113)

ARA, acid-reducing agent; G/P, glecaprevir/pibrentasvir; PPI, proton pump inhibitor.

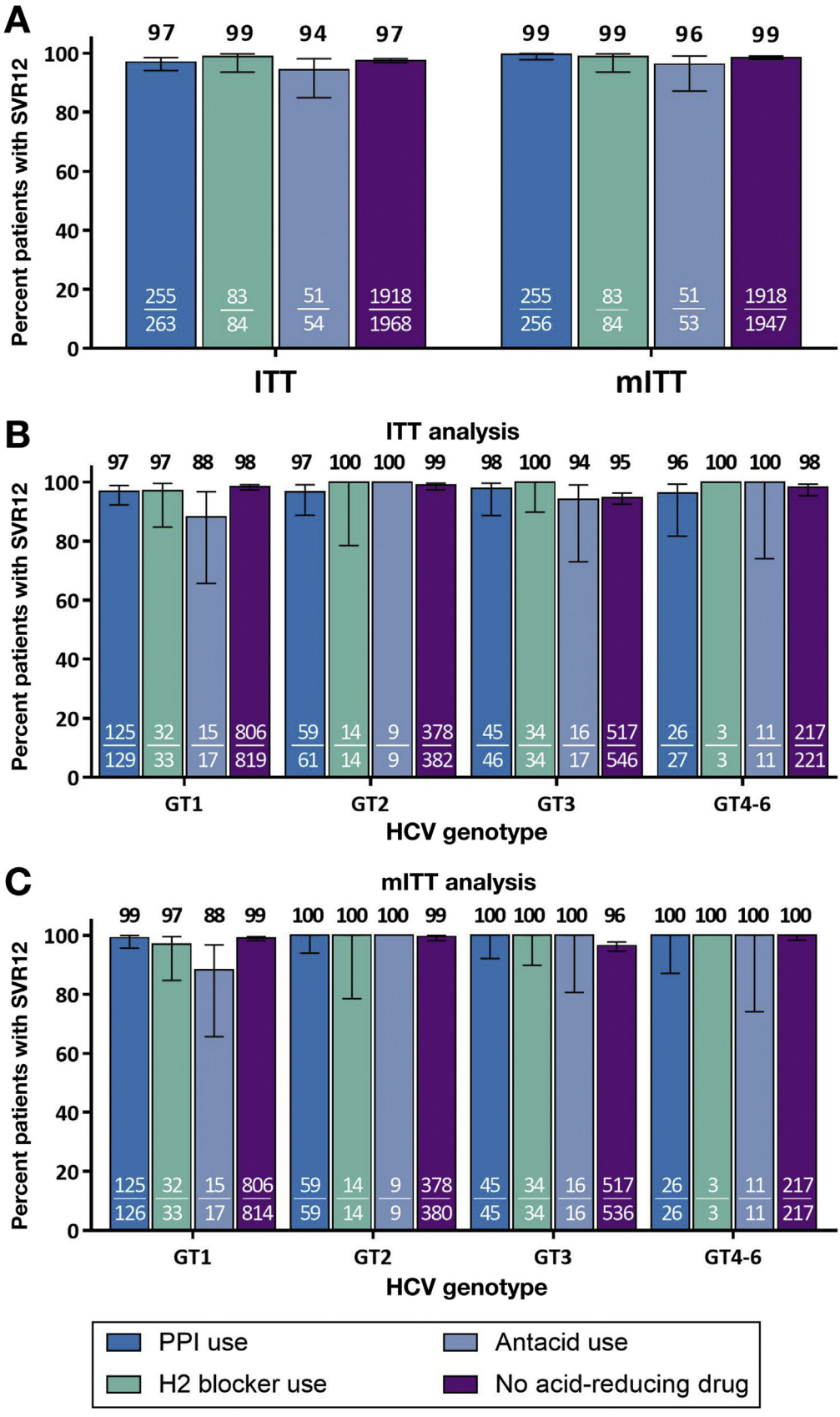

Figure 1. SVR12 for each ARA by ITT and mITT analyses. G/P efficacy defined as SVR12 reported for each ARA overall (*A*) by ITT and mITT analyses. SVR12 data further stratified by HCV genotype for each ARA using ITT (*B*) and mITT (*C*) analyses.

