Efficacy and Safety of Glecaprevir/Pibrentasvir in Japanese Patients with Chronic Genotype 2 Hepatitis C Virus Infection

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KEYWORDS

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Footnote Page

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List of Abbreviations

HCV - hepatitis C virus

GT2 - genotype 2

SOF – sofosbuvir

ITT - intention-to-treat

TESAE - treatment-emergent serious adverse event

HCC - hepatocellular carcinoma

DAA - direct-acting antiviral agent

SVR - sustained virologic response

RBV – ribavirin

OBV - ombitasvir

PTV – paritaprevir

r – ritonavir

JSH - Japan Society of Hepatology

GLE – Glecaprevir

G/P - pangenotypic regimen

IFN – interferon

peg – pegylated

LLOQ - lower limit of quantitation

CTCAE - Common Terminology Criteria for Adverse Events

mITT - modified ITT

CI - confidence interval

AEs - adverse events

ALT - alanine aminotransferase

AST - aspartate aminotransferase

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ABSTRACT

Glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor) (G/P), a coformulated once-daily, all oral, ribavirin (RBV)-free, direct-acting anti-viral (DAA) regimen was evaluated for safety and efficacy in Hepatitis C Virus GT2-infected Japanese patients, including those with compensated cirrhosis. CERTAIN-2 is a phase 3, open-label, multicenter study assessing the safety and efficacy of G/P (300/120mg) once daily (QD) in treatment-naïve and interferon (IFN) ± RBV treatment-experienced non-cirrhotic Japanese patients with GT2 infection. Patients were randomized 2:1 to receive 8 weeks of G/P (Arm A) or 12 weeks of sofosbuvir (400 mg QD) + RBV (600 -1000 mg weight-based, BID) (Arm B). The primary endpoint was non-inferiority of G/P compared to SOF+RBV by assessing sustained virologic response at post-treatment week 12 (SVR12) among patients in the intent-to-treat (ITT) population. SVR12 was also assessed in treatment-naïve and IFN ± RBV treatment-experienced patients with GT2 infection and compensated cirrhosis who received G/P for 12 weeks in the phase 3, open-label, multicenter CERTAIN-1 study. A total of 136 patients were enrolled in CERTAIN-2. SVR12 was achieved by 88/90 (97.8%) patients in Arm A and 43/46 (93.5%) patients in Arm B. No patient in Arm A experienced virologic failure, while two did in Arm B. The primary endpoint was achieved. In CERTAIN-1, 100% (18/18) of GT2-infected patients with compensated cirrhosis achieved SVR12. Treatment-emergent serious adverse events were experienced by two non-cirrhotic patients in each arm and no cirrhotic patient. Results demonstrate high efficacy and favorable tolerability of G/P in GT2-infected Japanese patients.

Introductory Statement

Approximately 1.5 million individuals in Japan have chronic HCV infection;(1-4) 30% with genotype 2 (GT2).(5, 6) The Japanese HCV patient population tends to be older and at a higher risk for developing hepatocellular carcinoma (HCC) than non-Japanese patients.(7-9) The burden of HCV infection in Japan is expected to rise due to disease progression combined with an aging population.(10)

Sofosbuvir (SOF), a nucleoside direct-acting antiviral agent (DAA) was demonstrated to have a high rate of sustained virologic response (SVR) in Japanese patients with chronic GT2 HCV infection when coadministered with ribavirin (RBV).(11) The 2-DAA regimen ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) (ritonavir is a pharmacoenhancer with no anti HCV activity) coadministered with RBV also achieved high SVR rates in HCV GT2-infected Japanese patients without cirrhosis.(12) The Japan Society of Hepatology (JSH) currently recommends SOF+RBV for 12 weeks for HCV GT2-infected patients with or without compensated cirrhosis or OBV/PTV/r + RBV for 16 weeks for HCV GT2a-infected patients without cirrhosis as a first line of treatment.(11, 13) As RBV is known to have adverse events related to decreases in hemoglobin and elevations of indirect bilirubin, its elimination from HCV regimens can improve tolerability. Furthermore, SOF is contraindicated in Japan in patients with severe renal impairment (creatinine clearance < 30 mL/min) while RBV is contraindicated in moderate and severe renal impairment (creatinine clearance ≤50 mL/min).(11, 14) Therefore, no DAA treatment regimens are approved in Japan for HCV GT2 infected patients with advanced chronic kidney disease.

