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Effectiveness and safety of glecaprevir/pibrentasvir for 8 weeks in the treatment of patients with acute hepatitis C: A single-arm retrospective study

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Abstract

Background and Aims: No direct-acting antiviral is currently approved for acute HCV infection, delaying treatment. We investigated the effectiveness and safety of 8-week glecaprevir/pibrentasvir (G/P) in patients with acute HCV infection.

Approach and Results: This noninterventional, single-arm, retrospective chart review was designed to enroll adults/adolescents with acute HCV infection. Analyses were conducted on a full analysis set (FAS; all enrolled)

Abbreviations: DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; FAS, full analysis set; G/P, glecaprevir/pibrentasvir; mFAS, modified FAS; PSS, principal safety stratum; PWID, people who inject drugs; SOF/VEL, sofosbuvir/velpatasvir; SVR12, sustained virologic response at posttreatment week 12; TEAE, treatment-emergent adverse event; WHO, World Health Organization.

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and modified FAS (FAS excluding nonvirologic failures). The primary end point (modified FAS) was sustained virologic response at posttreatment week 12 (SVR12) with superiority to 92.6% threshold determined by historic chronic HCV G/P SVR12 rates. Secondary end points (FAS) included SVR12, on-treatment virologic failure, posttreatment relapse, and reinfection. Adverse events and safety laboratory values were assessed. Overall, 202 adults were enrolled; in the modified FAS, 150/151 (99.3%; 95% CI: 96.3–99.9) achieved SVR12, demonstrating superiority to efficacy threshold. In the FAS, the SVR12 rate was 74.3% and the on-treatment virologic failure rate was 0%. Relapse and reinfection rates after the final treatment visit (FAS) were 0.5% and 3%, respectively; 39 patients had missing SVR12 data. No on-treatment alanine aminotransferase elevations $> 3 \times$ upper limit of normal with total bilirubin $> 2 \times$ upper limit of normal were reported. All 53 patients with alanine aminotransferase Grade ≥ 2 at baseline improved to Grade 0/1 on treatment. No adverse eventss of hepatic decompensation/failure or leading to G/P discontinuation occurred. Two patients had serious adverse events unrelated to G/P.

Conclusions: Eight-week G/P therapy was effective and well-tolerated in patients with acute HCV infection. Data support further investigation of G/P in acute HCV to shorten care cascades, reduce transmission, and support HCV elimination.

INTRODUCTION

Chronic HCV infection affects an estimated 58 million people worldwide, with ~1.5 million new infections each year. Following the development and increased availability of highly effective and well-tolerated direct-acting antivirals (DAAs) for the treatment of chronic HCV infection, the World Health Organization (WHO) set a target for the elimination of HCV infection by 2030. While the standard of care for chronic HCV infection is well established, effective treatment options for acute HCV infection need to be approved to meet the WHO elimination targets.[1]

Approximately 20%–30% of patients with acute HCV infection undergo immune-mediated spontaneous viral clearance within 6 months of infection; the remaining 70%–80% of infections progress to chronic hepatitis C.[2] Clearance rates have also been shown to vary among patient populations; a recent study in an HIV-positive cohort of predominantly MSM showed an HCV clearance rate of 11.2%.[3] In the absence of label-approved DAAs for acute HCV infection, treatment is commonly deferred until HCV infection is considered chronic. Thus, the focus of disease management has remained on chronic disease and associated comorbidities despite a large proportion of acute infections progressing to chronic infection.[2]

In recent years, increased rates of acute HCV infections have been observed in key populations, including people who inject drugs (PWID), who are incarcerated and homeless, and those who have MSM (with HIV infection and without).[4–8] Despite the availability of effective treatment for chronic HCV infection, barriers remain in the care cascade, particularly in targeting these key populations.[9] These patient groups may also be at high risk of not returning for follow-up or referral appointments. Under current care cascade models, the waiting period for confirmation of chronicity poses a significant risk for the loss of patients from care.[9–11] Therefore, streamlining the process to start treatment earlier would be key to increasing the likelihood of patients linking to care and initiating and completing treatment. As these patients are also at high risk of transmission to others, earlier intervention may also reduce onward transmission and reinfection, supporting the WHO target of HCV elimination. Danesh et al have used phylogenetic analysis and modelling to study HCV transmission in the MSM population. They determined that the doubling time of the epidemics in the MSM population

is 0.44 years, with a significant amount of transmission occurring in the acute phase of the infection.[12] Additionally, treating acute HCV-infected patients may have economic benefits due to potential cost savings from reduced transmission and the consequent decline in infection rates.[10,13]

Several DAA-based regimens, approved for the treatment of chronic HCV infection, have been assessed in patients with acute/recently acquired HCV infection. For example, REACT was an open-label, randomized, phase IV trial in which a 6-week course of sofosbuvir/velpatasvir (SOF/VEL) failed to demonstrate noninferiority to a 12-week course.[14] HepNet was a phase II, single-arm study that found an 8-week course of SOF/VEL to be effective for patients who adhered to the protocol.[15] Additionally, an open-label, single-arm pilot study found that a 6-week glecaprevir/pibrentasvir (G/P) course remained efficacious, demonstrating a 90% sustained virologic response at posttreatment week 12 (SVR12) rate.[16] Finally, a study of several interferon-free therapies in patients coinfected with HIV given for similar durations as in chronic HCV infection demonstrated an SVR12 rate of 100%. In this study, the overall population included 38, with no more than 16 patients treated with a single regimen.[17] Although evidence exists of the applicability of DAA regimens approved for chronic HCV infection to be used in an acute/recently acquired setting, further studies in acute HCV infection are required.

This noninterventional, retrospective study was designed to assess the effectiveness and safety of an 8-week course of the interferon-free, all-oral DAA G/P in adults and adolescents with confirmed acute HCV infection.

