

1.0 Abstract

Title

Real World Evidence of the Effectiveness and Clinical Practice Use of Glecaprevir plus Pibrentasvir in Patients with Chronic Hepatitis C Genotypes 1 to 6

Keywords

Post Marketing Observation Study (PMOS), glecaprevir plus pibrentasvir, GLE/PIB, hepatitis C virus (HCV), chronic hepatitis C (CHC), real world

Rationale and Background

The interferon (IFN)- and ribavirin (RBV)-free combination regimen of glecaprevir plus pibrentasvir (GLE/PIB) for the treatment of genotypes 1 to 6 (GT1 – GT6) of chronic hepatitis C (CHC) viral infection has been shown to be safe and effective in randomized controlled clinical trials.

The rationale for this observational study was to determine how the efficacy and safety of GLE/PIB as demonstrated in pivotal trials translated into real world clinical settings, which means evaluating its effectiveness. Whereas efficacy can be defined as a measure of the capacity of a treatment to produce the desired effect in a controlled environment, as in a well-controlled setting as a randomized trial, effectiveness is the extent to which a drug achieves its intended effect in the real world. Effectiveness trials typically have limited exclusion criteria and will involve broader patient populations in routine clinical practice which might have been underrepresented in pivotal trials. Examples of this in the CHC disease landscape were those patients who use illicit non prescribed drugs (PWUD), the elderly, patients with renal impairment, different ethnic groups, patients with heterogeneous compliance patterns due to socioeconomic factors, and patients with significant comorbid conditions or extrahepatic manifestations. Effectiveness research allows for external patient-, provider-, and system-level factors and can therefore be more relevant for health-care decisions by both health care providers and policy-makers.

This observational study was the first effectiveness research examining the GLE/PIB regimen in Poland, Austria, Switzerland, Israel, Portugal, Belgium, Greece, Italy, and France.

Glecaprevir plus pibrentasvir is the first pangenotypic RBV-free regimen allowing for a treatment duration as short as 8 weeks for all treatment-naïve patients with chronic hepatitis C virus (HCV) GT1 – GT6 infection. However, the label of the GLE/PIB regimen will recommend longer therapy (e.g., 12 or 16 weeks) for certain patient subpopulations. It is therefore relevant to understand and characterize the clinical practice use and whether variations have an effect on virologic outcome.

With a pangenotypic approach there is potential for treatment strategy simplification, e.g., therapy initiation without genotyping and with point-of-care HCV ribonucleic acid (RNA) testing, possibly resulting in a shift of CHC treatment to community based primary care physicians. The ease of use, good safety and tolerability profile (RBV-free), and short treatment duration might simplify monitoring during therapy and thus reduce healthcare resource utilization (HCRU) at the centers. This observational study strived to document visit frequencies and laboratory assessments in light of varying clinical practice use of the GLE/PIB regimen and different patient subpopulations like cirrhotic vs non-cirrhotic patients.

In addition, this study provides data on the adherence to treatment in subpopulations of real world interest, which may help treating physicians improve the management of patients under their care.

The aim of this observational study was to provide evidence of the effectiveness, clinical practice use, and HCRU of the GLE/PIB regimen across a variety of patient populations in a real world clinical practice setting.

Research Question and Objectives

The primary objective of this study was to describe in routine clinical practice the effectiveness of GLE/PIB overall and by subpopulations of interest: Hepatitis C virus

(HCV) genotype/subgenotype, cirrhotic and non-cirrhotic patients, treatment-experienced (prior treatment with pegylated interferon, and/or ribavirin and/or sofosbuvir [PRS]) and treatment-naïve, elderly (≥ 65 years) and non-elderly (< 65 years), PWUD and non-drug users, as evidenced by sustained virological response at 12 weeks (SVR₁₂) after end of treatment (EoT).

The secondary objectives of this study were to evaluate the extent of HCRU overall and by subpopulations of interest; describe the clinical practice use of the GLE/PIB regimen overall and by subpopulations of interest; document the adherence to the prescribed GLE/PIB regimen overall and by subpopulations of interest; collect information on co-morbidities and concomitant medication; describe the tolerability of GLE/PIB; evaluate HCRU, demographics, and baseline characteristics as predictors of response; describe effectiveness and tolerability of GLE/PIB in patients with renal impairment; measure changes in health related quality of life, fatigue and/or work productivity (all countries), and changes in sleep quality (France only) by patient-reported outcome questionnaires; and to collect information on the patient care pathway and social patient characteristics (France only).

Study Design

This was a prospective, multi-center observational study in patients with CHC GT1 – GT6 infection receiving the GLE/PIB regimen.

The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice, international guidelines and/or label, was made independently from this observational study, and preceded the decision to offer the patient the opportunity to participate in this study.

Setting

This was a prospective, multi-center, observational study in Poland, Austria, Switzerland, Israel, Portugal, Belgium, Greece, Italy, and France in which patients with CHC GT1 – GT6 infection were evaluated and treated.