Glecaprevir (GLE, formerly ABT-493, identified by AbbVie and Enanta), an NS3/4A protease inhibitor co-formulated with pibrentasvir (PIB, formerly ABT-530), an NS5A inhibitor, is currently being evaluated as a pangenotypic regimen (G/P) for the treatment of patients with HCV infection including those with

compensated cirrhosis, as well as other patient subpopulations that have been previously considered difficult to treat. Preclinical and previous clinical studies have demonstrated that this combination regimen has a high barrier to resistance and potency against common NS3 and NS5A polymorphisms(15). High efficacy of G/P in various patient populations over short treatment durations compared to currently-recommended treatments have been demonstrated outside of Japan (16). Here we report the safety and efficacy of once-daily (QD) G/P administered for 8 weeks compared to SOF + RBV administered for 12 weeks in DAA-naïve GT2 HCV-infected Japanese patients without cirrhosis, and on a separate, small cohort of DAA-naïve Japanese patients with GT2 and compensated cirrhosis who received G/P for 12 weeks.

Experimental Procedures

Study Design

CERTAIN-1 (NCT02707952) and CERTAIN-2 (NCT02723084) are phase 3, open-label, multicenter studies assessing the safety and efficacy of G/P (300/120mg QD) in Japanese patients with HCV infection. The same dose has been used in various studies assessing the efficacy and safety of G/P outside Japan (16). Patients enrolled in CERTAIN-2 had GT2 HCV infection without cirrhosis and were randomized 2:1 to receive 8 weeks of treatment with G/P (Arm A) or 12 weeks of treatment with SOF (400 mg QD) + RBV (600-1000 mg weight-based, divided, twice daily) (Arm B). The randomization was stratified by prior interferon (IFN)/pegylated (peg) IFN experience (naïve versus experienced) and HCV RNA viral load (< or ≥6 million IU/mL). A cohort of patients enrolled in Substudy 2 of CERTAIN-1 (Arm C) who had HCV GT2 infection and compensated cirrhosis were assigned to treatment with G/P for 12 weeks. Prior to study

initiation, the number of GT2 cirrhotic patients to be enrolled in CERTAIN-1 Substudy 2 was predetermined to be 15 based on the relative distribution of GT2 infection with cirrhosis in Japan Patients were followed for 24 weeks after the final dose of study drug. Figure 1 shows the study design.

All patients provided written, informed consent to participate and the study was conducted consistent with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. The study was approved by an institutional review board of each study site prior to the initiation of any screening or study-specific procedures. Supporting Figure 1 shows patient disposition.

Patients

Patients were screened from February 22, 2016 to July 15, 2016 at 56 study sites in Japan. Adults ≥18 years of age with GT2 HCV infection without cirrhosis were eligible for enrollment in CERTAIN-2 and those with GT2 HCV infection and compensated cirrhosis were eligible for enrollment in CERTAIN-1 Substudy 2. Patients were required to be either HCV treatment-naïve or to have failed prior IFN/pegIFN ± RBV therapy, be DAA treatment naïve, test positive for anti-HCV Ab, have a plasma HCV RNA load >1,000 IU/mL at the time of screening and have a laboratory result indicating HCV infection with GT2 only.

Patients enrolled in CERTAIN-2 were required to demonstrate absence of cirrhosis with one of the following criteria: a liver biopsy demonstrating absence of cirrhosis (e.g. METAVIR Score of ≤3 or an Ishak score of ≤4), a Fibroscan score <12.5 kPa, or FibroTest score ≤0.72 and Aspartate Aminotransferase

to Platelet Ratio Index ≤2, or Screening Discriminant Score (z) <0. Patients with compensated cirrhosis (Child-Pugh A) enrolled in CERTAIN-1 Substudy 2 were required to have one of the following: a liver biopsy with a METAVIR (or equivalent) fibrosis score >3 or Ishak fibrosis score >4, a FibroTest score ≥0.73 with an Aminotransferase to Platelet Ratio Index >2, a FibroScan score ≥14.6 kPa or z >0. Absence of HCC was confirmed with a negative ultrasound, Computed Tomography scan or Magnetic Resonance Imaging scan within 3 months prior to screening or a negative ultrasound at screening. HCV genotype was assessed with the Versant® HCV Genotype Inno LiPA Assay, version 2.0 or higher; if the Versant® Assay failed to provide the result, a Sanger sequencing assay of the NS5B region was used.

Patients were excluded if they had a positive test result for hepatitis B surface antigen or anti-human immunodeficiency virus antibody, eGFR <30 mL/min/1.73m^2 (CERTAIN-1 Substudy 2) or CrCl ≤50 mL/min (CERTAIN-2), any current or past clinical evidence of Child-Pugh B or C classification or clinical history of decompensated liver disease such as ascites, hepatic encephalopathy or variceal bleeding, any cause of liver disease other than HCV infection, any clinically significant abnormalities or co-morbidities that made the patient an unsuitable study candidate in the opinion of the investigator, or abnormal screening laboratory results as listed in Supporting Table 1.

