Research Article

EASL JOURNAL OF HEPATOLOGY

Viral Hepatitis

Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1–6 without cirrhosis

Paul Y. Kwo[1,*], Fred Poordad[2], Armen Asatryan[3], Stanley Wang[3], David L. Wyles[4], Tarek Hassanein[5], Franco Felizarta[6], Mark S. Sulkowski[7], Edward Gane[8], Benedict Maliakkal[9], J. Scott Overcash[10], Stuart C. Gordon[11], Andrew J. Muir[12], Humberto Aguilar[13], Kosh Agarwal[14], Gregory J. Dore[15], Chih-Wei Lin[3], Ran Liu[3], Sandra S. Lovell[3], Teresa I. Ng[3], Jens Kort[3], Federico J. Mensa[3]

[1]*Stanford University Division of Gastroenterology and Hepatology, Palo Alto, CA, USA;* [2]*Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas, USA;* [3]*AbbVie Inc., North Chicago, Illinois, USA;* [4]*University of Colorado School of Medicine, Denver, Colorado, USA;* [5]*Southern California GI and Liver Centers and Southern California Research Center, Coronado, California, USA;* [6]*Private Practice, Bakersfield, California, USA;* [7]*Johns Hopkins University School of Medicine, Baltimore, Maryland, USA;* [8]*University of Auckland, Auckland, New Zealand;* [9]*University of Rochester Medical Center, Rochester, New York, USA;* [10]*eStudySite, San Diego, California, USA;* [11]*Henry Ford Health System, Detroit, Michigan, USA;* [12]*Duke University School of Medicine, Durham, NC, USA;* [13]*Louisiana Research Center, Shreveport, LA, USA;* [14]*Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK;* [15]*Kirby Institute, UNSW Sydney, and St. Vincent's Hospital, Sydney, NSW, Australia*

Background & Aims: Hepatitis C virus (HCV) therapy that is highly efficacious, pangenotypic, with a high barrier to resistance and short treatment duration is desirable. The efficacy and safety of 8- and 12-week treatments with glecaprevir (ABT-493; NS3/4 A protease inhibitor) and pibrentasvir (ABT-530; NS5A inhibitor) were evaluated in non-cirrhotic patients with chronic HCV genotype 1–6 infection.

Methods: SURVEYOR-I and SURVEYOR-II were phase II, open-label, multicenter, dose-ranging trials including patients with chronic HCV genotype 1–6 infection who were either previously untreated or treated with pegylated interferon plus ribavirin. Patients received once-daily glecaprevir plus pibrentasvir at varying doses with or without ribavirin for 8 or 12 weeks. The primary efficacy endpoint was the percentage of patients with a sustained virologic response at post-treatment week 12 (SVR12).

Results: Of the 449 patients who received varying doses of glecaprevir plus pibrentasvir, 25%, 29%, 39%, and 8% had HCV genotype 1, 2, 3, and 4–6 infection, respectively. Twelve-week treatment achieved SVR12 in 97–100%, 96–100%, 83–94%, and 100% in genotypes 1, 2, 3, and 4–6, respectively. Eight-week treatment with 300 mg glecaprevir plus 120 mg pibrentasvir in genotype 1-, 2-, or 3-infected patients yielded 97–98% SVR12 with no virologic failures. Three (0.7%) patients discontinued treatment due to adverse events; most events were mild (grade 1) in severity. No post-nadir alanine aminotransferase elevations were observed.

Conclusions: Glecaprevir plus pibrentasvir was well tolerated and achieved high sustained virologic response rates in HCV genotypes 1–6-infected patients without cirrhosis following 8- or 12-week treatment durations.

Lay summary: The combination of direct-acting antivirals glecaprevir and pibrentasvir comprise a once-daily, all-oral, pangenotypic treatment for HCV genotype 1–6 infection. This article describes results from two phase II trials investigating a range of doses at treatment durations of 8 or 12 weeks in 449 patients without cirrhosis. Efficacy of the optimal dose, as determined by rates of sustained virologic response at post-treatment week 12, ranged from 92%-100%; treatment was well tolerated and significant laboratory abnormalities were rare.

Clinical trial registration: clinicaltrials.gov Identifiers: NCT02243280 and NCT02243293. http://www.clinicaltrials.gov/show/NCT02243280, http://www.clinicaltrials.gov/show/NCT01939197.

