Accepted Manuscript

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PII: S1542-3565(17)31162-X
DOI: [10.1016/j.cgh.2017.09.027](https://doi.org/10.1016/j.cgh.2017.09.027)
Reference: YJCGH 55459

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 8 September 2017

Please cite this article as: Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, Colombo M, Calinas F, Aguilar H, de Ledinghen V, Mantry PS, Hezode C, Marinho RT, Agarwal K, Nevens F, Elkhashab M, Kort J, Liu R, Ng TI, Krishnan P, Lin C-W, Mensa FJ, Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients with HCV Genotype 2, 4, 5, or 6 Infection Without Cirrhosis, *Clinical Gastroenterology and Hepatology* (2017), doi: 10.1016/j.cgh.2017.09.027.

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Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients with HCV Genotype 2, 4, 5, or 6 Infection Without Cirrhosis

Short Title: Glecaprevir/pibrentasvir for HCV Infection

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Abbreviations: HCV, hepatitis C virus; G/P, glecaprevir/pibrentasvir; DAA, direct-acting antiviral; SVR12, sustained virologic response 12 weeks post-treatment; LLOQ, lower limit of quantification; SOF, sofosbuvir; IFN, interferon; RBV, ribavirin; NS, non-structural protein; ITT, intent to treat; mITT, modified ITT; ALT, alanine aminotransferase; AST, aspartate aminotransferase

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DISCLOSURES

The design, study conduct, analysis, and financial support of the studies were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the content. All authors had access to all relevant data and participated in writing, review, and approval of this manuscript.

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KV Kowdley: Grant/Research Funding: Gilead, AbbVie, Merck, Trio Health Advisory Group; Consultant/Advisor: AbbVie, Gilead, Merck, Trio Health Advisory Group; Speakers Bureau: Gilead

T Hassanein: Research/grant support AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Gilead, Idenix, Ikaria, Janssen, La Jolla Pharmaceuticals, Merck, Mochida, NGM BioPharmaceuticals, Obalon, Roche, Ocera, Sundise, Salix, Taigen, Takeda, Tobira, Trek Therapeutics, Vertex, Vital Therapies; Speaker: AbbVie, Baxter, Bristol-Myers Squibb, Gilead, Janssen, Salix; Advisor: AbbVie, Bristol-Myers Squibb.

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P Mantry: Grant/Research funding: AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Mass Biologics, Merck, Bayer-Onyx, Santaris, Salix, Vital Therapies, Tacere, Shinogi; Tobira, Intercept, GSK, Novartis, Consultant/Advisor: AbbVie, BMS, Gilead, Johnson

and Johnson, Merck, Salix, Genentech, Fees for Non-CME/CE services: Bristol Myers Squibb, Gilead, Merck, Salix, Intercept, Abbvie

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WRITING ASSISTANCE: Zoe Hunter, Ph.D. of AbbVie, Inc. provided medical writing support.

AUTHOR CONTRIBUTIONS

Federico Mensa, Neddie Zadeikis, Stanley Wang, Jens Kort, Tarik Asselah, Kris Kowdley, Tarek Hassanein, Ran Liu, Teresa I. Ng, and Chih-Wei Lin participated in the design of the study. Tarik Asselah, Kris Kowdley, Tarek Hassanein, Christophe Hezode, Parvez Mantry, Humberto Aguilar, Kosh Agarwal, Frederik Nevens, Magdy Elhashab, Rui Tato Marinho, Victor de Ledinghen, Yves Horsmans, Massimo Colombo, and Filipe Calinas conducted the study and collected data. Ran Liu, Teresa I. Ng, and Chih-Wei Lin participated in data analysis. All authors participated in the interpretation of the data, preparation, review and approval of the manuscript, as well as the decision to submit for publication.

Background & Aims: Hepatitis C virus (HCV) has high genotypic diversity and global distribution. Agents that are effective against all major HCV genotypes, with shorter treatment duration, are needed to reduce disease burden. Glecaprevir (an NS3/4A protease inhibitor) and pibrentasvir (an NS5A inhibitor) have a high barrier to resistance and synergistic antiviral activity. We evaluated the safety and efficacy of 8 and 12 weeks' treatment with glecaprevir/pibrentasvir in patients with HCV genotype 2, 4, 5, or 6 infection without cirrhosis in 3 separate phase 3 trials.