Study Assessment

Virologic response was assessed using serum HCV RNA concentration with a lower limit of quantitation of 15 IU/mL. Samples were collected at the screening visit, Day 1 visit and treatment weeks 1, 2, 4, 8 (and week 12 for Arm B patients and patients with compensated cirrhosis) and post treatment weeks 2, 4, 8, 12 and 24. The primary efficacy endpoint for GT2 HCV-infected patients without cirrhosis was to

demonstrate non-inferiority of 8 weeks of G/P compared to 12 weeks of SOF+RBV in achieving SVR12 among patients in the intent-to-treat (ITT) population, defined as those who received at least one dose of study drug. For GT2 infected patients with compensated cirrhosis, SVR12 was assessed in the ITT population. Additional secondary endpoints for all patients reported here were the percentage of patients with on-treatment virologic failure and post-treatment relapse.

Next-generation sequencing was conducted on HCV NS3 and NS5A genes from samples collected from all patients at baseline, and presence of HCV baseline polymorphisms was evaluated using a 15% detection threshold. Blood samples for pharmacokinetic assessment of the study drugs were collected from patients during each study visit (G/P: N=90 for patients without cirrhosis and N=18 for patients with compensated cirrhosis; SOF+RBV: N = 46 patients without cirrhosis). Patients consenting to intensive pharmacokinetic sampling had samples drawn at the Study Day 1 (at hour 2, 4 and 6 hours post-dose) and at week 4 visit at hour 0 (before study drug administration) and 2 and 4 hours post-dose. Plasma concentrations for GLE, PIB, SOF, GS-331007 (primary metabolite of SOF) and RBV were summarized as steady-state trough levels (C_{trough}) based on binning of PK samples that fall in the interval of 22 to 26 hours after dosing. Plasma concentrations were determined using a validated liquid chromatography assay.

Adverse events and laboratory tests were assessed and recorded at each visit throughout the treatment period and 24 weeks post-treatment for safety evaluations. From the time of study drug administration until 30 days following discontinuation of study treatment, all treatment-emergent AEs were collected, whether solicited or spontaneously reported by the patient. After 30 days following completion of study treatment and throughout the post-treatment period, only spontaneously reported serious AEs were

collected. All adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical Analysis

The primary analysis was conducted after all enrolled patients completed the post-treatment Week 12 visit or prematurely discontinued the study. Efficacy, safety, and demographic analyses were performed on all patients in the intention-to-treat (ITT) population. For the primary efficacy endpoint in CERTAIN-2, the difference in SVR12 rate between Arm A and Arm B and the two-sided 95% CI were computed using the normal approximation to the binomial distribution. Non-inferiority was considered established if the lower bound of the CI for this difference is above –10%. SVR12 was also assessed in the modified ITT (mITT) population that excluded patients who did not achieve SVR12 due to reasons other than virologic failure. The number and percentage of patients meeting the primary and secondary endpoints were determined for each endpoint and a 2-sided 95% confidence interval (CI) was computed for the percentage. Safety analyses compared the rate of adverse events and laboratory abnormalities between treatment groups (Arm A vs Arm B) with the use of Fisher's exact test.

Results

Baseline patient demographics and characteristics

A total of 136 patients with HCV GT2 infection without cirrhosis were randomized to Arms A (8 weeks with G/P; n=90) and B (12 weeks of SOF+RBV; n=46) in CERTAIN-2. Of those patients, 53% and 54% were female in Arms A and B, respectively, and 17% in each Arm were treatment-experienced with

IFN/pegIFN ± RBV. The median age was 57 and 58 in Arms A and B, respectively. The mean HCV RNA at baseline was 6.0 ± 0.8 $\log_{10}$ IU/mL and 6.1 ± 0.8 $\log_{10}$ IU/mL, respectively.

A total of 18 patients with GT2 HCV infection and compensated cirrhosis were enrolled in CERTAIN-1 Substudy 2.Of the patients with cirrhosis, 61% were female, 39% were treatment-experienced with IFN/pegIFN ± RBV with a median age of 70. The mean HCV RNA at baseline was 5.3 ± 1.0 $\log_{10}$ IU/mL. Detailed patient demographic and baseline characteristics are shown in Table 1.