Keywords: Direct-acting antiviral; Pangenotypic; ABT-493; ABT-530; SURVEYOR; D-alanine transaminase; Sustained virologic response; Hepatitis C, chronic; Liver cirrhosis; Interferons; Genotype.

Received 7 October 2016; received in revised form 16 March 2017; accepted 27 March 2017; available online 13 April 2017

* Corresponding author. Address: Stanford University, Division of Gastroenterology and Hepatology, 750 Welch Rd., Suite 210, Palo Alto, CA 94304, USA. Tel.: +1 650 498 6080; fax: +1 650 498 5692.

E-mail address: pkwo@stanford.edu (P.Y. Kwo).

Introduction

Hepatitis C virus (HCV) infection is a global disease burden, with 350,000 deaths attributed to HCV-related complications annually.[1,2] Geographic distributions of HCV genotypes vary widely.[2,3] Of the six major HCV genotypes, genotype 3 infection accounts for approximately 30% of global HCV infections and is now considered the most difficult to cure with interferon (IFN)-free

Research Article

direct-acting antiviral (DAA) therapy.[3,4] Highly effective and safe IFN-free DAA HCV treatments are available, and some may provide broad coverage for all six major genotypes with 12 weeks of treatment.[5–8] However, a regimen involving other DAA classes with a shorter treatment duration and high barrier to viral resistance that preserves efficacy would further enhance HCV therapeutic management. Indeed, regimens with shorter treatment durations are associated with enhanced patient convenience, adherence and tolerability, and can thereby improve access to care.[1,9]

Glecaprevir (formerly ABT-493; GLE) is an HCV non-structural (NS) protein 3/4A protease inhibitor identified by AbbVie and Enanta, and pibrentasvir (formerly ABT-530; PIB) is an HCV NS5A inhibitor. Both DAA compounds have potent antiviral activity *in vitro* against all six major HCV genotypes with a high barrier to the selection of common variants with resistance-associated substitutions. The *in vitro* half maximal effective concentration (EC_{50}) of GLE is 0.85–2.8 nM across HCV genotypes 1–6, and PIB has EC_{50} values of 1–5 pM across genotypes 1–6. Following 3-day monotherapy in treatment-naïve patients with HCV genotype 1 infection, GLE and PIB each displayed approximately 4 log_{10} IU/ml declines in HCV genotype 1 RNA from baseline across a range of doses.[10,11]

Here, we present results from two phase II studies (SURVEYOR-I and SURVEYOR-II, parts 1 and 2) designed to evaluate the efficacy and safety of various doses of GLE in combination with PIB with or without ribavirin (RBV) for the treatment of non-cirrhotic patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who were previously untreated or pegylated interferon (PegIFN) plus RBV (PegIFN/RBV) treatment-experienced patients. The impact of RBV, treatment duration, and baseline polymorphisms in NS3 and NS5A on SVR12 rates, as well as treatment-emergent substitutions in NS3 and NS5A in patients who experienced virologic failure, were also assessed.

Patients and methods

Patients

Patients were screened at 80 sites in the United States, Canada, Europe, Australia, New Zealand, and Puerto Rico. Patients 18–70 years of age were eligible if they had chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection with an HCV RNA level greater than 10,000 IU/ml at screening. HCV genotype was determined using the Versant® HCV Genotype Inno Line Probe Assay (LiPA), version 2.0 or higher (Siemens, Malvern, PA). Absence of cirrhosis was documented by means of a liver biopsy (METAVIR score <3, Ishak score <4), a FibroScan score <12.5 kPa, or a FibroTest score ⩽0.72 and aspartate aminotransferase-to-platelet ratio index ⩽2. Patients could either have never received any HCV treatment or been previously treated with PegIFN/RBV; patients with prior DAA treatment experience were excluded. Patients co-infected with hepatitis B virus, HIV, or more than one HCV genotype at screening were also excluded.