Methods: We performed 2 open label, single-arm studies (SURVEYOR-II, Part 4 and ENDURANCE-4) and a randomized, double-blind, placebo-controlled study (ENDURANCE-2). In the ENDURANCE-2 study, adult patients with untreated or previously treated HCV genotype 2 infection without cirrhosis were randomly assigned (2:1) to groups given once-daily oral glecaprevir/pibrentasvir (n=202; 300 mg/120 mg) or placebo (n=101) for 12 weeks. In the SURVEYOR-II, Part 4 and ENDURANCE-4 studies, adult patients with untreated or previously treated patients with HCV genotype 2, genotype 4, genotype 5, or genotype 6 infection, without cirrhosis, were given once-daily oral glecaprevir/pibrentasvir (n=121 in ENDURANCE-4 and n=145 in SURVEYOR-II) for 12 or 8 weeks, respectively. In all studies the primary endpoint was sustained virologic response at 12 weeks after treatment (SVR12) in the intention-to-treat population.

Results: Among patients receiving glecaprevir/pibrentasvir for 8 weeks, rates of SVR12 were 98% (95% CI, 94.1–99.3) in those infected with HCV genotype 2 and 93% (95% CI, 83.6–97.3) in those infected with HCV genotypes 4, 5, or 6. Among patients receiving glecaprevir/pibrentasvir for 12 weeks, rates of SVR12 were 99.5% (95% CI, 98.5–100) in those infected with HCV genotype 2 and 99% (95% CI, 97.6–100) in those infected with HCV genotype 4, 5, or 6. No virologic failures occurred in patients with HCV genotype 4, 5, or 6 infections. The frequency and severity of adverse events in patients receiving glecaprevir/pibrentasvir were similar to those of patients who received placebo.

Conclusion: In 3 Phase 3 studies, 8 weeks' treatment with glecaprevir/pibrentasvir produced an SVR12 in at least 93% of patients with chronic HCV genotype 2, 4, 5, or 6 infection without cirrhosis, with virologic failure in less than 1%. The drug combination had a safety profile comparable to 12 week's treatment with glecaprevir/pibrentasvir. ClinicalTrials.gov numbers: NCT02640482 (ENDURANCE-2), NCT02636595 (ENDURANCE-4), and NCT02243293 (SURVEYOR-II)

KEY WORDS: direct-acting antiviral, DAA, short-duration, pangenotypic

INTRODUCTION

Hepatitis C virus (HCV) genotypes 2, 4, 5, and 6 account for approximately 23% of the estimated 80 million HCV viremic infections worldwide¹. Of the 6 major HCV genotypes, genotypes 4 and 6 have the most genetic diversity, and together account for approximately 50% of the 67 known HCV subtypes^{2,3}. Direct-acting antiviral (DAA) therapies for HCV infection have vastly improved treatment options and outcomes for infected patients⁴. Rates of cure, as measured by sustained virologic response (HCV RNA below the lower limit of quantification [LLOQ]) 12 weeks post-treatment (SVR12), range from 89–100% for the six major HCV genotypes when treated according to label guidelines⁵⁻⁸. For the majority of approved treatments, United States and European guidelines recommend 12-week treatment durations^{9, 10}. At the time of study design, an approved, RBV-free regimen with a treatment duration shorter than 12 weeks was unavailable for patients with HCV genotype 2, 4, 5 or 6 infection. Eight-week treatments were available with restrictions in patients with genotype 1 infection only, highlighting the unmet need for pangenotypic 8-week treatment options for patients infected with other HCV genotypes^{7, 10}. A safe, effective pangenotypic HCV treatment option with a shorter treatment duration may require fewer medical resources and allow for the treatment of more patients worldwide.

Glecaprevir (NS3/4A protease inhibitor identified by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor) each demonstrate a high barrier to resistance in vitro; in combination, they demonstrate synergistic antiviral activity¹¹. In the phase 2 studies SURVEYOR-I Part 2 and SURVEYOR-II Parts 1 and 2, 8-week treatment with all oral, once-daily, RBV-free 300 mg glecaprevir plus 120 mg pibrentasvir yielded SVR12 rates of 97-98% in patients with genotype 1-3 infection; 12-week treatment yielded a 100% SVR12 rate in patients with genotype 4-6 infection¹².