Efficacy outcomes

A total of 97.8% (88/90) of patients enrolled in Arm A achieved SVR12; no virologic failures occurred resulting in an SVR12 rate of 100% in the mITT population. One patient not achieving SVR12 was lost to follow-up after achieving SVR4, while the other prematurely discontinued study drug due to an AE of Grade 2 nausea and vomiting after 18 days of treatment. SVR12 was achieved by 93.5% (43/46; 95%CI: 92.5%-97.8) of patients enrolled in Arm B; virologic relapse occurred in two patients by post-treatment week 12 resulting in an SVR12 rate of 95.6% in the mITT population; the third patient not achieving SVR12 prematurely discontinued study drug due to an AE of Grade 1 malaise. The CERTAIN-2 study met the primary endpoint, demonstrating that G/P for 8 weeks was non-inferior to SOF+RBV for 12 weeks, as the lower bound of the 95% CI for the difference in SVR12 between Arms A and B (4.3; 95% CI:-3.5, 12.1) was above the predefined threshold of -10%.

All 100% (18/18) of HCV GT2-infected patients with compensated cirrhosis enrolled in Arm C of CERTAIN-1 Substudy 2 and treated with G/P for 12 weeks achieved SVR12. Figure 2 shows the SVR12 rates and 95% CIs for all cohorts in the ITT and mITT populations.

Impact of baseline polymorphism

Prevalence of baseline polymorphisms relative to a reference sequence was determined using a 15% detection threshold at amino acid positions 155, 156 and 168 in NS3 and 24, 28, 30, 31, 58, 92 and 93 in NS5A for patients in Arms A and C. The most common polymorphism in HCV GT2-infected patients was the NS5A L31M polymorphism, occurring at a prevalence rate of 94% and 80% in patients without cirrhosis and with compensated cirrhosis, respectively. The most common polymorphisms in HCV GT2b-infected patients were M31I/L/V in NS5A occurring at a combined prevalence rate of 18% in patients without cirrhosis, and NS5A L28F occurring at a prevalence rate of 30% in patients with compensated cirrhosis. There were no virologic failures among GT2-infected DAA-naïve patients treated with G/P, therefore baseline polymorphisms did not have an impact on treatment outcome. Prevalence of baseline polymorphisms is shown in Supporting Table 2.

Pharmacokinetic Results

Following administration of G/P, GLE and PIB plasma concentrations attained steady state by Week 1 visit and remained constant throughout the treatment period (Week 1 to Week 8 for DAA-naïve GT2-infected patients without cirrhosis and Week 1 to Week 12 for DAA-naïve GT2-infected patients with cirrhosis). No apparent drug accumulation was observed. GLE plasma concentrations were higher in GT2 HCV-infected DAA-naïve patients with compensated cirrhosis compared to patients without cirrhosis while PIB plasma concentrations were comparable between patients with and without cirrhosis.

Safety outcomes

Treatment-emergent AEs were experienced by 48% and 76% of patients in Arm A (administered G/P for 8 weeks) and Arm B (administered SOF+RBV for 12 weeks) of CERTAIN-2, respectively, with 18% and 50% of patients having AEs assessed as study drug related. The lower rates of AEs in Arm A compared to Arm B were statistically significant (p=0.002 and p<0.001 for all AEs and drug-related AEs, respectively). AEs that occurred at a statistically significant lower rate in Arm A than Arm B (*P* <0.05) were anemia, blood bilirubin increase and hyperuricaemia. Two serious AEs (2%) occurred in Arm A, spontaneous pneumothorax in one patient and unstable angina in the other, neither of which was assessed by the investigator as being related to study drug. Two serious AEs (4%) occurred in Arm B, pneumonia and Castleman's disease, the former assessed as not study-drug related and the latter as study-drug related. One patient (1%) in Arm A discontinued study drug due to a Grade 2 AE (nausea and vomiting) after 18 days of treatment, and one patient (2%) in Arm B discontinued treatment due to an AE (malaise) after 12 days of treatment and withdrew consent; both AEs were assessed as study-drug related by the investigator and neither patient achieved SVR12. No AEs occurred with a frequency > 10% in Arm A. AEs with a frequency >10% in Arm B of CERTAIN-2 included anemia (35%) and increased blood bilirubin (15%).

AEs were experienced by 67% of GT2-infected patients with compensated cirrhosis in CERTAIN-1 Substudy 2 and 39% patients had events that were assessed as study-drug related by the investigator; no serious AEs occurred. One patient (6%) discontinued study drug due to a Grade 2 drug-related AE (drug eruption, on Day 12, characterized as a patchy purpuric rash and eczema) which resolved on Day 29; the patient discontinued study drug on day 14 and achieved SVR12. AEs with a frequency >10% were

pruritus (22%), nasopharyngitis (11%) and increased blood bilirubin (11%). No drug-related liver injury or liver decompensation events occurred in any arm. Table 2 provides a listing of AEs in the safety population.