Study designs and conduct

SURVEYOR-I (for genotypes 1, 4, 5, and 6) and SURVEYOR-II (for genotypes 2 and 3) were both open-label, multicenter, phase II studies. Complete study design schematics for each study are included in Supplementary materials. Part 1 of each study evaluated different doses of GLE and PIB for 12 weeks and was followed by Part 2, which examined a once-daily optimized dose combination (GLE 300 mg/PIB 120 mg) for a shorter, 8-week treatment duration. Although results presented herein are for patients without cirrhosis, patients with cirrhosis were enrolled in both SURVEYOR studies, and the results were reported previously.[12]

For the initial dose-ranging assessments, treatment-naïve or PegIFN RBV-experienced patients with genotype 1, 2, or 3 infection were administered once-daily GLE plus PIB at various doses with or without RBV for 12 weeks. As shown in Fig. 1A, patients with genotype 1 infection received 200 mg GLE in combination with either 120 mg or 40 mg PIB for 12 weeks. Patients with genotype 2

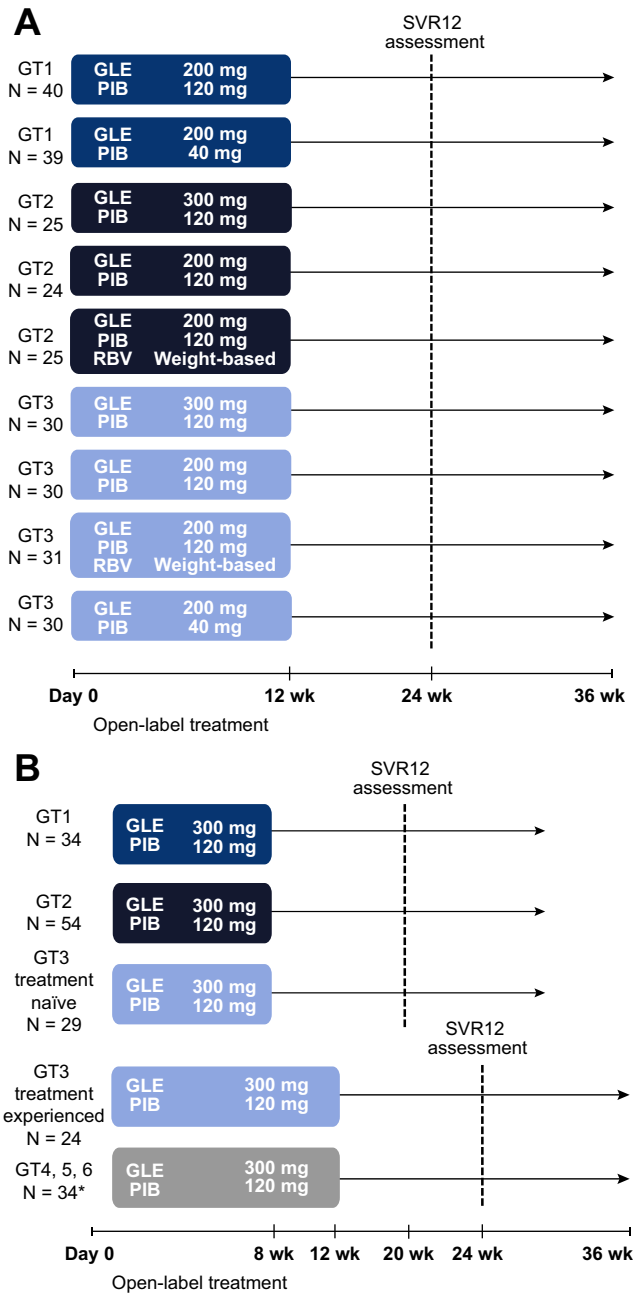

Fig. 1. Study designs. Patients with hepatitis C virus (HCV) genotype 1 (SURVEYOR-I), 2, or 3 (SURVEYOR-II) infection previously untreated or treated with PegIFN/RBV initially received varying doses of GLE and PIB with or without weight-based RBV for 12 weeks (A). On the basis of the results from the initial dose-ranging studies, patients with genotype 1, 2, or 3 infection were assigned to receive the optimized dose of 300 mg GLE and 120 mg PIB for 8 weeks (previously treated or untreated for genotype 1 and 2; previously untreated for genotype 3) or 12 weeks (genotype 3 treatment-experienced patients). Patients with genotype 4, 5, or 6 infection were assigned to 12 weeks of the same regimen (B). Patients were followed-up through 24 weeks after the end of treatment. GLE, glecaprevir; PIB, pibrentasvir; GT, genotype; RBV, ribavirin; PegIFN, pegylated interferon. *Includes two patients who received GLE 200 mg + PIB 120 mg for 12 weeks.