Here, we report the primary safety and efficacy results from three registrational studies investigating 8- or 12-week treatment durations of co-formulated glecaprevir/pibrentasvir (G/P) in patients with chronic HCV genotype 2, 4, 5 or 6 infection without cirrhosis.

METHODS

Patients

The three studies had the same eligibility criteria. Eligible patients with at least a 6-month history of HCV genotype 2, 4, 5, or 6 infection were aged 18 years or older, with a BMI of 18 kg/m² or more, and could be either HCV treatment-naïve or experienced with IFN or pegylated IFN (pegIFN) with or without RBV, or sofosbuvir (SOF) plus RBV with or without pegIFN. Absence of cirrhosis was documented by liver biopsy, transient elastography or serum markers. Patients co-infected with HIV, HBV, more than one HCV genotype, and patients with creatinine clearance below 50 mL/min were excluded. Complete inclusion/exclusion criteria for each study and cutoffs for cirrhosis assessments are listed in the Supplement. All patients provided written informed consent. ENDURANCE-2 (NCT02640482), ENDURANCE-4 (NCT02636595), and SURVEYOR-II (NCT02243293) were designed and conducted according to Good Clinical Practice guidelines, Declaration of Helsinki, and applicable local regulations, with independent ethics committee or institutional review board approval for all study sites.

Design

The three studies were conducted at over 60 clinical sites; G/P was dosed as three coformulated 100 mg/40 mg oral tablets taken once-daily with food, for a total dose of 300 mg/120 mg. All authors had access to the study data, and reviewed and approved the final manuscript for submission.

ENDURANCE-2 was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study. HCV genotype 2-infected, non-cirrhotic patients treated for 12 weeks were randomized in a 2:1 ratio to receive either G/P or placebo during the double-blind treatment period. Patients randomized to the placebo arm received open-label G/P for 12 weeks following completion of placebo (data not included). Randomization was stratified by treatment experience.

ENDURANCE-4, an open label, multicenter, single arm, phase 3 study, evaluated 12 weeks of G/P in non-cirrhotic patients with HCV genotype 4, 5 or 6 infection.

SURVEYOR-II Part 4 was an open label, multicenter, single arm, phase 3 study that evaluated 8 weeks of G/P in non-cirrhotic patients with HCV genotype 2, 4, 5 or 6 infection.

Assessments

HCV genotype and subtype were determined at screening using the Versant® HCV Genotype Inno LiPA Assay, version 2.0 (Siemens Healthcare Diagnostics, Tarrytown, NY), and confirmed by phylogenetic analysis of viral sequences. Plasma HCV RNA was quantified by PCR; assay details are described in the supplement. Next-generation sequencing was conducted on samples from all patients at baseline; presence of baseline polymorphisms in NS3 and NS5A relative to subtype specific reference sequence was evaluated using a 15% detection threshold. Treatment-emergent substitutions were analyzed for patients with virologic failure. Treatment compliance was determined by pill count.

Adverse events and clinical laboratory abnormalities were monitored in all patients who received at least one dose of study drug.

Endpoints

The primary efficacy endpoint for each of the three studies was the percentage of patients achieving SVR12, assessed in patients who received at least one dose of study drug. Secondary endpoints included the proportion of patients with on-treatment virologic failure and post-treatment relapse.

Statistical Analyses

All analyses were conducted according to the pre-specified statistical analysis plan for each study. Data from the three studies were not pooled, and no post-hoc efficacy analyses were conducted comparing 8- versus 12-week treatment. All efficacy analyses were performed on the intention-to-treat (ITT) population unless otherwise specified. Statistical tests and confidence intervals were two-sided with a significance level of 0.05. For 8-week treatment duration efficacy analyses, confidence intervals were calculated using the Wilson Score method. For 12-week treatment duration efficacy analyses and all superiority and non-inferiority analyses, confidence intervals were calculated using the normal approximation to the binomial distribution. For all other secondary endpoints and subgroup analyses, confidence intervals were calculated using the Wilson Score method.