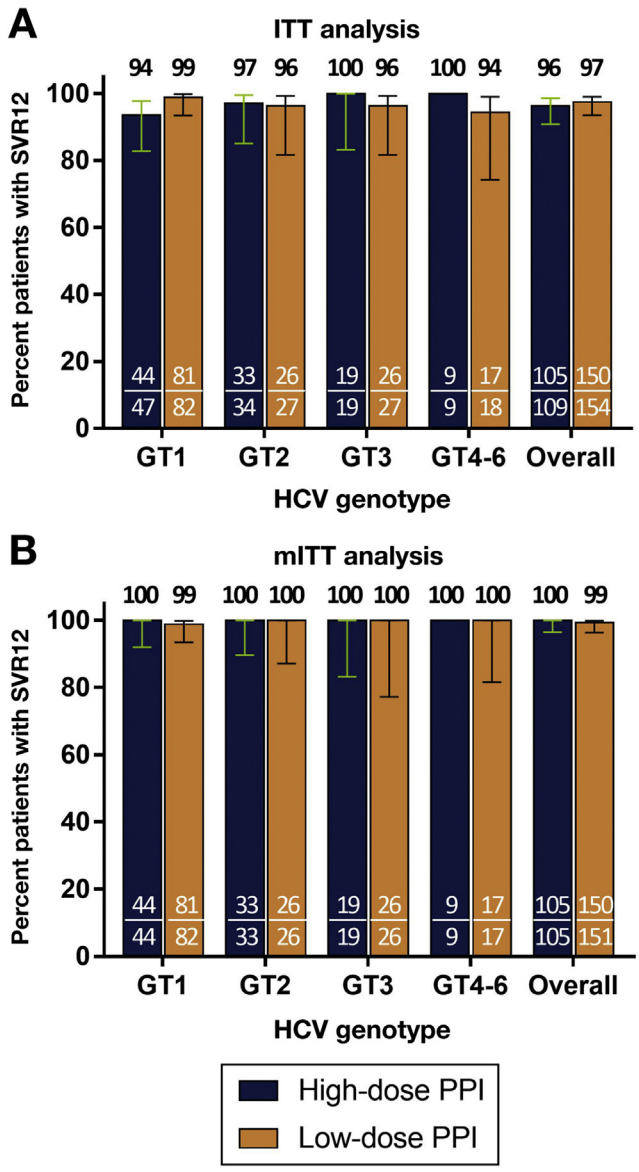

Figure 2. SVR12 for high- and low-dose PPI users by ITT and mITT analyses. G/P efficacy defined as SVR12 reported overall and stratified by HCV genotype for each ARA using ITT (*A*) and mITT (*B*) analyses.

Overall SVR12 rates were further stratified for patients taking PPIs into those using high- or low-dose PPI regimens based on a 20-mg omeprazole dose-equivalent as defined in the Methods section (Figure 2). Across all genotypes, SVR12 rates in the ITT population were 96.3% (105/109; 95% CI, 90.9–98.6) and 97.4% (150/154; 95% CI, 93.5–99.0) in patients taking high- or low-dose PPI regimens, respectively (Figure 2*A*; Fisher exact test, $P = .7$). The mITT SVR12 rates were 100% (105/105) for the high-dose PPI users and 99.3% (150/151) for the low-dose PPI users (Figure 2*B*).

The rate of virologic failure across all patients using an ARA was less than 1% (4/401) compared with 1.5% (29/1968) in patients not taking any ARAs (Table 3). In patients taking antacids, there were 2 (4%) virologic failures, specifically 1 breakthrough at Day 89 and 1 relapse at post-treatment week 4 following 12-week G/P treatment, in which these GT1a-infected patients were treatment-experienced with both a protease inhibitor and NS5A inhibitor. Similarly, in patients taking H_2 blockers, there was 1 (1%) breakthrough at Day 46 leading to treatment discontinuation, in which the GT1a-infected patient was treatment-experienced with both a protease inhibitor and NS5A inhibitor. In patients taking low-dose PPIs, 1 (<1%) relapse occurred by post-treatment week 12 in a GT1a-infected patient who had compensated cirrhosis and prior treatment experience with pegIFN/ribavirin. No patients receiving high-dose PPIs experienced virologic failure (Table 3). More information on these virologic failures is included in the Supplementary Table 2.