Grade ≥3 laboratory abnormalities were rare across all treatment arms. In Arm A patients, no grade ≥3 abnormalities occurred in hemoglobin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. One patient with compensated cirrhosis treated with G/P (Arm C) had a Grade 3 elevation in total bilirubin (predominantly indirect bilirubin) at Week 1, which had returned to baseline (Grade 2) on the Day 15 visit, with no concomitant ALT elevation. One patient in Arm B treated with SOF+RBV had a Grade 3 elevation in total bilirubin level lasting for approximately 58 days. The rates of post-baseline Grade ≥2 levels in hemoglobin and total bilirubin were statistically significantly lower in patients in Arm A compared to Arm B (Table 3).

Discussion

Once-daily 8-week treatment with G/P was non-inferior to 12-week treatment with SOF+RBV in DAA-naïve HCV GT2-infected patients without cirrhosis, as demonstrated by the primary endpoint being met in the CERTAIN-2 study. SVR12 was achieved in 97.8% Japanese patients with HCV GT2 infection without cirrhosis treated with G/P for 8 weeks; no virologic failures occurred. Additionally, 100% of patients with HCV GT2 infection and compensated cirrhosis in CERTAIN-1 Substudy 2 (Arm C) achieved SVR12 following 12-week treatment with G/P. The patient population treated with G/P included patient subgroups that have been previously considered difficult to treat such as those with a high baseline viral load (i.e. ≥6 million IU/mL; n=6), those with non-CC IL28 genotype (n=26), those who failed to achieve SVR with prior IFN-based treatment (n=22) and those with NS3 and/or NS5A baseline polymorphisms

(n=83). High prevalence rates of baseline polymorphisms were detected in patients with HCV GT2a infection with no impact on treatment outcome as no virologic failures occurred in patients treated with G/P.

G/P was well-tolerated in patients without cirrhosis and with compensated cirrhosis with no drug-related serious AEs reported, no clinically significant laboratory abnormalities in hemoglobin, ALT or AST levels and only one patient experiencing a grade ≥3 transient bilirubin elevation. Two patients (<2%) discontinued study drug due to an AE. In patients without cirrhosis, no AEs occurred with a frequency >10%. Three AEs, pruritis (22%), increased blood bilirubin (11%) and nasopharyngitis (11%), occurred with a frequency >10% in the 18 patients with compensated cirrhosis. Additionally, no patient experienced laboratory abnormalities indicating liver disease progression, no patient experienced hepatic decompensation, and no cases occurred that were consistent with drug-induced liver injury.

Currently, no HCV treatment for GT2 is approved in Japan for a duration of less than 12 weeks or without RBV. The elimination of RBV from DAA regimens can improve tolerability and reduce rates of treatment discontinuation due to AEs, as RBV is associated with decreases in hemoglobin and elevations of indirect bilirubin (17). In the CERTAIN-2 study, 35% of patients receiving SOF + RBV had anemia and 15% had elevations in blood bilirubin levels compared to no cases of anemia in patients treated with G/P and 1% with elevations in blood bilirubin level. The reduced treatment duration of 8 weeks for DAA-naïve GT2-infected patients without cirrhosis compared to the currently recommended treatment for Japanese patients (12 weeks of SOF + RBV for HCV GT2-infected patients or 16 weeks of OBV/PTV/r + RBV for HCV GT2-infected patients), is a significant reduction in treatment duration that in addition to simplifying treatment can help reduce the burden of managing concomitant medications, particularly in

Japan's HCV patient population where about 70% are older than 60 years.(18) A total of 39% and 15% of patients treated with G/P and reported on here were older than 65 and 75 years of age, respectively, 23% used liver protectants, 27% used calcium channel blockers and 18% used proton-pump inhibitors and none of these patients experienced virologic failure. As no virologic failures occurred in patients with HCV GT2a (n= 75) or GT2b infection (n=33), these results indicate that HCV GT2 subtyping may not be required with G/P. The high efficacy and favorable tolerability observed with G/P in this study were similar to those observed in Japanese patients with GT1 HCV infection treated with G/P for 8 weeks(19) and are consistent with studies of G/P conducted outside Japan(16).

Limitations of this study include an open label design and the lack of an active comparator for patients with compensated cirrhosis. The use of objective, laboratory-based efficacy endpoints and laboratory assessments for safety, however, mitigate this limitation. The relatively small number of patients in certain subgroups included in this study such as GT2 HCV-infected patients with cirrhosis, patients with prior treatment experience, patients with a viral load ≥6 million $\log_{10}$ IU/mL, and patients with the IL28 non-CC genotype precludes drawing further conclusions. However, high SVR12 rates have been observed in those subpopulations with relatively large number of patients in studies outside Japan(16, 20). An additional limitation is the use of SOF + RBV as an active comparator since other DAA regimens are approved to treat GT2 patients in regions other than Japan. Twelve-week treatment with either SOF/ledipasvir (LDV) or SOF/velpatasvir (VEL) both demonstrate high SVR12 rates with favorable safety profiles in GT2 patients outside Japan (21-23). However, while SOF/LDV is approved to treat GT1 infections in Japan, neither of these regimens is currently approved or recommended for treatment of GT2 in Japan. Therefore, SOF + RBV was chosen as the comparator for this study because it is the standard of care for GT2 infection in Japan.