METHODS

Study design

This investigation was a noninterventional, single-arm, retrospective patient chart review study in the United States and Puerto Rico, the United Kingdom, Spain, Italy, France, Canada, and Australia to assess the effectiveness and safety of 8-week G/P for the treatment of acute HCV infection. During the treatment period, G/P was prescribed as 300 mg/120 mg once daily oral tablets. The treatment was either prescribed by the site to the patients in 1 prescription or divided across 2 prescriptions, determined on a site-by-site basis. Pre-existing records of patients meeting the eligibility criteria who were treated at each site from July 26, 2017 (approval of G/P in the European Union), through end dates that were 5 months before site initiation (to allow for enrolled patients to have SVR12 data before site initiation) were assessed by retrospective chart review and entered into the Rave® electronic data capture system (Medidata Solutions Inc., New York, NY, USA). To address potential sampling bias, all patients who were documented in their medical records as meeting the inclusion/exclusion criteria during the predefined study periods were to be included. Data were collected from 6 months before the first dose of G/P to 24 weeks after G/P treatment completion. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. All research was approved by the appropriate ethics and/or institutional review committee(s). No information that would enable the identification of any patients was captured, and all actual dates were anonymized before data entry. In this retrospective analysis of de-identified patient charts, formal patient consent was not required in most regions. To comply with local laws, all French patients were informed that their personal health data from their patient records would be collected and analyzed for this study and were offered the opportunity to decline their inclusion in the study.

Patient eligibility criteria

Eligible patients were adolescents and adults, 12 years of age or older, naïve to HCV treatment for the current infection; PWID and patients with HIV coinfection were not excluded. To qualify for study inclusion, a physician diagnosis of acute HCV infection was required, and patients had to meet at least 1 baseline acute HCV infection criterion:

a) Negative anti-HCV antibody, HCV RNA, and/or HCV core Ag followed by a positive HCV RNA or HCV core Ag followed by initiation of G/P, all within a 9-month period.
b) Negative anti-HCV antibody, HCV RNA, and/or HCV core Ag followed by a positive HCV RNA or HCV core Ag followed by initiation of G/P treatment, all within a 12-month period, and risk behavior for HCV infection within 6 months before positive HCV RNA or HCV core Ag.
c) Clinical signs and symptoms compatible with acute hepatitis (ALT $>$ 5 $\times$ ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen followed by initiation of G/P treatment, all within a 9-month period, and risk behavior for HCV infection within 6 months before positive HCV RNA or HCV core Ag.
d) Negative anti-HCV antibody with a positive HCV RNA or HCV core Ag followed by initiation of G/P treatment, all within a 6-month period.

Additionally, evidence of an 8-week total prescription of G/P and investigator confirmation of the patient having taken at least 1 G/P dose were required.

Patients were excluded from the study if they had a history of liver decompensation or liver or kidney transplant.

Study end points

The primary end point was the achievement of SVR12, defined as HCV RNA < 50 IU/mL between day 57 and day 126 (ie, > 8–≤ 18 wk) after the last dose of G/P, in the modified full analysis set (mFAS). If SVR12 was unavailable, sustained virologic response at posttreatment week 24, defined as HCV RNA < 50 IU/mL between day 127 and day 210 (ie, > 18–≤ 30 wk) after the last dose of G/P was used. If appropriate HCV RNA levels were not available, physician attestation of SVR was used.

Secondary end points assessed outcomes using the full analysis set (FAS) and included achievement of SVR12, on-treatment virologic failure, posttreatment relapse after having completed at least 52 days of treatment, and posttreatment reinfection with HCV. On-treatment virologic failure was defined as breakthrough (≥ 1 measurement of HCV RNA ≥ 100 IU/mL after HCV RNA < 50 IU/mL during treatment) or as end-of-treatment failure (no HCV RNA < 50 IU/mL during treatment, provided the last on-treatment value was on or after 42 days of treatment for a patient who received ≥ 42 d of treatment). Posttreatment relapse was defined as HCV RNA < 50 IU/mL at the end of treatment or the last on-treatment HCV RNA measurement, followed by HCV RNA ≥ 50 IU/mL posttreatment (excluding reinfection). Relapse was also defined as initiating another treatment for HCV infection before SVR12 status was obtained if there was no indication that the patient had been reinfected. Posttreatment reinfection with HCV was defined as confirmed posttreatment relapse with posttreatment detection of an HCV genotype, subtype, or clade that differed from baseline. If appropriate HCV RNA levels were not available, the physician attestation of outcome was used. In addition, if there was no indication in the patient's medical record that the patient did not complete treatment and the investigator could not supply attestation to treatment completion, the patient was considered to have completed treatment and was likely to have end-of-treatment failure or relapse.

Safety was assessed using on-treatment ALT elevations of National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03) Grade 1, 2, 3, or 4 and increased from baseline, on-treatment ALT > 3 × ULN with on-treatment bilirubin > 2 × ULN, reports of treatment-emergent adverse events (TEAEs, defined as adverse events with onset on or after the day of the first G/P dose and no more than 30 days after the last G/P dose) of hepatic decompensation or failure, TEAEs leading to discontinuation of G/P, and serious TEAEs. Each safety end point was assessed for the FAS and the principal safety stratum (PSS).

Statistical analysis

Analysis sets included the FAS (all patients enrolled), the mFAS (all patients in the FAS, excluding those who did not achieve SVR12 for reasons other than virologic failure), and the PSS (all patients in the FAS who had ALT and bilirubin values recorded at both baseline and during G/P treatment).

To determine whether the effectiveness and safety of G/P treatment for acute HCV infection were similar to the established efficacy and safety of G/P treatment for chronic HCV infection, a historic chronic HCV comparator group was identified. For the primary end point, an efficacy threshold was determined based on the weighted average of G/P chronic HCV SVR12 rates for PWID and non-PWID from the G/P US prescribing information Section 14.9,[18] excluding patients who did not achieve SVR12 due to reasons other than virologic failure, and calculated as (proportion of current/recent PWID in the mFAS of current study [0.333] × 98.2%) + (proportion of former/non-PWID in the mFAS of current study [0.667] × 98.8%) − 6% = 92.6%. Demonstration of superiority to this threshold shows noninferiority to the historic chronic HCV SVR12 rate. In addition, a historic chronic HCV comparator group, consisting of all adult and adolescent patients treated with G/P in phase II/III clinical trials (Supplemental Table S1, http://links.lww.com/HEP/I447) who were assigned 8 weeks of G/P and specified whether they were PWID (2598 patients), was used for secondary effectiveness end points.