Pharmacokinetics

Using a nonlinear mixed effects model, ARAs including those on any PPI dose did not significantly impact glecaprevir or pibrentasvir PK.[23] However, high-dose PPI use significantly decreased glecaprevir bioavailability ($P < .001$), but there was no significant effect on pibrentasvir bioavailability ($P = .345$). Among patients with high-dose PPI use, 24 patients had PK observations both on high-dose PPI and off all PPIs during G/P treatment. Mean glecaprevir AUC decreased 41% when patients were on high-dose PPI (3890 ng*h/mL; range, 1200–15,600) compared with when these patients were off all PPIs (6640 ng*h/mL; range, 2060–26,700).

Safety Outcomes

Overall, 1603/2369 (67.7%) patients experienced a treatment-emergent AE with 12 (0.5%) patients discontinuing because of an AE, 5 (0.2%) of which were considered DAA-related. Seventy-three (3.1%) patients experienced serious AEs, of which only 1 (<0.1%) was determined to be study drug-related. Because of the low rates of serious AEs and subsequent study drug discontinuations, data were not stratified by concomitant ARA use.

Discussion

The once-daily DAA regimen of G/P achieved high SVR12 rates across all HCV genotypes, including in patients with concomitant ARA use. G/P exhibited ≥96% SVR12 rates by mITT analysis across all genotypes for each concomitant ARA used. Despite the reduction in glecaprevir exposure, G/P exhibited 100% SVR12 by mITT analysis with no virologic failures in patients on high-dose PPI. Overall, G/P was well-tolerated with low rates of serious AEs or discontinuations of study drug because of an AE.

Until G/P, a pangenotypic DAA regimen was not available for patients taking ARAs regardless of PPI dose.

Table 3. Summary of Intent-to-Treat Efficacy Outcomes

Outcome	PPI use n = 263		H2 blocker use n = 84	Antacid use n = 54	No acid-reducing drug n = 1968
	High-dose n = 109	Low-dose n = 154			
SVR12, % (n/N) [95% CI]	96.3 (105/109) [90.9–98.6]	97.4 (150/154) [93.5–99.0]	98.8 (83/84) [93.6–99.8]	94.4 (52/54) [84.9–98.1]	97.5 (1918/1968) [96.7–98.1]
Reason for nonresponse, n (%)					
On-treatment virologic failure	0	0	1 (1)	1 (2)	9 (<1)
Relapse	0	1 (<1)	0	1 (2)	20 (1)
Premature study drug discontinuation	2 (2)	1 (<1)	0	1 (2)	8 (<1)
Missing SVR_{12} data	2 (2)	2 (1)	0	0	13 (<1)

CI, confidence interval; PPI, proton pump inhibitor; SVR12, sustained virologic response at post-treatment week 12.

Both LDV and VEL exposures decrease with concomitant PPI use because of their pH-dependent solubility and as such the concomitant use of PPIs was an exclusionary criteria in clinical trials.[5,6] Recent real-world evidence for LDV/SOF demonstrated lower SVR12 rates with high-dose PPIs.[24-26] Phase 3 clinical trials with SOF/VEL (ASTRAL 1-5) and SOF/VEL/voxilaprevir (POLARIS 1-4) excluded concomitant PPI use and restricted use of other ARAs.[27-32] In contrast, G/P demonstrates high SVR12 rates across all genotypes for all ARAs including high-dose PPI despite a 41% reduction in glecaprevir exposure in patients when on high-dose PPI. These data are in agreement with the phase 1 omeprazole drug-drug interaction findings and the reported exposure-efficacy relationship for G/P showing that glecaprevir plasma concentrations are not a significant predictor of SVR12.[22] G/P is now approved in the United States and European Union for concurrent use with ARAs regardless of PPI dose.

Among the patients taking ARAs, less than 1% (4/401) experienced virologic failure, including 2 relapses and 2 on-treatment breakthroughs. Of these 4 patients, both patients with breakthrough and 1 patient with relapse had prior treatment experience with both an NS5A and protease inhibitor. Based on data from G/P's clinical trials and subsequent guidelines, G/P is not recommended for treatment in this dual DAA-experienced patient population.[17,21] SOF/VEL/voxilaprevir can be used in patients taking ARAs with prior treatment experience with both an NS5A and protease inhibitor; however, there are restrictions for its use with ARAs, including limiting PPIs to the low-dose.[6]

There are limitations to this integrated analysis inherent to its design. This was a post hoc analysis integrating data from 9 controlled clinical trials, thus endpoints were not prespecified and the studies were not designed to answer the impact of ARA on efficacy. Patient populations from the real world also may inherently be more heterogeneous than this clinical trial population.