In summary, a high SVR12 rate was achieved with 8 weeks of G/P in treatment naïve and IFN ± RBV treatment- experienced (DAA-naïve) patients with GT2 HCV infection without cirrhosis; no virologic failures occurred. Non-inferiority of the 8-week treatment with G/P compared to the 12-week treatment with SOF + RBV was achieved. A 100% SVR12 rate was achieved in the 18 patients with GT2 HCV infection and compensated cirrhosis following 12 weeks of treatment with G/P; however, the size of this patient subgroup precludes drawing further conclusions. The regimen was well tolerated. These findings suggest that G/P may provide an all-oral, IFN- and RBV-free treatment option with high efficacy and favorable tolerability for GT2 HCV-infected patients, largely independent of baseline patient demographics and disease characteristics, and a shorter treatment duration for GT2 HCV-infected patients without compensated cirrhosis than currently recommended regimens.

DISCLOSURES

AbbVie sponsored the studies (NCT02723084 and NCT02707952), contributed to its design, the collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the abstract. All authors had access to relevant data.

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REFERENCES

1. Bennett H, Waser N, Johnston K, Kao JH, Lim YS, Duan ZP, Lee YJ, et al. A review of the burden of hepatitis C virus infection in China, Japan, South Korea and Taiwan. Hepatol Int 2015;9:378-390.
2. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, Amarapurkar D, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int 2011;31 Suppl 2:61-80.
3. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333-1342.
4. Liu GG, DiBonaventura M, Yuan Y, Wagner JS, L'Italien GJ, Langley P, Kamae I. The burden of illness for patients with viral hepatitis C: evidence from a national survey in Japan. Value Health 2012;15:S65-71.
5. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol 2009;24:336-345.
6. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77-87.
7. Tanaka J, Kumagai J, Katayama K, Komiya Y, Mizui M, Yamanaka R, Suzuki K, et al. Sex- and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. Intervirology 2004;47:32-40.
8. Mizokami M, Tanaka Y, Miyakawa Y. Spread times of hepatitis C virus estimated by the molecular clock differ among Japan, the United States and Egypt in reflection of their distinct socioeconomic backgrounds. Intervirology 2006;49:28-36.
9. Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology 2010;53:39-43.
10. Chayama K, Hayes CN, Ohishi W, Kawakami Y. Treatment of chronic hepatitis C virus infection in Japan: update on therapy and guidelines. J Gastroenterol 2013;48:1-12.
11. Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, Toyoda H, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepat 2014;21:762-768.
12. Sato K, Chayama K, Alves K, Toyoda H, Suzuki F, Kato K, Rodrigues L, Jr., et al. Randomized Phase 3 Trial of Ombitasvir/Paritaprevir/Ritonavir and Ribavirin for Hepatitis C Virus Genotype 2-Infected Japanese Patients. Adv Ther 2017;34:1449-1465.
13. Japan Society of Hepatology Guidelines for the Management of Hepatitis C Virus Infection. In.
14. Sovaldi tablets [package insert]. In. Tokyo, Japan.
15. Ng TI, Krishnan P, Pilot-Matias T, Kati W, Schnell GB, J , Reisch T, Lu L, et al. *In Vitro* Antiviral Activity and Resistance Profile of the Next-Generation Hepatitis C Virus NS5A Inhibitor Pibrentasvir Antimicrob. Agents Chemother. 2017;61:e02558-02516.
16. Puoti M, Foster G, Wang S, Mutimer D, Gane E, Moreno C, Chang TT, et al. High SVR rates with eight and twelve weeks of pangenotypic glecaprevir/pibrentasvir: integrated efficacy and safety analysis of genotype 1–6 patients without cirrhosis. Journal of Hepatology 2017;66:S721.
17. Banerjee D, Reddy KR. Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. Aliment Pharmacol Ther 2016;43:674-696.
18. Kurosaki M. Treatment strategy for eldery patients with chronic hepatitis C. Igakunoayumi 2014;249:247-252.