Among genotype 2-infected patients treated for either 8 (SURVEYOR-II, Part 4) or 12 (ENDURANCE-2) weeks, the primary efficacy analysis was non-inferiority to the SVR12 rate of the standard-of-care at the time of study design (95% with 12-week SOF/RBV). Patients who failed a previous sofosbuvir-containing regimen were excluded from the primary analysis, and the SVR12 rate in this population was separately assessed. For HCV genotype 2-infected SOF-naïve patients treated for 8 weeks, a sample size of 90 patients, assuming an SVR12 rate of 97%, would provide greater than 80% power to demonstrate non-inferiority to the historical standard-

of-care regimen. For HCV genotype 2-infected SOF-naïve patients treated for 12 weeks, a sample size of 180 patients, assuming an SVR12 rate of 96%, would provide greater than 90% power to demonstrate non-inferiority to the historical standard-of-care. Non-inferiority (8 and 12 weeks) was assessed using a 6% margin and demonstrated if the lower confidence bound (LCB) of the 2-sided 95% confidence interval (CI) was greater than 89%.

Superiority to the historical SVR12 rate (95% with SOF/RBV) was also assessed in genotype 2-infected patients treated with G/P for 12 weeks (ENDURANCE-2), and was demonstrated if the LCB of the 2-sided 95% CI for the percentage of SOF-naïve patients with SVR12 was greater than 95%. A fixed sequence testing procedure was used to proceed from the primary efficacy analysis (non-inferiority) to the first secondary efficacy analysis (superiority) in order to control the Type I error rate at 0.05¹³.

Descriptive statistics (number of observations, mean, and standard deviation for continuous variables, and counts and percentages for discrete variables) are provided. SAS software for the UNIX operating system (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

The studies were conducted in 13 countries between October 1st, 2014 and October 25th, 2016. Overall, 145 and 302 genotype 2-, 46 and 76 genotype 4-, 2 and 26 genotype 5-, and 10 and 19 genotype 6-infected patients were treated for 8 and 12 weeks, respectively (**Figures 1, 2**). The baseline demographics and disease characteristics of randomized patients with genotype 2 infection receiving G/P (N=202) versus placebo (N=100) were similar. The majority of patients were treatment-naïve, and the proportion of treatment-experienced patients treated for 8 weeks was lower than those treated for 12 weeks (**Table 1**). The majority of patients infected with genotype 2, 4 or 6 had baseline polymorphisms in NS5A but none in NS3 (**Table 2**). In genotype

2a-infected patients, M31 in NS5A was the predominant polymorphism (20/21 [95%] and 64/70 [91%] in genotype 2a patients treated for 8 and 12 weeks, respectively) [eTable 2].

Efficacy of G/P Treatment

Efficacy and reasons for non-response for each study are shown in **Table 3** and **eFigure 1**.

ENDURANCE-2

In HCV genotype 2-infected, SOF-naïve patients, 12-week G/P yielded an SVR12 rate of 99% (195/196, 95% CI 98.5–100.0) with no virologic failures, demonstrating both non-inferiority (primary efficacy analysis) and superiority (secondary efficacy analysis) to the historical standard-of-care (SOF/RBV). The six patients with prior SOF treatment experience excluded from the primary analysis all achieved SVR12, yielding an overall SVR12 rate of 99.5% (201/202).

ENDURANCE-4

The overall SVR12 rate in patients with genotype 4 (N=76), 5 (N=26), or 6 (N=19) infection treated for 12 weeks was 99% (120/121; 95% CI 97.6–100.0), with no virologic failures. The SVR12 rate by genotype is also presented in **Table 3**.

SURVEYOR-II, Part 4

The SVR12 rate in HCV genotype 2-infected patients treated for 8 weeks was 98% (142/145, 95% CI 94.1–99.3), with two virologic failures. Five of 6 SOF-experienced patients treated for 8 weeks achieved SVR12; in the subset of SOF-naïve patients, 8-week G/P treatment was non-inferior to the historical standard-of-care (99%; 135/137, 95% CI 96.5–100). In patients with

genotype 4 (N=46), 5 (N=2) or 6 (N=10) infection, 8-week G/P yielded a combined SVR12 rate of 93% (54/58, 95% CI 83.6–97.3) with no virologic failures.