This pooled dataset demonstrated high SVR12 rates across HCV genotypes 1–6, including in patients receiving concurrent ARAs. Although phase 1 data showed decreased glecaprevir exposure when patients were on high-dose PPI, this larger dataset of HCV-infected patients receiving G/P for 8–16 weeks achieved similar efficacy in patients receiving high-dose PPIs or other ARAs compared with those not receiving ARAs. Overall, G/P was well-tolerated with few serious AEs, discontinuations caused by an AE, and DAA-related serious AEs. Thus, G/P is a pangenotypic DAA regimen suitable for patients taking concomitant ARAs, including high-dose PPI.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical*

Gastroenterology and Hepatology at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.07.003.

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Supplementary Appendix

Hepatitis C Virus RNA Assays

For the 201 patients enrolled in phase 2 trials and 203 patients enrolled in the phase 3 SURVEYOR-II Part 4 study, specimen preparation was done manually with the High Pure System and plasma hepatitis C virus (HCV) RNA levels were determined for each sample collected by the central laboratory using the COBAS TaqMan real-time reverse-transcriptase polymerase chain reaction assay version 2.0 (Roche Molecular Diagnostics, Pleasanton, CA), which has a lower limit of quantification of 25 IU/mL, regardless of genotype. The lower limit of detection is 15.0 for genotypes 1 and 3, and 5.6, 12, 3.7, and 20.4 IU/mL for HCV genotype 2 and genotypes 4, 5, and 6, respectively. For patients enrolled in phase 3 trials (n = 1965, excluding the 203 enrolled in SURVEYOR-II Part 4), plasma HCV RNA levels were determined for each sample collected by the central laboratory using the COBAS Ampliprep/TaqMan real-time reverse-transcriptase-polymerase chain reaction assay version 2.0 (Roche Molecular Diagnostics), which has a lower limit of quantification and a lower limit of detection of 15 IU/mL, regardless of genotype.

Eligibility Criteria

Inclusion

1. Male or female, at least 18 years of age at time of screening.
2. If female, subject must be either:
   - Practicing 1 effective method of birth control with male partners from screening to 30 days after stopping study drug
   - Postmenopausal for at least 2 years before screening
   - Or permanently surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or has vasectomized partners
3. Females of childbearing potential must have a negative serum pregnancy test result at screening, and a negative urine pregnancy test at Study Day 1. Females of nonchildbearing potential (either postmenopausal or permanently surgically sterile) at screening do not require pregnancy testing.
4. Sexually active males must be surgically sterile or have male partners only, or if sexually active with female partners of childbearing potential must agree to practice at least 1 effective form of birth control.
5. Screening laboratory result indicating HCV GT1, 2, 3, 4, 5, or 6 infection; infection with more than 1 genotype was not permitted.
6. Subject has positive anti-HCV antibody and plasma HCV RNA viral load $\geq$1000 IU/mL in Phase 3 trials or $\geq$10,000 in Phase 2 trials at screening visit.
7. Chronic HCV infection defined as 1 of the following:
   - Positive for anti-HCV antibody or HCV RNA at least 6 months before screening
   - A liver biopsy consistent with chronic HCV infection
   - Abnormal alanine aminotransferase levels for at least 6 months before screening (only in Phase 3 trials)
8. Subject must be HCV treatment-naive (ie, subject has not received a single dose of any approved or investigational anti-HCV medication) or HCV treatment-experienced (subject has failed prior interferon or pegylated interferon with or without ribavirin or sofosbuvir plus ribavirin with or without pegylated interferon). Previous HCV treatment must have been completed $\geq$2 months before screening.
9. Body mass index is $\geq$18.0 kg/m^2 at the time of screening. Body mass index is calculated as weight measured in kilograms divided by the square of height measured in meters.
10. Subject must be documented as noncirrhotic or cirrhotic defined as meeting 1 of the following criteria:

    Noncirrhotics

    - A liver biopsy within 24 months before or during screening demonstrating the absence of cirrhosis (eg, a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of $\leq$3, Ishak fibrosis score of $\leq$4); or
    - A FibroScan score of $<$12.5 kPa within $\leq$6 months of screening or during screening period (FibroScan must be approved by the local regulatory agency to qualify for entrance criteria); or
      i. Subjects with indeterminate FibroScan score (12.5 $\leq$ score $<$14.6), must have a qualifying liver biopsy
    - A Screening FibroTest score of $\leq$0.48 and aspartate aminotransferase to platelet ratio index (APRI) $<$1
      i. Subjects with indeterminate FibroTest (0.48$<$ result $<$0.75), or conflicting FibroTest and APRI results (eg, FibroTest $\leq$0.48, but APRI $\geq$1) must have a qualifying liver FibroScan or biopsy
11. Subject must voluntarily sign and date an informed consent form, approved by an institutional review board/independent ethics committee before the initiation of any screening or study-specific procedures.
12. Subjects must be able to understand and adhere to the study visit schedule and all other protocol requirements.

For MAGELLAN-I, SURVEYOR-I and -II, and EXPEDITION-1 and -4

Cirrhotic

- Previous histologic diagnosis of cirrhosis on liver biopsy (eg, METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of >3, Ishak score of >4) or on a liver biopsy conducted during screening; or
- A FibroScan score of ≥12.5 kPa within ≤6 months of screening or during screening period (FibroScan must be approved by the local regulatory agency to qualify for entrance criteria); or
- A Screening FibroTest result that is ≥0.75 and an APRI >2.

In the absence of a definitive diagnosis of presence or absence of cirrhosis by FibroTest/APRI using the previously mentioned criteria (indeterminate FibroTest [0.48 < result < 0.75], or conflicting FibroTest and APRI results [eg, FibroTest ≤0.48, but APRI ≥1]), a liver biopsy or FibroScan is required. Liver biopsy results supersede FibroTest/APRI or FibroScan results and are considered definitive. FibroScan results supersede FibroTest/APRI results for the determination of presence or absence of cirrhosis.

13. Cirrhotic subjects only: Compensated cirrhosis defined as Child-Pugh score of ≤6 at screening and no current or past evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites noted on physical examination, hepatic encephalopathy, or esophageal variceal bleeding.
14. Cirrhotic subjects only: Absence of hepatocellular carcinoma as indicated by a negative ultrasound, computed tomography scan, or magnetic resonance imaging within 3 months before screening or a negative ultrasound at screening. Subjects who have an ultrasound with results suspicious of hepatocellular carcinoma followed by a subsequent negative computed tomography or magnetic resonance imaging of the liver are eligible for the study.

For MAGELLAN-1 only

15. 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 include, but are not limited to, daclatasvir + simeprevir, daclatasvir + sofosbuvir, asunaprevir + daclatasvir, sofosbuvir + simeprevir, ombitasvir + paritaprevir/ritonavir for chronic HCV genotype 1 infection, with treatment outcome as either on-treatment virologic failure or
16. Post-treatment relapse, defined as:
    - On-treatment failure: The patient is considered to have experienced on-treatment failure of the prior direct-acting antiviral-containing treatment regimen if the patient did not achieve unquantifiable HCV RNA before 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 the patient was documented to have met futility criteria as defined in the product label (eg, for telaprevir or boceprevir-containing regimens); or
    - Post-treatment relapse: The patient is considered to have experienced post-treatment relapse if the HCV RNA was less than the lower limit of quantification at the planned end of the prior direct-acting antiviral-containing treatment regimen, but was confirmed to be quantifiable after the end-of-treatment
17. Treatment must have been completed at least 1 month before screening visit.