For data analysis, primary and secondary end points were summarized with numbers and percentages of patients and 2-sided 95% CIs, calculated using the Wilson score method. To assess the primary end point, superiority of 8-week G/P treatment for acute HCV infection to the efficacy threshold was established if the lower bound of the 2-sided 95% CI for the mFAS SVR12 rate was greater than the threshold.

For patients with missing SVR12 results, sustained virologic response at posttreatment week 24 data were used. If sustained virologic response at posttreatment week 24 data were also missing, the patient was considered a nonvirologic failure. Patients who initiated another treatment for HCV without experiencing reinfection were to be considered virologic failures for summaries of viral response at all time points after the start of the new HCV treatment; no patients in the study initiated another HCV therapy.

Enrollment of 135 patients in the mFAS population was determined to provide 90% power to show that an SVR12 rate of 98.2% among patients with acute HCV infection was superior to a historic threshold SVR12 rate of 92.2% based on historic SVR12 rates among

patients with chronic HCV infection using a 2-sided 95% CI. For assessment of safety, enrollment of a sufficient number of patients with acute HCV infection was planned such that 250 patients would be included in the PSS, providing > 91% probability to detect any toxicity/adverse event that occurs in ≥ 1% of the general acute HCV population. However, enrollment was prematurely terminated owing to the inability to meet PSS enrollment requirements.

Role of the funding source

AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data, in the writing, reviewing, and approval of the manuscript, and in the decision to submit the manuscript. No honoraria or payments were made for authorship.

RESULTS

Patient disposition

Overall, 202 adult patients with acute HCV infection were documented in their medical records as meeting the eligibility criteria and were included in the FAS. In the FAS, 67.3% of patients received their medication as 1 prescription and 32.7% as 2 prescriptions. Of the 202 patients, 189 (93.6%) completed G/P treatment and 13 patients (6.4%) discontinued G/P treatment prematurely: 6 (3%) due to noncompliance with the study drug, 2 (1%) lost to follow-up, and 5 (2.5%) for other reasons. In the FAS, patients who discontinued treatment prematurely with < 52 days of study treatment and no evidence of SVR12 response were defined as SVR12 nonresponders, and patients who were lost to follow-up were those who had an unknown SVR12 status and a treatment duration of ≥ 52 days. In the FAS, 51 patients experienced nonvirologic failure: 39 (19.3%) had missing SVR12 data, 6 (3.0%) discontinued G/P prematurely, and 6 (3.0%) had HCV reinfection. The mFAS comprised 151 patients, and the PSS comprised 64 patients (Figure 1). To obtain insights into factors associated with premature discontinuation, we compared the baseline characteristics between patients who discontinued (n = 13) and those who completed the treatment (n = 189; Supplemental Table S2, http://links.lww.com/HEP/I448). Despite the small sample size, we noted a tendency for premature discontinuation among current/recent PWID, patients from North America, and those without HIV coinfection.

Demographic and baseline characteristics

Within the FAS, the majority of patients were former/non-PWID (107/186, 57.5% vs. current/recent PWID: 79/186, 42.5%), male (172/202, 85.1%), White (147/166, 88.6%), diagnosed with HCV genotype 1 (92/170,

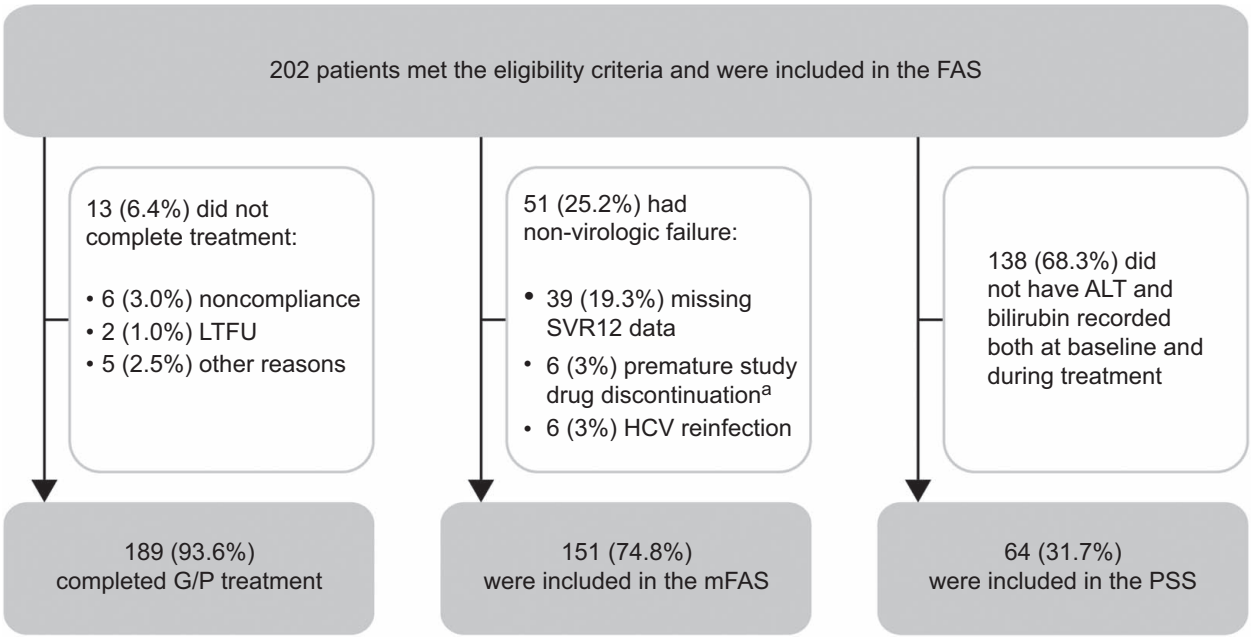


FIGURE 1 Patient disposition. SVR12 nonresponder who received ≥ 52 days of study treatment and did not meet the definitions of reinfection, relapse, or OTVF (EOT failure or breakthrough). Abbreviations: EOT, end of treatment; FAS, full analysis set; G/P, glecaprevir/pibrentasvir; LTFU, lost to follow-up; mFAS, modified FAS; OTVF, on-treatment virologic failure; PSS, principal safety stratum; SVR12, sustained virologic response at posttreatment week 12.