Two genotype 2 patients treated for 8 weeks had virologic failure, both relapses. There were no treatment-emergent substitutions in either NS3 or NS5A at the time of failure; at baseline, neither patient had polymorphisms in NS3, whereas both had the M31 polymorphism in NS5A. One patient with prior SOF/RBV treatment experience relapsed at post-treatment day 29. Although the patient was 100% treatment compliant, glecaprevir exposures were nearly undetectable in the context of a history of gastric bypass. The second patient was pegIFN/RBV-experienced, 100% treatment compliant, and relapsed on post-treatment day 55. The relapse rate in genotype 2-infected patients following 8-week G/P (2/144; 1%) was similar to 12-week G/P (0%; 0/195).

Safety and Tolerability

The G/P safety profile was similar between the 8- and 12-week treatment durations. In the randomized placebo controlled treatment arm, adverse events occurred at similar rates to the active G/P treatment arm. The most common events (occurring in $\geq 10\%$ of patients) were headache and fatigue (**Table 4**). Serious adverse events were rare ($\leq 1\%$) [**eTable 2**]. Three patients discontinued treatment due to adverse events; all in the 12-week treatment arm(s). One patient discontinued treatment on day 12 due to a serious adverse event of transient ischemic attack, deemed related to G/P. Two patients discontinued on day 20 and day 73 due to adverse events of anxiety and dyspepsia, respectively; the dyspepsia had a reasonable possibility of being related to study drug, and both patients achieved SVR12.

One patient treated with G/P experienced an asymptomatic Grade 3 ALT elevation with simultaneous Grade 2 total bilirubin (direct and indirect) and Grade 3 AST, alkaline phosphatase, and gamma glutamyl transferase elevations consistent with a cholestatic pattern at treatment week 12. Five days later, bilirubin levels returned to normal while ALT normalized at post-treatment week 2. An abdominal ultrasound was conducted at post-treatment week 2 and revealed cholelithiasis. The clinical picture was consistent with transient obstruction; the patient achieved SVR12. Two of 626 total patients, one treated for 12 weeks and another for 8 weeks, had pre-treatment Grade 2 bilirubin elevations with indirect predominance and experienced isolated Grade 3 bilirubin elevations while on treatment. These elevations occurred in the absence of concomitant ALT elevations, were predominantly indirect, and returned to pre-treatment levels without treatment interruption.

DISCUSSION

A once-daily, pangenotypic regimen with shorter treatment durations for most HCV patient populations remains a high priority in the public health setting as it would simplify HCV treatment, potentially improving patient access to care and potentiating the global eradication of HCV¹⁴. Here, eight-week treatment with G/P in non-cirrhotic patients with HCV genotypes 2, 4, 5 or 6 infection yielded high SVR12 rates similar to those observed with 12-week treatment, and had a low (<1%) relapse rate. In SOF-naïve, genotype 2-infected patients, G/P was statistically non-inferior to the standard-of-care at the time of study design (SOF/RBV), and yielded SVR12 rates of 99% when administered for 8 or 12 weeks. The SVR12 rate in all genotype 2-infected patients treated for 12 weeks (including those with SOF experience) was 99.5%, with no virologic failures. There were no virologic failures in patients with HCV genotype 4, 5 or 6 infection.

Of the 526 total patients treated with G/P, two experienced virologic failure. Both were white, genotype 2a-infected patients with treatment-experience who received 8-week G/P; one of the patients who relapsed had a history of gastric bypass and significantly lower exposures of glecaprevir. Both patients who relapsed in SURVEYOR-II Part 4 had the M31 polymorphism in NS5A at baseline. However, of the 21 patients with HCV GT2a infection treated for 8 weeks, 20 (95%) had M31 at baseline, and 18/20 (90%) achieved SVR12. Importantly, neither of these two patients had treatment-emergent substitutions in either NS3 or NS5A at the time of failure.

Additionally, in a previous study of 54 genotype 2-infected patients receiving 8-week glecaprevir plus pibrentasvir, including 7 with prior treatment experience, there were no virologic failures¹².

Some regimens containing HCV protease inhibitors have been associated with hepatotoxicity and gastrointestinal adverse events¹⁵⁻¹⁷. In contrast to these observations, the G/P regimen was well-tolerated, with a favorable safety profile regardless of treatment duration similar to that observed in the placebo-controlled arm. Clinically significant laboratory abnormalities, adverse events, and discontinuations due to adverse events were rare.