For ENDURANCE-1 only

18. Positive test result for anti–human immunodeficiency virus (HIV) antibody at screening.
19. Naive to treatment with any antiretroviral therapy (ART) (and have no plans to initiate ART treatment while participating in this study), or

    On a stable, qualifying HIV-1 ART regimen for at least 8 weeks before screening. The HIV-1 ART regimen must include at least 1 of the following antiretroviral agents:

    - For cirrhotic and noncirrhotic subjects:
        i. Raltegravir, PO BID
        ii. Dolutegravir, PO QD or PO BID
        iii. Rilpivirine, PO QD
        iv. Elvitegravir/cobicistat, PO QD
    - For noncirrhotic subjects, the following regimens are also allowed:
        i. Darunavir coadministered with ritonavir, PO QD
        ii. Darunavir/cobicistat, PO QD
        iii. Lopinavir/ritonavir, PO BID

    In addition to the previously mentioned medications, subjects (both cirrhotic and noncirrhotic) may take a nucleoside/nucleotide reverse transcriptase inhibitor backbone containing any of the following:

    - Tenofovir disoproxil fumarate, PO QD
    - Tenofovir alafenamide, PO QD

- Abacavir, PO QD or BID
- Emtricitabine, PO QD
- Lamivudine, PO QD or BID

Subjects receiving any other HIV-1 ART in addition to those noted previously are not eligible for enrollment in the study.

20. Subjects naive to ART must have the following:
    - $CD4^+$ count $\geq$500 cells/mm^3 (or $CD4^+$ $\geq$29%) at screening; and
    - Plasma HIV-1 RNA <1000 copies/mL at screening (by the COBAS Ampliprep/COBAS Taqman HIV-1 Test, version 2.0) and at least once during the 12 months before screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS Ampliprep/COBAS Taqman HIV-1 Test, version 2.0 or Abbott RealTime HIV-1 assay).
21. Subjects on a stable ART regimen must have the following:
    - $CD4^+$ count $\geq$200 cells/mm^3 (or $CD4^+$ $\geq$14%) at screening; and
    - Plasma HIV-1 RNA below lower limit of quantification at screening (by the COBAS Ampliprep/COBAS Taqman HIV-1 Test, version 2.0) and at least once during the 12 months before screening (by an approved plasma HIV-1 RNA quantitative assay including but not limited to: COBAS Ampliprep/COBAS Taqman HIV-1 Test, version 2.0 or Abbott RealTime HIV-1 assay).

For EXPEDITION-4 only

22. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 as estimated by the modification of diet in renal disease method at screening according to the following formula.
    - Estimated glomerular filtration rate (mL/min/1.73 m^2) = 175 $\times$ (serum creatinine)$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ (0.742 if female) $\times$ (1.212 if black), or hemodialysis-dependent.
    - Patients requiring dialysis should have been receiving hemodialysis for at least 1 month before enrollment.

Exclusion

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study; or a male whose partner is pregnant or planning to become pregnant during the study.
2. Recent (within 6 months before study drug administration) history of drug or alcohol abuse that could preclude adherence to the protocol in the opinion of the investigator.
3. Subjects on peritoneal dialysis.
4. Positive test result at screening for hepatitis B surface antigen (for all HCV genotypes 1–6) or HIV antibody (for HCV genotypes 2–6).
5. HCV genotype performed during screening indicating coinfection with more than 1 HCV genotype.
6. Requirement for and inability to safely discontinue the medications or supplements listed in Supplementary Table 1 at least 2 weeks or 10 half-lives (whichever is longer) before the first dose of any study drug.
7. Clinically significant abnormalities or comorbidities, other than HCV/HIV-1 coinfection, based on the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram that make the subject an unsuitable candidate for this study in the opinion of the investigator, including, but not limited to:
    - Uncontrolled diabetes as defined by a glycated hemoglobin (hemoglobin A_{1C}) level >8.5% during screening.
    - Active or suspected malignancy or history of malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric, or other medical disease or disorder, which is unrelated to the existing HCV infection.
8. Any cause of liver disease other than chronic HCV infection, including but not limited to the following:
    - Hemochromatosis
    - α_1-Antitrypsin deficiency
    - Wilson disease
    - Autoimmune hepatitis
    - Alcoholic liver disease
    - Steatohepatitis on liver biopsy considered to be the primary cause of the liver disease rather than concomitant/incidental with HCV infection
9. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Alanine aminotransferase >10 $\times$ ULN (upper limit of normal)
    - Aspartate aminotransferase >10 $\times$ ULN
    - Calculated creatinine clearance (using Cockcroft-Gault method) of <50 mL/min except in EXPEDITION-4
    - Direct bilirubin greater than ULN
    - Albumin <3.0 g/dL