54.1%), without a prior HCV infection (137/200, 68.5%), without cirrhosis (136/138, 98.6%), and with HIV coinfection (99/193, 51.3%); the median (IQR) age of patients was 38.0 (32.0–47.0) years, and the median (IQR) estimated duration of acute HCV infection at G/P start was 99.5 (64.0–137.0) days (Table 1). Patient demographics and baseline characteristics for patients included in the FAS who had nonvirologic failure and for patients with no PSS are reported in Supplemental Tables S3, http://links.lww.com/HEP/I449, and 4, http://links.lww.com/HEP/I450. Of the 6 patients who experienced reinfection, 3 had current or past contact with contaminated needles or IV drug use, 1 had contact with an infected individual, and 2 had no previous risk behaviors. The proportion of patients meeting acute HCV infection criterion "a" was 39.6% (n = 80), "b" was 29.2% (n = 59), "c" was 65.8% (n = 133), and "d" was 13.9% (n = 28; Table 2); patients could meet more than 1 definition.

Effectiveness

In the mFAS, 150/151 patients (99.3%, 95% CI: 96.3–99.9) achieved SVR12, with 1 patient experiencing posttreatment relapse. The lower bound of the 95% CI was above the efficacy threshold of 92.6%, demonstrating superiority to the efficacy threshold and noninferiority to the historic chronic HCV SVR12 rate (Figure 2).

In the FAS, 150/202 patients (74.3%, 95% CI: 67.8–79.8) achieved SVR12, which was lower than that of the historic chronic HCV comparator rate (97.6%, 2536/2598 patients, 95% CI: 97.0–98.1). This was primarily due to a large percentage of patients in the FAS with missing SVR data (19.3%) (Figure 3). SVR12 rates by PWID and HIV status are presented in Supplemental Table S5, http://links.lww.com/HEP/I451.

No cases of on-treatment virologic failure were reported in the FAS (0/202, 95% CI: 0.0–1.9), comparable with 0.2% of patients reported in the historic chronic HCV group (4/2598, 95% CI: 0.1–0.4). A similarly low incidence of relapse was reported for the FAS (1/191 patients, 0.5%, 95% CI: 0.1–2.9), which was also comparable with the historic chronic HCV group (19/2564, 0.7%, 95% CI: 0.5–1.2). Few patients in the FAS had reinfection (6/202 patients, 3%, 95% CI: 1.4–6.3) compared with no cases of reinfection in the historic chronic HCV group (0/2598, 0%, 95% CI: 0.0–0.1). Of the patients who had reinfection in the FAS, 3 were current/recent PWID, 1 was a former PWID, and 2 had unknown PWID status.

Patients excluded from the mFAS due to nonvirologic failure were more likely to be from North America, be current/recent PWID, and have no HIV coinfection compared with patients in the mFAS (Supplemental Table S3, http://links.lww.com/HEP/I449). A similar trend was observed for patients with no PSS compared with those included in PSS (Supplemental Table S4, http://links.lww.com/HEP/I450).

Safety

Two patients experienced on-treatment ALT elevations, both of which were from Grade 0 at baseline to a maximum severity of Grade 1 during G/P treatment (FAS: 2/88 [2.3%], PSS: 2/64 [3.1%]). No on-treatment ALT elevations of Grade 2 or higher that showed worsening from baseline (if the baseline was available) or on-treatment ALT $> 3 \times$ ULN with total bilirubin $> 2 \times$ ULN (values did not need to be concurrent) were reported. These results are comparable to those for the historic chronic HCV group (Table 3).

All patients with an ALT Grade $\geq$ 2 at baseline improved to a severity of Grade 0 or 1 during G/P treatment (FAS: 53/53, PSS: 42/42). One patient with Grade 4 bilirubin levels at baseline had a maximum severity of Grade 4 during G/P treatment, which decreased to Grade 2 while still on treatment. No patient had Grade 3 bilirubin levels at baseline, and of the 5 patients who had Grade 2 bilirubin levels at baseline, all improved to Grade 0 or 1 during G/P treatment (Figure 4).

Two patients (FAS: 2/202 [1.0%], PSS: 2/64 [3.1%]) reported serious TEAEs; 1 patient experienced Grade 3 blood creatinine increase, and 1 patient experienced an increase in bilirubin related to acute HCV infection (as judged by the investigator). Neither serious TEAE was related to G/P. No patient experienced TEAEs of hepatic decompensation or hepatic failure nor TEAEs that led to G/P discontinuation. These low incidences of events are comparable with those seen in the historic chronic HCV group (Table 3). However, the study failed to enroll the protocol-specified number of patients in the PSS to effectively assess liver safety.

DISCUSSION

To achieve the WHO goal of HCV elimination, barriers to care must be addressed, including shortening and streamlining the HCV care cascade. The lack of approved treatments for acute HCV infection can result in the delay of treatment by 6 months or more while waiting for chronicity to be confirmed.[19,20] For vulnerable patients such as PWID, who are often disengaged from traditional care pathways, this may result in loss from care and continued risk for onward transmission. Approval of safe and effective treatments for acute HCV infection remains a key unmet need in the management of hepatitis C.