European and United States guidelines recommend 12 weeks or more of DAA-based regimens to treat HCV genotype 2, 4, 5 or 6 infection^{10, 18}; twelve-week sofosbuvir/velpatasvir is approved for non-cirrhotic patients with HCV genotype 1-6 infection, and yielded SVR12 rates of 99%, 100%, 97%, and 100% in those with genotype 2, 4, 5, or 6 infection respectively^{19, 20}. Eight-week sofosbuvir/velpatasvir/voxilaprevir did not meet the primary endpoint (non-inferiority to 12-weeks sofosbuvir/velpatasvir) in treatment-naïve, non-cirrhotic patients with HCV genotype 1-6 infection²¹; the 8-week duration of this regimen is approved in Europe, while the U.S. label indicates that sofosbuvir/velpatasvir/voxilaprevir be administered for 12 weeks, and only in patients with HCV genotype 1–6 infection who failed prior DAA treatment²². In contrast, 8-week

glecaprevir/pibrentasvir is approved in the U.S and Europe for non-cirrhotic patients with HCV genotype 1-6 infection²³.

Baseline polymorphisms have been shown to impact the efficacy of certain DAAs; in genotype 2a the M31 polymorphism in NS5A confers 12-fold resistance to ledipasvir and >1000-fold resistance to daclatasvir, and regimens containing these DAAs are not approved for treatment of genotype 2 infection^{24, 25}. In contrast, pibrentasvir retains its activity against common polymorphisms in genotype 2, including L/M31 in NS5A¹¹. Although cross-study comparisons should be interpreted with caution, the results presented here - particularly the low (<1%) rate of relapse - suggest that 8-week G/P compares favorably to available treatments for patients with HCV genotype 2, 4, 5 or 6 infection. Other phase 3 studies evaluating 8-week G/P have reported 99% and 95% SVR12 in non-cirrhotic, HCV genotype 1- and 3-infected patients, respectively, suggesting that G/P may represent the first pangenotypic HCV 8-week treatment for patients without cirrhosis^{26, 27}.

There are some limitations to these studies. First, a relatively low number of genotype 5- or 6-infected patients enrolled in the 8-week treatment arm; these numbers are reflective of the low global prevalence of these genotypes. The 100% mITT SVR12 rate in genotype 5- and 6-infected patients is consistent with the high antiviral activity demonstrated *in vitro* by glecaprevir and pibrentasvir^{11, 28}. Second, the exclusion of patients with compensated cirrhosis, who were investigated in separate, dedicated studies^{29, 30}. Third, a low number of patients with prior SOF experience enrolled, particularly in patients with genotype 4, 5, or 6 infection. The high SVR rates achieved with SOF/RBV results in a small number of patients with SOF failure, especially those infected with the less common HCV genotypes. Still, there is no evidence patients with prior SOF treatment experience would respond any differently to G/P treatment than those with

prior IFN/RBV experience, since G/P and SOF have different mechanisms of action. In the 12 patients with prior SOF experience treated with G/P, 11 (92%) achieved SVR12; the one virologic failure in this subset was the patient with a history of gastric bypass and significantly lower glecaprevir exposures. Lastly, a randomized comparison of 8- versus 12-week G/P treatment was not included in any of the study designs. However, 8-week G/P was non-inferior to 12-week G/P in non-cirrhotic, HCV genotype 1-infected patients, and a recent multivariate logistic regression analysis of 2,041 non-cirrhotic HCV genotype 1–6 infected patients treated with G/P for either 8 or 12 weeks demonstrated that treatment duration did not impact achievement of SVR12^{27, 31}.

In conclusion, the all-oral, IFN- and RBV-free G/P regimen yielded high SVR12 rates in patients with HCV genotype 2, 4, 5 or 6 infection without cirrhosis following a treatment duration of eight weeks. These rates were achieved regardless of baseline factors including baseline HCV RNA or presence of baseline NS3/NS5A polymorphisms. G/P was well-tolerated; the frequency and severity of adverse events and laboratory abnormalities in patients randomized to G/P were similar to those randomized to matching placebo. Simple DAA regimens with high efficacy and tolerability, and with shorter treatment durations may improve patient adherence and reduce the burden of medical and diagnostic procedures, thereby increasing access to treatment.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the patients who participated in the studies and their families, the study investigators and their staff, as well as AbbVie colleagues Yiran B. Hu, George Liossis, Kerstin Krauss, and Nela Hayes for their contributions. Medical writing support was provided by Zoë Hunter, PhD, of AbbVie.