- International normalized ratio $>1.5 \times$ ULN, unless subject has known hemophilia or is on a stable anticoagulant regimen affecting international normalized ratio
- Hemoglobin <10 g/dL for women; <11 g/dL for men
- Platelets $<60{,}000$ cells/mm^3 for subjects with cirrhosis; $<90{,}000$ cells/mm^3 for subjects without cirrhosis

10. History of solid organ transplantation.
11. Receipt of any investigational product within a time period equal to 10 half-lives of the product, if known, or a minimum of 6 weeks (whichever is longer) before study drug administration.
12. Any current or past clinical evidence of decompensated liver disease, such as ascites noted on physical examination, use of β-blockers for portal hypertension, hepatic encephalopathy or esophageal variceal bleeding.
13. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-493/ABT-530.
14. Requirement for chronic use of systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks), azathioprine, or monoclonal antibodies (eg, infliximab).
15. History of severe, life-threatening, or other significant sensitivity to any excipients of the study drug.
16. Treatment for an AIDS-associated opportunistic infection within 6 months of screening (only in SURVEYOR-I).
17. Patients who cannot participate in the study per local law.

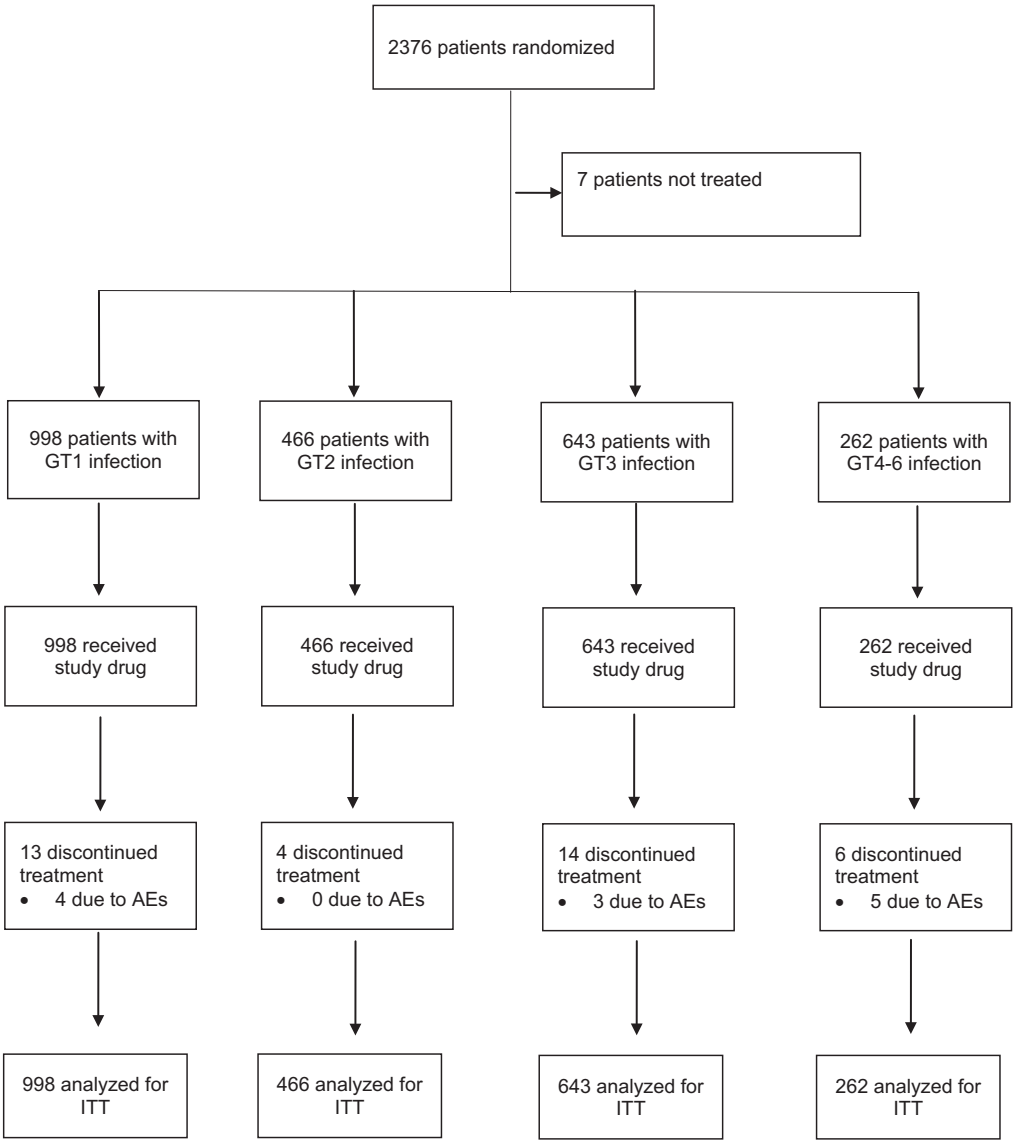
Concomitant Medications

Subjects should be on stable doses of concomitant medications (including, but not limited to, proton pump inhibitors [PPIs] and other acid-reducing agents) for at least 2 weeks before the initiation of study drugs. Investigators advised patients to take PPIs and H_2 blockers once daily 12 hours before glecaprevir/pibrentasvir.

For defining low- and high-dose PPI use, the following parameters were used and are consistent with a 20-mg omeprazole daily dose-equivalent:

Low-dose PPI: up to and including omeprazole, 20 mg, dexlansoprazole, 60 mg, esomeprazole, 20 mg, ilaprazole, 10 mg, lansoprazole, 30 mg, pantoprazole, 20 mg, or rabeprazole, 20 mg total daily dosing.

High-dose PPI: over omeprazole, 20 mg, dexlansoprazole, 60 mg, esomeprazole, 20 mg, ilaprazole, 10 mg, lansoprazole, 30 mg, pantoprazole, 20 mg, or rabeprazole, 20 mg total daily dosing. If a subject received at least 1 daily dose of high-dose PPI, they were classified as a high-dose PPI user.



Supplementary Figure 1. Patient disposition.