19. Chayama K, Suzuki F, Karino Y, Kawakami Y, Sato K, Atarashi T, Naganuma A, et al. CERTAIN-1: efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis. Journal of Hepatology 2017;66:S527.
20. Forns X, Lee S, Valdes J, Lens S, Ghalib R, Aguilar H, Felizarta F, et al. EXPEDITION-I: efficacy and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis. Journal of Hepatology 2017;66:S3-S4.
21. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, Abergel A, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015;373:2599-2607.
22. Asselah T, Boyer N, Saadoun D, Martinot-Peignoux M, Marcellin P. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver Int 2016;36 Suppl 1:47-57.
23. Gane EJ, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, Brainard DM, McHutchison JG, et al. Efficacy of Ledipasvir Plus Sofosbuvir for 8 or 12 Weeks in Patients With Hepatitis C Virus Genotype 2 Infection. Gastroenterology 2017;152:1366-1371.

Table 1. Baseline Demographics and disease characteristics of GT2 HCV-infected patients without cirrhosis enrolled in arms A and B of CERTAIN-2, and GT2 HCV-infected patients with compensated cirrhosis enrolled in Arm C of CERTAIN-1 Substudy 2

Characteristic	CERTAIN-2 Without Cirrhosis		CERTAIN-1 Substudy 2 Compensated Cirrhosis
	Arm A G/P 8 weeks N=90	**Arm B SOF + RBV 12 weeks N=46**	**Arm C G/P 12 weeks N=18**
Female, n (%)	48 (53)	25 (54)	11 (61)
Age, median (range), years	57 (26-83)	58 (21-84)	70 (49-85)
Age, n (%) ≥65 ≥75	 29 (32) 10 (11)	 17 (37) 8 (17)	 13 (72) 6 (33)
BMI, mean ± SD, kg/m^2	22.9 ± 3.3	23.0 ± 4.2*	22.2 ± 3.5
IL28B non-CC genotype, n (%)	23 (26)	9 (20)	3 (17)
Treatment-experienced (IFN-based +/- RBV), n (%)	15 (17)	8 (17)	7 (39)
HCV subtype†			

2a, n (%)	65 (72)	30 (65)	10 (56)
2b, n (%)	25 (28)	16 (35)	8 (44)
HCV RNA, mean ± SD, log_{10} IU/mL	6.0 ± 0.8	6.1 ± 0.8	5.3 ± 1.0
FIB-4 index, median (range)	1.6 (0.6 – 7.7)	2.1 (0.6 – 7.3)	5.1 (1.6 – 17.0)
Proton pump inhibitors use, n (%)	12 (13)	2 (4)	7 (39)
Liver protectant use, n (%)	15 (17)	12 (26)	10 (56)
Calcium channel blockers use, n (%)	23 (26)	11 (24)	6 (33)

BMI, body mass index; G/P, glecaprevir/pibrentasvir; *IL28B*, interleukin 28B; SOF+RBV, sofosbuvir+ ribavirin.

*N = 45.

†HCV subtype determined by phylogenetic analysis of baseline NS3/4A and/or NS5A sequence.

Table 2. Treatment-emergent AEs.

Event	CERTAIN-2 Without Cirrhosis		CERTAIN-1 Substudy 2 Compensated Cirrhosis
	Arm A G/P N=90 n (%)	Arm B SOF + RBV N=46 n (%)	Arm C G/P N=18 n (%)
Any AE[*]	43 (48)	35 (76)	12 (67)
Any drug-related AE[†]	16 (18)	23 (50)	7 (39)
Any serious AE	2 (2)[‡]	2 (4)[§]	0
Any study-drug related serious AE	0	1 (2)	0
Any AE leading to D/C of study drug	1 (1.1)[‖]	1 (2.2)[¶]	1 (6)
Any AE leading to interruption of study drug	0	2 (4.3)[**]	0
Common AEs (occurring in ≥5% and ≥2 patient in any group)			
Anaemia[††]	0	16 (35)	1 (6)
Pruritus	3 (3)	2 (4)	4 (22)
Blood bilirubin increased[‡‡]	1 (1)	7 (15)	2 (11)
Nasopharyngitis	9 (10)	5 (11)	2 (11)
Malaise	5 (6)	4 (9)	1 (6)
Headache	6 (7)	1 (2)	0
Nausea	3 (3)	3 (7)	0

Stomatitis	1 (1)	3 (7)	0
Hyperuricaemia§§	0	3 (7)	0

*Difference between Arm A and Arm B is statistically significant (*P* = .002).

†Difference between Arm A and Arm B is statistically significant (*P* <.001).

‡Pneumothorax spontaneous and angina unstable.

§Pneumonia and Castleman's disease, the former assessed as not drug-related and the latter as drug related.

llNausea and vomiting.

¶Malaise.

**Pneumonia and anaemia, the latter assessed as study-drug related.

††Difference between Arm A and Arm B is statistically significant (*P* <.001).

‡‡Difference between Arm A and Arm B is statistically significant (*P* = .002).

§§Difference between Arm A and Arm B is statistically significant (*P* = .037).