This study demonstrated the effectiveness of 8-week G/P for acute HCV infection, achieving an

TABLE 1 Patient demographics and baseline characteristics

	FAS (N = 202)	mFAS(N = 151)	PSS (N = 64)	Historic chronic HCV group (N = 2598)
Male	172 (85.1)	132 (87.4)	53 (82.8)	1391 (53.5)
Race	n = 166	n = 133	n = 58	—
White	147 (88.6)	118 (88.7)	53 (91.4)	1455 (56.0)
Black	5 (3.0)	3 (2.3)	1 (1.7)	152 (5.9)
Asian	2 (1.2)	2 (1.5)	1 (1.7)	962 (37.0)
Other[a]	12 (7.2)	10 (7.5)	3 (5.2)	29 (1.1)
Hispanic or Latino	n = 149	n = 116	n = 50	—
	40 (26.8)	36 (31.0)	21 (42.0)	255 (9.8)
Age (y)	38.0 (32.0–47.0)	40.0 (34.0–49.0)	39.5 (32.0–49.0)	53.0 (43.0–61.0)
BMI (kg/m^2)	n = 112	n = 95	n = 52	n = 2597
	22.9 (21.3–25.4)	22.8 (21.3–24.9)	23.4 (21.3–26.0)	25.0 (22.4–28.1)
< 30	108 (96.4)	92 (96.8)	48 (92.3)	2178 (83.9)
Geographic region				
Europe	115 (56.9)	104 (68.9)	48 (75.0)	751 (28.9)
North America	60 (29.7)	37 (24.5)	15 (23.4)	741 (28.5)
Rest of world	27 (13.4)	10 (6.6)	1 (1.6)	1106 (42.6)
Genotype	n = 170	n = 129	n = 58	—
1	92 (54.1)	69 (53.5)	27 (46.6)	1403 (54.0)
2	8 (4.7)	6 (4.7)	4 (6.9)	604 (23.2)
3	44 (25.9)	30 (23.3)	11 (19.0)	368 (14.2)
4	25 (14.7)	24 (18.6)	16 (27.6)	91 (3.5)
5	0	0	0	23 (0.9)
6	1 (0.6)	0	0	109 (4.2)
Fibrosis stage	n = 162	n = 121	n = 54	n = 2235
F0-1	51 (75.0)	41 (77.4)	24 (75.0)	1475 (66.0)
F2	14 (20.6)	9 (17.0)	8 (25.0)	160 (7.2)
F3	2 (2.09)	2 (3.8)	0	253 (11.3)
F4	1 (1.5)	1 (1.9)	0	347 (15.5)
Unknown	94	68	22	0
Noncirrhotic	n = 138	n = 107	n = 52	—
	136 (98.6)	105 (98.1)	52 (100)	2255 (86.8)
HCV RNA level ($\log_{10}$ IU/L)	n = 178	n = 143	n = 62	—
	5.6 (4.7–6.4)	5.6 (4.6–6.4)	5.9 (5.2–6.6)	6.3 (5.7–6.7)
eGFR (mL/min/1.73 m^2)	n = 117	n = 95	n = 44	n = 2573
	91.0 (81.0–107.0)	91.0 (82.0–103.0)	91.0 (82.5–102.7)	91.3 (77.3- 107.0)
ALT (U/L)	n = 191	n = 143	n = 64	—
	201.0 (69.0–425.0)	189.0 (69.0–405.0)	215.0 (76.5–575.0)	45.0 (28.0–80.0)
AST (U/L)	n = 183	n = 138	n = 59	—
	99.0 (44.0–208.0)	92.0 (43.0–199.0)	101.0 (56.0–231.0)	38.0 (28.0–60.0)
Total bilirubin (μmol/L)	n = 179	n = 132	n = 64	—
	11.0 (7.0–15.2)	12.0 (7.5–17.1)	12.0 (7.8–17.1)	9.0 (6.8–13.0)
Platelet count (10^9/L)	n = 181	n = 140	n = 63	n = 2596
	242.0 (199.0–285.0)	244.0 (197.5–282.0)	232.0 (193.0–272.0)	209.5 (168.0–254.0)
Serum albumin (g/L)	n = 119	n = 77	n = 37	—
	42.0 (39.0–45.0)	42.0 (40.0–45.0)	44.0 (41.0–45.0)	44.0 (42.0–46.0)
No prior HCV infection[b]	n = 200	—	—	—
	137 (68.5)	102 (67.5)	45 (70.3)	NA
PWID status	n = 186	n = 144	n = 61	—

TABLE 1. (*continued*)

	FAS (N = 202)	mFAS(N = 151)	PSS (N = 64)	Historic chronic HCV group (N = 2598)
Current/recent PWID	79 (42.5)	48 (33.3)	17 (27.9)	34 (1.3)
Ongoing injection at G/P start	52 (28.0)	35 (24.3)	4 (6.6)	NA
Injecting <6 mo before G/P start	22 (11.8)	9 (6.3)	11 (18.0)	NA
Injecting 6–12 mo before G/P start	5 (2.7)	4 (2.8)	2 (3.3)	NA
Injecting ≤ 12 mo before G/P start	NA	NA	NA	34 (1.3)
Former/non-PWID	107 (57.5)	96 (66.7)	44 (72.1)	2402 (92.5)
Former PWID: Injecting > 12 mo before G/P start	1 (0.5)	1 (0.7)	0	509 (19.6)
Non-PWID	99 (53.2)	91 (63.2)	42 (68.9)	1893 (72.9)
Injection timing unknown	7 (3.8)	4 (2.8)	2 (3.3)	N/A
PWID timing unknown[c]	NA	NA	NA	162 (6.2)
History of opiate substitution therapy	n = 161	n = 125	n = 51	n = 2369
Yes, ongoing at G/P start	36 (22.4)	25 (20.0)	4 (7.8)	NA
Yes, < 6 mo prior to G/P start	2 (1.2)	0	1 (2.0)	NA
Yes, 6–12 mo before G/P start	0	0	0	NA
Yes, > 12 mo before G/P start	1 (0.6)	0	0	NA
Yes, timing unknown	5 (3.1)	3 (2.4)	0	121 (5.1)
No	117 (72.7)	97 (77.6)	46 (90.2)	2248 (94.9)
Risk behavior for HCV infection	n = 192	n = 142	n = 57	n = 955
Contaminated needle or IV drug use	87 (45.3)	55 (38.7)	17 (29.8)	388 (40.6)
Contact with infected individual	74 (38.5)	68 (47.9)	30 (52.6)	92(9.6)
Occupational exposure	0	0	0	11 (1.2)
Blood product transfusion	NA	NA	NA	348 (36.4)
Surgery/operation	NA	NA	NA	63 (6.6)
Vertical transmission	NA	NA	NA	53 (5.5)
None	31 (16.1)	19 (13.4)	10 (17.5)	0
HIV coinfection	n = 193	n = 149	n = 64	nv2598
	99 (51.3)	88 (59.1)	44 (68.8)	156 (6.0)
Estimated duration of acute HCV infection (d)[d]	99.5 (64.0–137.0)	101.0 (64.0–139.0)	104.8 (75.0–144.0)	NA
Estimated duration of acute HCV infection (mo)[d]				
< 3	92 (45.5)	66 (43.7)	26 (40.6)	NA
3–< 6	87 (43.1)	65 (43.0)	30 (46.9)	NA
≥ 6	23 (11.4)	20 (13.2)	8 (12.5)	NA

