1.0 Abstract

Title

A Single-Arm Retrospective Study to Evaluate Safety and Efficacy in Patients with Acute Hepatitis C Virus (HCV) Infection Treated with 8 Weeks of Glecaprevir/Pibrentasvir

Keywords

Post Marketing Observational Study (PMOS), glecaprevir plus pibrentasvir, GLE/PIB, hepatitis C virus (HCV), acute hepatitis C

Rationale and Background

HCV infection is a global health problem, with 1.75 million new infections worldwide in 2015 and an estimated 44,700 new infections in the United States (US) in 2017. There are currently no approved direct acting antiviral agents options for use in patients with acute HCV infection. Because of this, treatment is frequently delayed by 6 months (i.e., until the HCV infection is considered chronic). A majority of new HCV infections today are in people who inject drugs (PWID) and men who have sex with men. Since PWID are often disconnected from care, waiting 6 months to confirm chronic infection results in the loss of many such patients to care and accelerates community transmission of HCV as patients infect others during the acute phase. Spontaneous clearance of acute HCV occurs in this early 6-month period in 15 to 45% of those infected. Regulatory approval of antiviral treatment in patients with acute HCV would prevent loss of patients to care, simplify decision-making for clinicians in the community setting, shorten the time to treatment of HCV infection, and would decrease the risk of community transmission.

This study aimed to demonstrate safety and efficacy for once-daily (QD) (glecaprevir 300 mg/pibrentasvir 120 mg; hereafter referred to as GLE/PIB) in patients with acute HCV infection.

Research Question and Objectives

GLE/PIB will achieve a high sustained virologic response 12 weeks after the last dose of the drug (SVR_{12}) rate in patients acutely infected with HCV, with an acceptable safety profile.

The primary objective of this study was to demonstrate the efficacy of GLE/PIB prescribed for 8 weeks in patients with acute HCV genotype (GT)1 – GT6 infection by comparing the SVR_{12} rate from this study to the historical SVR_{12} rate in people with chronic HCV infection who were treated with GLE/PIB. The primary efficacy objective was assessed based on a modified Full Analysis Set (mFAS) population, which included all eligible patients who enrolled in this study, excluding patients who failed to achieve SVR_{12} for reasons other than virologic failure.

The secondary objectives of this study were as follows:

- To determine the SVR_{12} rate among patients with acute HCV GT1 – GT6 infection following treatment with GLE/PIB (prescribed 8 weeks) based on all patients treated with GLE/PIB (the Full Analysis Set [FAS] population).
- To determine the on-treatment virologic failure, relapse, and reinfection rates among patients with acute HCV GT1 – GT6 infection based on the FAS population.

The safety objectives of this study were to examine the safety with respect to alanine aminotransferase (ALT) elevations, serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation, and AEs of hepatic decompensation during treatment with GLE/PIB (8-week prescription) in patients with acute HCV GT1 – GT6 infection in the Safety Analysis Set, which consisted of all patients treated with GLE/PIB, compared to historical safety results in patients with chronic HCV infection. The safety endpoints were also examined in the Principal Safety Stratum (PSS), which consisted of patients in the Safety Analysis Set who had ALT and bilirubin results both at baseline and during treatment with GLE/PIB.

Study Design

This was a non-interventional, single-arm, retrospective study (patient chart review) designed to include a sufficient number of patients with documented acute HCV, such that at least 250 patients were in the PSS (had both baseline and on-treatment ALT and bilirubin values) and were treated with GLE/PIB (8-week prescription) for comparison to historical safety and efficacy results from patients with chronic HCV.

Setting

This non-interventional, single-arm, retrospective study in the US/Puerto Rico, the United Kingdom, Spain, Italy, France, Canada, and Australia was designed to include adolescent and adult patients with acute HCV infection who were treated with GLE/PIB and whose data were collected through retrospective chart review.

Patients and Study Size, Including Dropouts

Eligible patients were treatment-naïve adolescents and adults (aged 12 years or older) with acute HCV GT1 – GT6 infection, who were prescribed an 8-week treatment course of GLE/PIB. Patients with history of liver decompensation or who had received a liver or kidney transplant were excluded from the study.

A sufficient number of patients with acute HCV infection who met the admission criteria were to be enrolled such that 250 patients with baseline and on-treatment ALT and bilirubin values were to have been included in the PSS. To detect any toxicity occurring in ≥ 1% of patients with acute HCV, a sample size of 250 patients in the PSS was to have provided > 91% probability and a sample size of 300 patients in the Safety Analysis Set was to have provided > 95% probability.

Enrollment was terminated prematurely due to futility in meeting enrollment requirements.

Variables and Data Sources

The primary efficacy endpoint was the achievement of SVR_{12} for each patient in the mFAS population. In this study, SVR_{12} was defined as HCV RNA < 50 IU/mL between Day 57 and Day 126 after the last dose of study drug, if available, or SVR 24 weeks after the last dose of the drug (SVR_{24}; defined as HCV RNA < 50 IU/mL between Day 127 and Day 210 after the last dose of study drug), if the SVR_{12} result was not available. If the appropriate HCV RNA levels were not available, physician attestation of SVR was used.