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57 TABLES

58 Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Genotype	2			4-6	
	Duration (weeks)	8	12		8	12
	N	145 ^d	G/P 202 ^d	Placebo 100	58	121
Male, n (%)		61 (42)	98 (49)	45 (45)	37 (64)	77 (64)
Race, n (%) ^a						
White		120 (83)	121 (60)	60 (60)	35 (60)	84 (71)
Black		11 (8)	7 (3)	7 (7)	10 (17)	10 (8)
Asian		10 (7)	69 (34)	32 (32)	13 (22)	24 (20)
Age, mean $\pm$ SD, years		54 $\pm$ 11.8	57 $\pm$ 12.8	58 $\pm$ 12.0	48 $\pm$ 13.8	53 $\pm$ 11.0
BMI, mean $\pm$ SD, kg/m ²		28.5 $\pm$ 6.9	25.8 $\pm$ 4.7	26.4 $\pm$ 4.1	25.9 $\pm$ 5.0	25.7 $\pm$ 4.8
Genotype ^b , n (%)						
2		145 (100)	202 (100)	100 (100)	–	–
4		–	–	–	46 (79)	76 (63)
5		–	–	–	2 (3)	26 (21)
6		–	–	–	10 (17)	19 (16)
<i>IL28B</i> non-CC genotype, n (%)		76 (52)	111 (55)	50 (50)	39 (67)	91 (75)
HCV RNA, median (range), log ₁₀ IU/mL		6.67 (0.75 – 7.62)	6.25 (2.5 – 7.3)	6.39 (3.4 – 7.2)	5.45 (4.3 – 7.5)	6.3 (3.6 – 7.3)
HCV treatment-naïve, n (%)		127 (88)	141 (70)	71 (71)	49 (84)	82 (68)
HCV treatment-experienced, (n%) ^c		18 (12)	61 (30)	29 (29)	9 (16)	39 (32)
IFN or pegIFN $\pm$ RBV, n (%)		12 (8)	55 (27)	27 (27)	9 (16)	39 (32)
SOF + RBV $\pm$ pegIFN, n		6 (4)	6 (3)	2 (2)	0	0

(%)					
Baseline fibrosis stage, n (%)					
F0-F1	123 (85)	154 (76)	85 (85)	47 (81)	104 (86)
F2	9 (6)	18 (9)	9 (9)	3 (5)	8 (7)
F3	13 (9)	30 (15)	6 (6)	8 (14)	9 (7)
Concomitant PPI use, n (%)	17 (12)	22 (11)	11 (11)	2 (3)	11 (9)
Former IDU, n (%)	71 (49)	32 (16)	18 (18)	21 (36)	32 (26)
BMI, body mass index; PegIFN/RBV, pegylated interferon/ribavirin; SOF, sofosbuvir; PPI, proton pump inhibitor; IDU, injection drug use. ^a Self-reported ^b Determined by the Versant HCV Genotype Inno-LiPA Assay Version 2.0 ^c Patients with SOF + RBV $\pm$ pegIFN experience counted as SOF-experienced. ^d Two and four GT2-infected patients receiving 8- and 12-week treatment, respectively, were later determined to be infected with GT1 by phylogenetic analysis					

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61 **Table 2. Prevalence of Baseline Polymorphisms* in NS3 or NS5A**

Genotype^a	GT2		GT4		GT5		GT6	
Treatment Duration	8 week	12 week	8 week	12 week	8 week	12 week	8 week	12 week
Number of patient samples with sequences available for both targets	N=123	N=160	N=41	N=71	N=1	N=26	N=6	N=11
Prevalence of baseline polymorphism, n (%)^b								
None	29 (24)	28 (18)	23 (56)	28 (39)	1 (100)	12 (46)	2 (33)	4 (36)
NS3 only	0	0	0	0	0	10 (38)	0	0
NS5A only	93 (76)	132 (83)	17 (41)	43 (61)	0	2 (8)	4 (67)	6 (55)
NS3 + NS5A	1 (0.8)	0	1 (2)	0	0	2 (8)	0	1 (9)
*Baseline polymorphisms detected by next generation sequencing at a 15% threshold in samples that had sequences available for both targets (N) at the following amino acid positions: NS3: 155, 156, 168 NS5A: 24, 28, 30, 31, 58, 92, 93 ^a Determined by phylogenetic analysis ^b Values over 100% due to rounding								