Note: Data are n (%) or median (IQR). Percentages are calculated on nonmissing, nonunknown values.
[a]Includes American Indian/Alaska Native or Native Hawaiian/Other Pacific Islander or multiple.
[b]Patients had previous HCV infections that were cured before the acute HCV infections under study that were treated with G/P.
[c]Patients with unknown timing in the historic chronic HCV group were not classified as current/recent PWID or former/non-PWID.
[d]Estimated duration of acute HCV infection (days) was calculated as (G/P start date − estimated HCV infection start date) + 1 day. A month was defined as 31 days. The estimated infection start date was defined as follows, using the HCV test(s), which defined the acute diagnosis criteria: criteria (a) and criteria (b), the midpoint between the negative HCV test and the positive HCV test; criteria (c) and criteria (d), 42 days before the date of the positive HCV test. Since a patient could qualify under multiple acute criteria, the following prioritization was used to estimate the infection start date: (d), (a), (b), (c).
Abbreviations: eGFR, estimated glomerular filtration rate; F, fibrosis stage; FAS, full analysis set; G/P, glecaprevir/pibrentasvir; mFAS, modified FAS; NA, not applicable; PSS, principal safety stratum; PWID, people who inject drugs.

SVR12 rate of 99.3% (mFAS) that was noninferior to the established clearance rate of chronic HCV infection after G/P treatment. Importantly, this SVR12 rate is similar to those observed in real-world studies of G/P in chronic HCV infection.[21–24] In addition, the SVR12 rate is substantially higher

TABLE 2 Patients meeting acute HCV infection criteria

Acute HCV infection criteria	FAS (N = 202)	mFAS (N = 151)	PSS (N = 64)
(a) Negative anti-HCV antibody, HCV RNA and/or HCV core Ag followed by a positive HCV RNA or HCV core Ag followed by initiating G/P, all within a 9-month period	80 (39.6)	63 (41.7)	19 (29.7)
(b) Negative anti-HCV antibody, HCV RNA and/or HCV core Ag followed by a positive HCV RNA or HCV core Ag followed by initiation of G/P treatment, all within a 12-month period; and risk behavior for HCV infection within 6 months before positive HCV RNA or HCV core Ag	59 (29.2)	52 (34.4)	12 (18.8)
(c) Clinical signs and symptoms compatible with acute hepatitis (ALT > 5 × ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core Ag followed by initiation of G/P treatment all within a 9-month period; and risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core Ag	133 (65.8)	98 (64.9)	49 (76.6)
(d) Negative anti-HCV antibody with a positive HCV RNA or HCV core Ag followed by initiation of G/P treatment, all within a 6-month period	28 (13.9)	24 (15.9)	7 (10.9)
Meeting criteria a, b, or d	92 (45.5)	73 (48.3)	22 (344)

Note: Data are given as n (%).
Patients could have met more than 1 criterion for defining acute HCV infection.
Abbreviations: FAS, full analysis set; G/P, glecaprevir/pibrentasvir; mFAS, modified FAS; PSS, principal safety stratum.

than those reported for spontaneous clearance of HCV.[2,3]

A small number of studies have evaluated treatments in acute HCV infection, including REACT and HepNet (SOF/VEL), a 6-week G/P study, and a study of IFN-free treatments. However, the studies conducted to date with IFN-free DAAs are heterogeneous in their design, have inconsistent criteria for the diagnosis of acute HCV infection, and include small numbers of patients, limiting their generalizability.[14–17] In this retrospective study, strict criteria related to the duration of HCV infection and other inclusion criteria were used to increase confidence that the cohort of patients had acute HCV infection. This study included key populations, those with HIV coinfection and PWID, who historically have had challenges with adherence but who represent a large and relevant pool of patients with acute HCV.[8,25] Finally, compared with some other studies, a larger number of patients were enrolled,[15–17] therefore providing a more reliable estimate of the SVR12 rate.

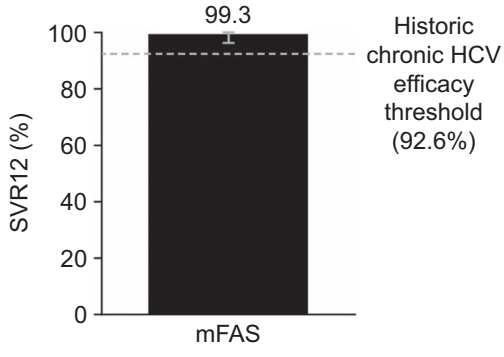
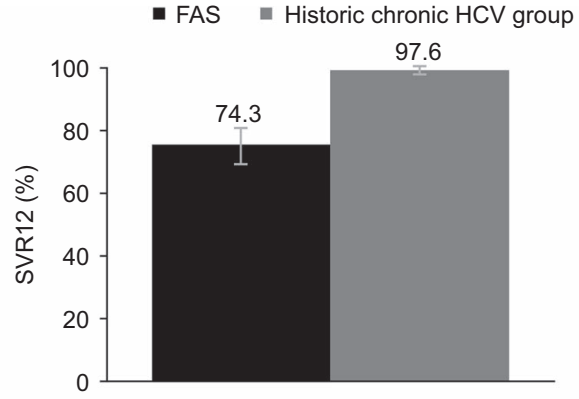


FIGURE 2 Patients achieving SVR12 in the mFAS (primary end point). Error bar represents 95% CI. Abbreviations: mFAS, modified full analysis set; SVR12, sustained virologic response at post-treatment week 12.