The secondary efficacy endpoints were as follows:

- SVR_{12} for each patient in the FAS population
- On-treatment virologic failure for each patient in the FAS population
- Post-treatment relapse for each patient in the FAS population who completed treatment as planned
- Post-treatment reinfection with HCV (defined as post-treatment relapse along with the post-treatment detection of a different HCV GT, subtype, or clade compared with baseline) for each patient in the FAS population

The safety endpoints were as follows:

- On-treatment ALT elevations of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 Grade 1, 2, 3, or 4 and increased from baseline
- On-treatment ALT > 3 × upper limit of normal (ULN) with on-treatment total bilirubin > 2 × ULN
- TEAEs of hepatic decompensation/hepatic failure according to the AbbVie Product Medical Dictionary for Regulatory Activities Query for Hepatic Decompensation and Hepatic Failure
- TEAEs leading to discontinuation of GLE/PIB
- Treatment-emergent SAEs

The patient populations used for analysis were the following:

- The FAS population included all patients in the study population who met eligibility criteria and were treated with GLE/PIB. The FAS population was used for all secondary efficacy analyses and subgroup and sensitivity analyses of SVR_{12} as well as for analyses of demographics, baseline disease characteristics, disease-related comorbidities, patient and site-specific feasibility/acceptability, and treatment and exposure data.
- The mFAS population included all patients in the FAS population, excluding patients who did not achieve SVR_{12} for reasons other than virologic failure (i.e., those with HCV reinfection, those who did not achieve SVR_{12} due to premature discontinuation of GLE/PIB, and those who did not have an SVR status available in the patient chart). The mFAS population was used for the primary efficacy analysis and the subgroup and sensitivity analyses of SVR_{12} as well as for analyses of demographics, baseline disease characteristics, disease-related comorbidities, patient and site-specific feasibility/acceptability, and treatment and exposure data.
- The Safety Analysis Set consisted of all patients who were treated with GLE/PIB and was used for analyses of safety data as well as for analyses of study drug interruptions and discontinuations, demographics, baseline disease characteristics, disease-related comorbidities, patient and site-specific feasibility/acceptability, prior and concomitant medications, and treatment and exposure data.
- The PSS consisted of all patients in the Safety Analysis Set who had ALT and bilirubin values at baseline and during GLE/PIB treatment and was used for analyses of safety data as well as for analyses of demographics, baseline disease characteristics, disease-related comorbidities, patient and site-specific feasibility/acceptability, prior and concomitant medications, and treatment and exposure data.

The comparator populations were defined as follows:

- The Chronic Phase 2/3 Analysis Set was the population with chronic HCV treated with GLE/PIB in Phase 2/3 clinical trials (Chronic Phase 2/3 Analysis

Set), restricted to adults and adolescents who specified whether or not they had a history of injection drug use and were assigned to 8 weeks of GLE/PIB. The Chronic Phase 2/3 Analysis Set included the following studies that evaluated GLE/PIB for 8 weeks: Studies M13-590, M13-594, M14-730, M14-867, M14-868, M15-410, M15-592, M15-594, M15-828, M16-123 (adolescents only), M16-126, M16-127, M16-133, M16-135, and M16-156. The definition of the Chronic Phase 2/3 Analysis Set paralleled that of the P20-315 Safety Analysis Set. This population was used for comparison of efficacy endpoints, demographic and baseline characteristics, and disease-related comorbidities (versus the P20-315 FAS population) and safety endpoints (versus the P20-315 Safety Analysis Set).

- The mITT-VF Chronic Phase 2/3 Analysis Set included patients in the Chronic Phase 2/3 Analysis Set, excluding those who did not achieve SVR_{12} due to reasons other than virologic failure. The definition of the mITT-VF Phase 2/3 Analysis Set paralleled that of the P20-315 mFAS population. This population was used for comparison of efficacy, demographic and baseline characteristics, and disease-related comorbidities (versus the P20-315 mFAS population).

Pre-existing patient records served as source data for the study. The data source for eligible patients included all sources of study-relevant information available to the investigator at the clinical study site, including (but not limited to) paper medical charts, electronic medical records, and clinical laboratory records. To avoid sampling, all patients who were documented in their medical record as meeting the inclusion/exclusion criteria and treated at each site from 26 July 2017 (approval of GLE/PIB in the European Union) through end dates that were 5 months prior to site initiation (to allow for enrolled patients to have SVR_{12} data prior to site initiation) were to be included. This study only collected retrospective information recorded in patient charts prior to the start of data collection from 6 months prior to the first dose of GLE/PIB, through the duration of GLE/PIB treatment, and for up to 210 days after the end of GLE/PIB treatment.