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Table 3. Virologic Response and Reasons for Non-Response

	Genotype	G/P Duration (weeks)	SVR12, n/N (%) (ITT population)	Reasons for Non-Response, n (%)				SVR12, n/N (%) (mITT population)
				Virologic Failure		Non-Virologic Failure		
				Breakthrough	Relapse	Missing SVR12 Data	Early Tx Discontinuation	
Primary Endpoint	2	8	142/145 (98)	0	2 (1)	0	1 (0.7) ^a	140/142 (99)
		12	195/196 (99) ^b	0	0	1 (0.5)	0	192/192 (100)
	4-6	8	54/58 (93)	0	0	3 (5) ^c	1 (2) ^d	54/54 (100)
		12	120/121 (99)	0	0	0	1 (0.8) ^e	120/120 (100)
Breakdown of Genotype 4-6	4	8	43/46 (93)	0	0	2 ^c	1 ^d	43/43 (100)
		12	75/76 (99)	0	0	0	1 ^e	75/75 (100)
	5	8	2/2 (100)	0	0	0	0	2/2 (100)
		12	26/26 (100)	0	0	0	0	26/26 (100)
	6	8	9/10 (90)	0	0	1 ^f	0	9/9 (100)
		12	19/19 (100)	0	0	0	0	19/19 (100)

^aPatient discontinued on day 15 due to loss to follow-up^bExcludes 6 SOF-experienced patients; all achieved SVR12 (SVR12 of total patients treated: 201/202; 99.5%)^cAll patients had HCV RNA <LLOQ at last visit^dGT4-infected patient discontinued on day 36 due to non-compliance^eGT4-infected patient discontinued on day 12 due to AE of transient ischemic attack^fPatient returned after post-treatment week 12 and had maintained HCV RNA <LLOQ

G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response at post-treatment week 12; ITT, intention-to-treat; Tx, treatment; mITT, modified ITT, which excludes patients with non-virologic failure and those with ineligible genotype

Table 4. Summary of Treatment-emergent Adverse Events* and Laboratory Abnormalities

	Genotype	2			4-6	
	Duration (weeks)	8	12		8	12
			G/P	Placebo		
Event, n (%)	N	145	202	100	58	121
Any adverse event		90 (62)	131 (65)	58 (58)	38 (66)	83 (69)
Discontinuation of treatment due to adverse event		0	0	0	0	3 (2)
Any serious adverse event		1 (0.7)	3 (1)	1 (1)	1 (2)	1 (0.8)
Adverse events occurring in $\geq 10\%$ of patients						
Headache		24 (17)	24 (12)	12 (12)	13 (22)	25 (21)
Fatigue		17 (12)	23 (11)	10 (10)	11 (19)	21 (17)
Nausea		18 (12)	15 (7)	3 (3)	5 (9)	12 (10)
Laboratory Abnormalities						
ALT $\geq$ Grade 3 ($>5 \times$ ULN) ^a		0	1 (0.5)	2 (2)	0	0
Total Bilirubin $\geq$ Grade 3 ($>3 \times$ ULN)		0	1 (0.5)	0	1 (2)	0
ALT, alanine aminotransferase; ULN, upper limit of normal						
^a Post-nadir increase in grade						

FIGURE LEGENDS**Figure 1. Trial Profiles**

Patient disposition from screening through end of treatment for the 3 studies. G/P, glecaprevir/pibrentasvir; GT, genotype; ITT, intention-to-treat; SVR12, sustained virologic response 12 weeks post-treatment; mITT, modified intention-to-treat.

Figure 2. Study Designs

Schematic of the design for ENDURANCE-2, ENDURANCE-4, and SURVEYOR-II, Part 4 studies. G/P, glecaprevir/pibrentasvir; SVR12, sustained virologic response at post-treatment week 12.