Patients and Study Size, Including Dropouts

Patients were treatment-naïve or PRS-experienced male or female adults with confirmed CHC, GT1, GT2, GT3, GT4, GT5, or GT6 infection, with or without compensated cirrhosis, who received combination therapy with the all oral GLE/PIB regimen according to standard of care, international guidelines and/or in line with the current local label; may have been enrolled up to 4 weeks after treatment initiation; voluntarily signed and dated a patient authorization (or informed consent where applicable) to use and/or disclose his/her anonymized health data prior to inclusion into the study; and must not have participated or intended to participate in a concurrent interventional therapeutic trial.

Each country had a maximum sample size for which they provided the width of the 95% confidence interval (CI) for a SVR₁₂ rate of 95%.

Variables and Data Sources

The primary variable for this study was the percentage of patients achieving SVR₁₂ (defined as HCV RNA < lower limit of quantification [LLoQ] 12 weeks [i.e., ≥ 70 days] after the last actual dose of GLE/PIB with a sensitive polymerase chain reaction test with an LLoQ of < 50 IU/mL) overall and in subpopulations of interest.

The secondary variables for this study were the following:

- Average number of HCRU over time overall and by subpopulations of interest.
 - Number and percentage of patients using each treatment regimen (intended treatment duration).
 - Average percentage of GLE/PIB dose taken by patient report in relation to the prescribed target dose (number of pills taken out of the number that should have been taken).
 - Number and percentage of patients with co-morbidities and taking concomitant medication of interest.
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- Number and percentage of patients with treatment emergent serious and non-serious adverse events (AEs) and increases in laboratory parameters of interest.
- Among patients with renal impairment the changes from baseline during treatment in estimated glomerular filtration rate (eGFR) (determined by Modification of Diet in Renal Disease equation) as well as the percentage of patients achieving SVR₁₂ by eGFR categories.
- Mean changes from baseline to EoT and Post-Treatment Week 12 in Mental Component Summary and Physical Component Summary from 36-Item Short Form Health Survey, total score from Fatigue Severity Scale, percent absenteeism, percent presenteeism, percentage of overall work impairment due to CHC and percentage of general activity impairment due to CHC from Work Productivity and Activity Impairment questionnaire, in Pictorial Representation of Illness and Self Measure score, in EuroQol 5 Dimensions 5 Levels Health State Instrument scores (France only), and in Pittsburgh Sleep Quality Index (PSQI) scores (France only) where applicable.
- For France only: number and percentage of patients followed up by health care professional or in a specific medical setting other than the prescribing physicians; number and percentage of patients in social protection categories; number and percentage of patients receiving training regarding the risk of reinfection.

The patient populations used for analysis were the following:

- The Target Population (TP) defined as all patients enrolled in the study and received GLE/PIB (prescribed regimen was known).
 - The Core Population (CP) was defined as all patients of the TP who received the treatment regimens recommended in the concurrent Summary of Product Characteristics in accordance with their disease characteristics. In addition, patients with missing cirrhosis status but treated as cirrhotic, patients with missing treatment history but treated with the 16-week duration, and patients without the necessary GTs (either test undone or undetermined because of a mixture of GTs that included GT3) but treated as GT3 were also included in the CP.
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- The Core Population with Sufficient Follow-up (CPSFU) was defined as all CP patients excluding patients who did not have an HCV RNA evaluation after post treatment Day 70 due to reasons not related to safety and efficacy (i.e., missing or lost to follow up). Each CPSFU patient must have had:
 - Evaluable HCV RNA data after the last actual dose of the GLE/PIB regimen or
 - HCV RNA value ≥ 50 IU/mL at the last measurement (only including on-treatment virologic failure and relapse) or
 - HCV RNA < 50 IU/mL at the last measurement, but no HCV RNA measurement ≥ 70 days after the last actual dose of the GLE/PIB regimen due to reasons related to safety (e.g., dropped out due to AE).
- The Safety Population (SP) was defined as all patients who received at least 1 dose of the GLE/PIB regimen.

Source documents were defined as original documents. The investigator documented patient data in his/her own patient files which served as source data for the study. Data were collected into an electronic data capture system from the source documents for each patient in the study, consisting of medical records containing demographic data, medical treatment and diagnostic documentation, and laboratory assessments.

The investigator(s)/institution(s) permitted study-related monitoring, audits, independent ethics committee/review board review, and regulatory inspection(s), providing direct access to source data documents.

Results

Overall, 2117 patients were enrolled in the study, 2052 patients were included in the TP/SP, 1930 patients were included in the CP, and 1708 patients were included in the CPSFU. The majority of patients were prescribed 8 weeks of GLE/PIB treatment. Overall in the TP/SP, 52.1%, 9.4%, 29.1%, and 9.4% of patients were GT1, GT2, GT3, and GT4-GT6-infected, respectively.