Since its approval in 2017, G/P has been shown to have a favorable safety profile for the treatment of patients with chronic HCV infection. In line with this, the historic chronic HCV comparator group included in this study showed low rates of serious TEAEs, TEAEs leading to G/P discontinuation, and TEAEs of hepatic decompensation or failure. Although this study did not enroll the protocol-specified number of patients in the PSS for the analysis of liver safety, only 1% of patients in the FAS experienced a serious TEAE; none were deemed related to G/P. No patients discontinued due to a TEAE or had a TEAE of hepatic decompensation or failure. These results are similar to those observed in real-world studies of patients with chronic HCV,[21–24] and no new or unexpected safety signals were seen in this study.

Elevation of ALT level is frequently observed in patients with acute HCV infection. In this study, all patients with baseline ALT elevations of Grade 2 or higher experienced decreases to Grade 0 or 1 during G/P treatment (53/53 in FAS; 42/42 in PSS). Similar results have been reported in a study on the use of a variety of interferon-free DAA regimens (including G/P) in acute HCV infection, where median ALT levels were decreased significantly within 4 weeks of treatment and remained stable at normal levels.[17] In addition, a study investigating 6-week SOF/VEL therapy in patients infected with acute HCV demonstrated that ALT levels in 85% of patients returned to normal within 4 weeks of treatment initiation.[15]

Although there are currently no US Food and Drug Administration-approved or European Medicines Agency-approved DAAs for the treatment of acute



Outcome	FAS, n/N (%) [95% CI]	Historic chronic HCV group, n/N (%) (95% CI)
On-treatment virologic failure	0/202 [0.1–1.9]	4/2598 (0.2) [0.1–0.4]
Relapse	1/191 (0.5) [0.1–2.9]	19/2564 (0.7) [0.5–1.2]
Reinfection	6/202 (3.0) [1.4–6.3]	0/2598 [0.0–0.1]
Premature G/P discontinuation	6/202 (3.0)	14/2598 (0.5)
Missing SVR12 data	39/202 (19.3)	25/2598 (1.0)

FIGURE 3 Patients achieving SVR12 and reasons for non-SVR12 in the FAS and historic chronic HCV group. Error bars represent 95% CIs. Abbreviations: FAS, full analysis set; G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response at posttreatment week 12.

HCV infection, current treatment guidelines, including the American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and European Association for the Study of the Liver, encourage clinicians to treat HCV infection upon acute diagnosis.[26,27] These data support further clinical investigation of the 8-week G/P regimen in acute HCV to enable the shortening of the care cascade, reducing onward HCV transmission, and helping to achieve HCV elimination. The immediate initiation of DAAs is expected to result in an effective and fast decline in blood HCV RNA levels, which is of particular importance in patients with risk behaviors to reduce the risk of transmission.[28] The regulatory approval of antiviral regimens for acute hepatitis C would remove the need for chronicity testing, simplify decision-making for

TABLE 3 Safety end points

Laboratory values	FAS	PSS	Historic chronic HCV group
On-treatment ALT elevations[ab]			
Grade 1	2/88 (2.3)	2/64 (3.1)	37/2591 (1.4)
Grade 2	0/88	0/64	18/2591 (0.7)
Grade 3	0/88	0/64	11/2591 (0.4)
Grade 4	0/88	0/64	0/2591
Grade ≥3	0/88	0/64	11/2591 (0.4)
On-treatment ALT > 3 × ULN with total bilirubin > 2 × ULN[c]	0/88	0/64	0/2591[d]
Adverse events	N = 202	N = 64	N = 2598
TEAE of hepatic decompensation/failure[e]	0	0	1 (<0.1)
TEAE leading to G/P discontinuation	0	0	6 (0.2)
Serious TEAE	2 (1.0)[f]	2 (3.1)[f]	58 (2.2)

Note: Data are n/N (%) or n (%).
[a]Grade must have been higher than the baseline grade if the baseline value is available. For the historic chronic HCV group, a baseline value was required.
[b]Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
[c]ALT and total bilirubin values not required to be concurrent.
[d]ALT was required to be post-nadir.
[e]Identified using AbbVie product MedDRA Query of "Hepatic decompensation and hepatic failure."
[f]Increased blood creatinine; acute HCV infection.
Abbreviations: FAS, full analysis set; G/P, glecaprevir/pibrentasvir; PSS, principal safety stratum; TEAE, treatment-emergent adverse event.