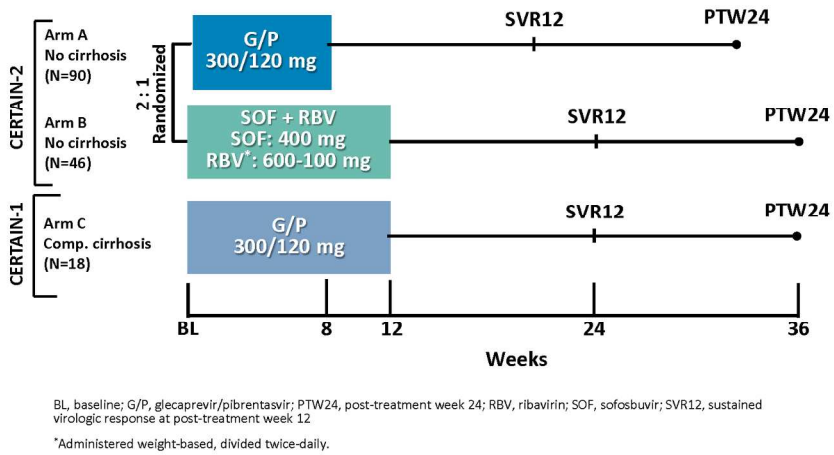
Table 3. Key laboratory abnormalities (worsening from baseline).

Laboratory abnormalities	CERTAIN-2 Without Cirrhosis		CERTAIN-1 Substudy 2 Compensated Cirrhosis
	Arm A G/P N=90 n (%)	**Arm B SOF + RBV N=46 n (%)**	**Arm C G/P N=18 n (%)**
Haemoglobin			
Grade 2 (<10–8 g/dL)*	1 (1)	4 (9)	2 (11)
Grade ≥3 (<8 g/dL)	0	1 (2)	0
Alanine aminotransferase			
Grade 2 (>3-5 x ULN)	0	0	0
Grade ≥3 (>5 × ULN)	0	0	0
Aspartate aminotransferase			
Grade 2 (>3-5 x ULN)	0	0	1 (6)
Grade ≥3 (>5 × ULN)	0	0	0
Total bilirubin			
Grade 2 (>1.5-3 x ULN)†	4 (4)	9 (22)	2 (11)
Grade ≥3 (>3 × ULN)	0	1 (2)	1 (6)

ULN, upper limit of the normal range

*Difference in Grade ≥2 between Arm A and B was statistically significant (p=0.017)

†Difference in Grade ≥2 between Arm A and B was statistically significant (p=0.005)



BL, baseline; G/P, glecaprevir/pibrentasvir; PTW24, post-treatment week 24; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12

*Administered weight-based, divided twice-daily.

Figure 1. Study design for GT2-infected DAA-naïve patients enrolled in the CERTAIN-2 study and a subset of patients (GT2 infected patients with compensated cirrhosis) enrolled in the CERTAIN-1 Arm C study.

254x190mm (200 x 200 DPI)

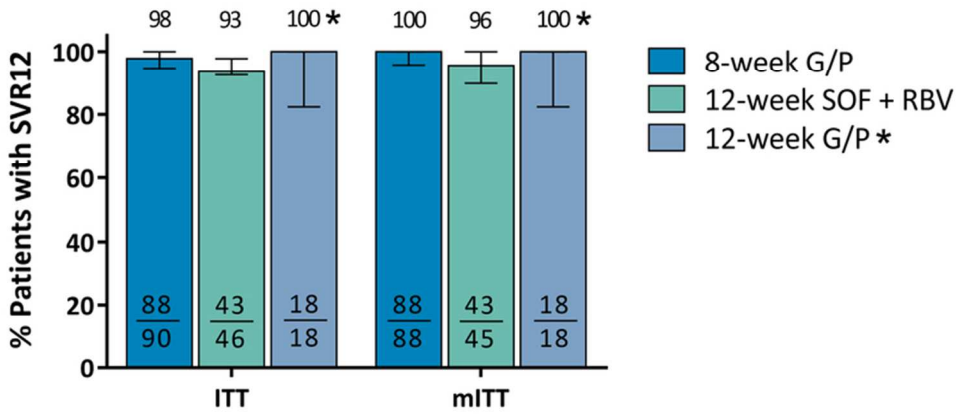


Figure 2. SVR12 rates for each arm in the ITT and mITT populations. The error bars represent the 95% CIs. Arm A: 8-week G/P treatment; Arm B: 12-week SOF+RBV treatment; Arm C: 12-week G/P treatment. SVR=sustained virologic response; ITT=intent-to-treat; mITT=modified ITT.‼ ┼ *GT2 patients with compensated cirrhosis from CERTAIN-1 Substudy 2.

70x32mm (300 x 300 DPI)