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PANCREAS, BILIARY TRACT, AND LIVER

Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients With Hepatitis C Virus Genotype 2, 4, 5, or 6 Infection Without Cirrhosis

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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 = 100) 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.**

Abbreviations used in this paper: ALT, alanine aminotransferase; CI, confidence interval; DAA, direct-acting antiviral; G/P, glecaprevir/pibrentasvir; HCV, hepatitis C virus; IFN, interferon; ITT, intention-to-treat; LLOQ, lower limit of quantification; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response 12 weeks after treatment.

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CONCLUSION: **In 3 Phase 3 studies, 8 weeks' treatment with glecaprevir/pibrentasivr 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).**

Keywords: Direct-acting Antiviral; DAA; Short-duration; Pangenotypic.

Hepatitis C virus (HCV) genotypes 2, 4, 5, and 6 account for approximately 23% of the estimated 80 million HCV viremic infections worldwide.[1] 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 patients.[4] Rates of cure, as measured by sustained virologic response (HCV RNA below the lower limit of quantification [LLOQ]) 12 weeks after treatment (SVR12) range from 89% to 100% for the 6 major HCV genotypes when treated according to label guidelines.[5–8] 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, ribavirin (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 pan-genotypic 8-week treatment options for patients infected with other HCV genotypes.[7,10] A safe, effective pan-genotypic 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 activity.[11] 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 infection.[12]

Here we report the primary safety and efficacy results from 3 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 3 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 body mass index of 18 kg/m^2 or more, and could be either HCV treatment-naive or experienced with interferon (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 coinfected with human immunodeficiency virus, hepatitis B virus, more than 1 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 Supplementary Data. 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 3 studies were conducted at more than 60 clinical sites; G/P was dosed as 3 co-formulated 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 after 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 by using the Versant HCV Genotype Inno LiPA