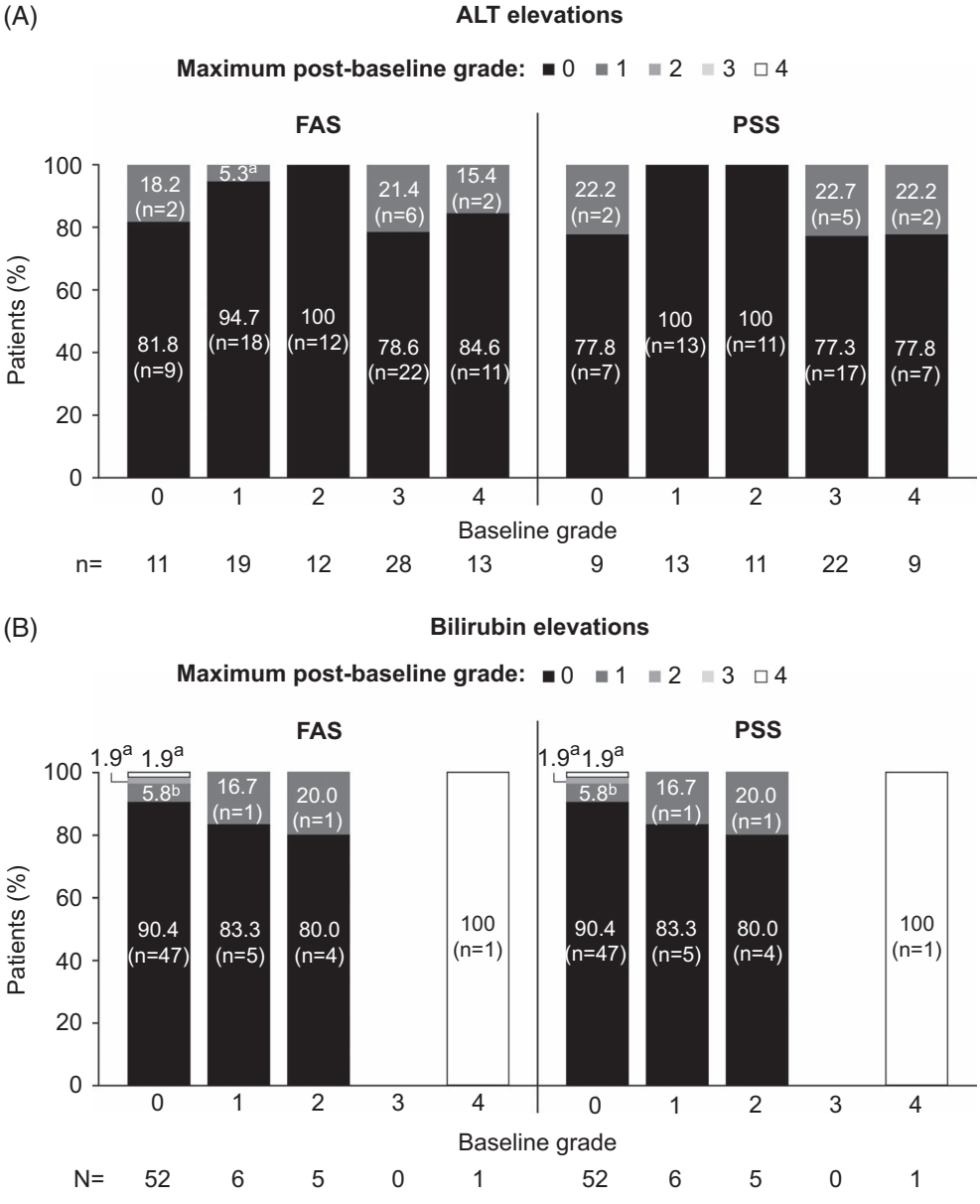


FIGURE 4 Shift from baseline to maximum level in (A) ALT and (B) total bilirubin during G/P treatment (FAS and PSS). [a]n = 1; [b]n = 3. Abbreviations: FAS, full analysis set; G/P, glecaprevir/pibrentasvir; PSS, principal safety stratum.

clinicians, especially those in community settings, prevent loss of patients from care, shorten the time to treatment initiation, and decrease the risk of community transmission.

As a real-world, retrospective analysis of patient charts, this study has limitations, including the dependence on accurate third-party record-keeping and the inability to acquire further data. In particular, the primary effectiveness outcome of this study was limited by the number of patients for whom HCV RNA data were available; physician attestation of SVR status was used for determining SVR12 response when HCV RNA data were unavailable. In mFAS, 118/151 patients (78.1%) achieved SVR12 based on both HCV RNA and physician attestation, 32/151 patients (21.1%) did not have HCV RNA data available and achieved SVR12 based on physician attestation only, and 1/151 (0.7%) failed SVR12 based on both methods. In addition, the lack of a comparison to untreated patients with acute HCV limited this study, although this was mitigated by using the historic chronic HCV cohort as a comparator. Another limitation of this chart review is that safety events outside of those recorded in the patient charts were not documented, owing to potential bias of the safety data. Because on-treatment monitoring of ALT and bilirubin is not recommended in the G/P label or in the European Association for the Study of the Liver (EASL) guidelines, these tests were not routinely conducted, resulting in incomplete records for the majority of patients who were therefore excluded from

the PSS for the analysis of liver safety. Nevertheless, no new safety signals were identified in the acute HCV population compared to the historic chronic HCV population. Overall, this highlights the need for prospective research investigating G/P in acute HCV infection.

In conclusion, 8-week G/P was found to be effective and well-tolerated for the treatment of acute HCV infection, with a high success rate in vulnerable populations. These data support further clinical investigation of the 8-week G/P regimen in acute hepatitis C to prevent the loss of patients from care and reduce onward transmission, ultimately contributing to the achievement of HCV elimination.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/

AUTHOR CONTRIBUTIONS

All authors had access to relevant data and participated in the writing, review, and approval of the manuscript. Stanislas Pol, Alexander J. Thompson, Elisa Venier, Laurent Cotte, Montserrat Laguno Centeno, Jorge Mera, Thomas Reiberger, and Joseph S. Doyle all contributed to the interpretation of the data and critical revision of the manuscript. Michelle Collins, Margaret Burroughs, Dimitri G. Semizarov, Alexandru M. Iacob, Anne Welhaven, and Linda M. Fredrick all contributed to the study concept and design, analysis and interpretation of the data, drafting the manuscript, and critical revision of the manuscript.

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CONFLICTS OF INTEREST

Stanislas Pol advises, is on the speakers' bureau, and received grants from AbbVie and Gilead. He consults and is on the speakers' bureau for Janssen, MSD, Biotest, LFB, Shinogi, and ViiV. He consults for Novo Nordisk. Alexander J. Thompson consults, advises, is on the speakers' bureau, and received grants from AbbVie, Gilead, and Roche. He consults for Assembly and Bristol Meyers Squibb. Michelle Collins is employed and owns stock in AbbVie. Elisa Venier advises, is on the speakers' bureau, and received grants from ElisaVenierMPC. Laurent Cotte received grants from AbbVie, Gilead, MSD, and ViiV. Monserrat Laguno Centeno is on the speakers' bureau and received grants from AbbVie, Gilead, Janssen, and ViiV. He received grants from MSD. Jorge Mera advises, is on the speakers' bureau, and received grants from AbbVie. He advises and received grants from Gilead. He advises Roche. He received grants from Merck. Thomas Reiberger consults, is on the speakers' bureau, and received grants from AbbVie, Gilead, Intercept, and MSD. He consults and received grants from Boehringer Ingelheim and Siemens. He is on the speakers' bureau and received grants from Gore and Roche. He consults for Bayer. He received grants from MYR, Philips Healthcare, and Pliant. Margaret Burroughs is employed and owns stock in AbbVie. Dimitri G. Semizarov is employed and owns stock in AbbVie. Alexandru M. Iacob is employed and owns stock in AbbVie. Anne Welhaven is employed and owns stock in AbbVie. Linda M. Fredrick is employed and owns stock in AbbVie. Joseph S. Doyle is on the speakers' bureau and received grants from AbbVie. He received grants from Gilead.

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