Overall, SVR₁₂ was achieved in 98.0% (1674/1708, 95% CI: 97.2, 98.6) of patients in the CPSFU population. Within the CPSFU population, SVR₁₂ was achieved at similar percentages across subpopulations of interest (range: 94.1 – 100%). SVR₁₂ was achieved in 86.7% (1674/1930, 95% CI: 85.1, 88.2) of patients in the CP which included all patients without sufficient follow-up as failures. Within the CP, SVR₁₂ was achieved in 81.5% and 89.5% of patients in the PWUD and non-PWUD subpopulations, respectively.

Overall, the percentages of patients in the CPSFU population with on-treatment virologic failure, relapse, and other types of virologic failure (i.e., virologic failures unable to be classified as either on-treatment virologic failure or relapse due to missing EoT HCV RNA) were 0.4% (6/1708, 95% CI: 0.2, 0.8), 1.2% (16/1285, 95% CI: 0.8, 2.0), and 0.4% (6/1708), respectively.

The mean number of HCRU over time overall for the CP was 3.68 (SD = 0.86). Similar mean numbers of HCRU were observed for CP subpopulations of interest overall (range: 3.00 – 3.91).

The mean percentage of GLE/PIB treatment adherence was 99.76% in both the CP and SP.

Overall, the mean duration of exposure to GLE/PIB in the SP was 61.4 days (SD = 13.43). The percentages of patients with ≥ 52 days for patients with 8-week planned duration, ≥ 77 days for patients with 12 weeks planned duration, and ≥ 103 days for patients with 16 weeks planned duration were 97.5%, 95.9%, and 95.1%, respectively.

Overall, 250 patients (12.2%) in the SP experienced at least 1 treatment-emergent adverse event (TEAE). In the SP, 141 patients (6.9%) experienced TEAEs with a reasonable possibility of being related to GLE/PIB. Twenty-one (21) patients (1.0%) experienced a severe TEAE. Nineteen (19) patients (0.9%) experienced a treatment-emergent serious AE (SAE). Four (4) patients (0.2%) experienced a treatment-

emergent fatal SAE (none of which were considered related to GLE/PIB). There were 8 deaths (0.4%) reported in the study (including 4 non treatment-emergent deaths).

The most frequently reported TEAEs ($\geq 1\%$) in the SP were asthenia (2.1%), fatigue (2.0%), headache (1.9%), and nausea (1.0%).

One non-cirrhotic patient experienced a SAE (acute pericarditis) that was assessed as having a reasonable possibility of being related to study drug. The SAE was ongoing at the end of the study.

In the SP, 2 patients (0.2%) had post-nadir alanine-aminotransferase (ALT) $> 5 \times$ upper limit of normal (ULN), and 1 patient had post-nadir ALT $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN.

One non-cirrhotic patient had post-nadir ALT $> 5 \times$ ULN on treatment Day 29. The patient's ALT value at baseline was elevated at 217 IU/L (reference range upper limit: 49 IU/L), the ALT value at the EoT Day 57 was 101 IU/L, and the last ALT value on post-treatment Day 91 was 65 IU/L. The patient completed treatment and achieved SVR₁₂.

Another non-cirrhotic patient had confirmed post-nadir ALT $> 5 \times$ ULN on treatment Days 28 and 59. The patient's ALT value at baseline was elevated at 160 IU/L (reference range upper limit: 40 IU/L), and the last ALT value on post-treatment Day 115 was 294 IU/L. The patient completed treatment but did not achieve SVR₁₂. The patient's HCV RNA was 209,000 IU/mL at the EoT Day 59, and 100 IU/mL at post-treatment Day 115.

One cirrhotic patient had post-nadir ALT $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN on treatment Day 43, the same time when the patient experienced onset of SAEs of respiratory tract infection and cardiac failure. The SAEs lasted for 16 days. The patient prematurely discontinued study drug because of the SAEs but achieved SVR₁₂. The patient's ALT value at baseline was elevated at 73 IU/L (reference range upper limit: 41 IU/L) while the total bilirubin was 12 μ mol/L (reference range upper limit:

19 mcmol/L), and the ALT value on EoT Day 43 was 159 IU/L while the total bilirubin was 63 mcmol/L. There were no other ALT or total bilirubin values after Day 43.

In the SP, 1 patient with cirrhosis (< 0.1%) reported a clinical outcome of interest of ascites, and 1 patient with cirrhosis (< 0.1%) reported a clinical outcome of interest of hepatocellular carcinoma (HCC). The one cirrhotic patient reported a non-serious TEAE of ascites on treatment Day 28. The patient was categorized in Child-Pugh class A (Score of 6). The TEAE was assessed as having a reasonable possibility of being related to study drug, and treatment was withdrawn. The TEAE was ongoing at the end of the study. The other cirrhotic patient reported a TEAE of HCC on treatment Day 60. The TEAE was serious and was not considered related to study drug. The TEAE was ongoing at the end of the study.

Discussion

This postmarketing study demonstrates effectiveness, as evidenced by SVR₁₂, of GLE/PIB overall and by subpopulations of interest. The safety results are consistent with the known safety profile of GLE/PIB.

Marketing Authorisation Holder(s)

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