Supplementary Table 1. Medications Contraindicated for Use With Study Drug

Prohibited Medications and Supplements
Any herbal supplement (including milk thistle), red yeast rice (monacolin K), St. John's wort
Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
Atorvastatin, lovastatin, simvastatin[a]
Astemizole, cisapride, terfenadine

[a]Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drugs. Subjects receiving these statins should either switch to pravastatin or rosuvastatin before the first dose of study drugs or may interrupt statin therapy throughout the treatment period and until 30 days after the last dose of study drug, based on investigator's judgement. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg QD when taking with the study drugs.

Supplementary Table 2. Characteristics for Each Patient Experiencing Virologic Failure Who Took ARAs During G/P Treatment: Prior Treatment Experience and NS3 and NS5A Polymorphisms at Baseline[a]

Arm	G/P treatment duration	HCV genotype	Concomitant ARA	Failure	Reported previous DAA regimens	NS3 variants[b]	NS5A variants[b]
EXPEDITION-1							
A	12-weeks	1a	Low-dose PPI	Relapse	PR	None	Y93N
MAGELLAN-1							
E	16 weeks	1a	H_2 blocker	Breakthrough	PR; TVR; SIM/SOF; LDV/SOF + RBV; OBV/PTV/r + DSV + RBV	Y56H + Q80K + D168E	K24Q + Y93H
E	16 weeks	1a	Antacid	Breakthrough	OBV/PTV/r + DSV + RBV	Q80K, D168A	Q30H + Y93H
D	12 weeks	1a	Antacid	Relapse	SIM/SOF; LDV/SOF	V36M + Q80L, V55I, R155K	M28V + Q30R

NOTE. NS3/4A protease inhibitors: TVR, SIM, and PTV. NS5A inhibitors: LDV and OBV. NS5B polymerase inhibitors: SOF and DSV.
ARA, acid-reducing agent; DAA, direct-acting antiviral; DSV, dasabuvir; G/P, glecaprevir/pibrentasvir; LDV, ledipasvir; OBV, ombitasvir; PR, pegylated-interferon with ribavirin; PTV, paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
[a]Detection of baseline polymorphisms was done with next-generation sequencing using a 15% detection threshold. For samples with multiple variants (polymorphisms/substitutions) within a target, if individual variants were detected at ≥90% prevalence, they are considered to be linked and denoted by "+," whereas if 1 or more of the variants was detected at <90% prevalence, the variants are separated by a comma.
[b]Amino acid positions included in analysis of patients: 36, 43, 54, 55, 56, 80, 155, 156, 166 (GT3 only), and 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 62 (GT1 only), 92, and 93 in NS5A.