Results

Overall, 202 patients were enrolled and treated in the study and were included in the FAS and Safety Analysis Set. Of these, 189 (93.6%) completed treatment. A majority of patients were male, white, not Hispanic or Latino, and from Europe, with a median (range) age of 38.0 (20.0 to 66.0) years in the FAS. A majority of patients in this study had HCV GT1 or GT3 infection, and the median baseline HCV RNA level was 5.6 $\log_{10}$ IU/mL. Over 88% of the patients had an estimated duration of acute HCV infection of < 6 months, and approximately three-quarters of the patients had been diagnosed with acute HCV infection for < 3 months at baseline. Nearly all patients were noncirrhotic, and a majority had a baseline fibrosis stage of F0 or F1 and had no prior history of HCV infection. Most had history of illicit drug use either ongoing at the start of the GLE/PIB treatment or within 6 months prior to baseline, and approximately half were former or non-PWID. A majority of patients met the acute HCV infection criterion that was based on a positive HCV RNA or core antigen test, clinical signs and symptoms compatible with acute HCV, and risk behaviors for HCV infection. Over half of the patients had human immunodeficiency virus (HIV) infection. The mean medical record duration was approximately 5 years.

The primary efficacy analysis of SVR_{12} was performed on the mFAS. The SVR_{12} rate was 99.3% (150/151; 95% CI: 96.3, 99.9), with 1 patient experiencing post-treatment relapse. Superiority to the efficacy threshold of 92.6% was demonstrated, thereby demonstrating non-inferiority to the historic chronic HCV SVR_{12} rate.

The SVR_{12} rate for the FAS was 74.3% (150/202), with 1 (0.5%) patient who experienced post-treatment relapse. No patients experienced on-treatment virologic failure. Six (3.0%) patients experienced HCV reinfection; other reasons for non-virologic failure were premature discontinuation of GLE/PIB (6 patients, 3.0%), with most due to noncompliance with study drug, and missing SVR_{12} data (39 patients, 19.3%).

Agreement of SVR_{12} response between physician attestation and as determined by HCV RNA was 78.8% for the mFAS and 84.2% for the FAS. No subgroup differences in SVR_{12} rates could be observed for the mFAS given the high SVR_{12} rate.

A majority of patients in the Safety Analysis Set and approximately half of the patients in the PSS had a single prescription for GLE/PIB during the study, and most physician attestation of patient dosing was based on patient reporting and/or a decrease of HCV RNA. The median (range) estimated treatment duration was 57.0 (8.0 to 110.0) days for the Safety Analysis Set and 57.0 (47.0 to 88.0) days for the PSS, and a majority of patients in both populations had at least 56 days of treatment.

There were 2 patients with on-treatment ALT elevations that were worse than the baseline grade in this study, both of which were Grade 1 elevations. There were no patients who met the criterion of "on-treatment ALT > 3 × ULN and total bilirubin > 2 × ULN," no AEs of hepatic decompensation or hepatic failure, and no AEs leading to discontinuation of GLE/PIB. Two patients had SAEs during the study, including 1 patient who experienced Grade 3 blood creatinine increased and 1 patient who experienced acute hepatitis C, which was reported as acute HCV infection with delayed clearance of bilirubin and increased risk for infection related to a pause in HIV medication. Both SAEs were assessed as not related to GLE/PIB.

Overall, few patients reported AEs in this study. Of those who did report AEs, most patients experienced AEs with a maximum severity of Grade 1 (9/13 in the Safety Analysis Set, 6/9 in the PSS). There were 2 patients with Grade 3 or higher AEs, but these were not assessed to be related to GLE/PIB. There were no patients who discontinued GLE/PIB due to an AE. There were 2 patients with SAEs, and both were not related to GLE/PIB. There were no deaths in the study. AEs reported by > 1 patient were fatigue, nausea, and insomnia.

Among patients with available laboratory data, few had values worsening from baseline to Grade 3 or 4 during GLE/PIB treatment. No patients had Grade 2 or higher hematology values that were worse than baseline reported during GLE/PIB treatment.

One patient had elevated creatinine (CTCAE Grade 2) reported on Day 39 of treatment with GLE/PIB, which was reported as a serious Grade 3 TEAE of blood creatinine increased. The event was assessed by the investigator to have no reasonable possibility of being related to study drug and resolved without a change of GLE/PIB dosing. No other laboratory abnormalities were reported as TEAEs.

Discussion

This postmarketing study demonstrates the efficacy of the 8-week treatment regimen of GLE/PIB in the treatment of acute HCV with a high SVR_{12} rate that was superior to a threshold based on SVR_{12} rates in subjects with chronic HCV who were treated with GLE/PIB in the chronic HCV program. Although the study did not enroll the protocol-specified number of patients in the PSS for the analysis of liver safety, no new safety signals were identified in the acute HCV population compared to the historic data from the chronic HCV population.

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IRB = internal review board; EC = ethics committee; N/A = not applicable

a. There may be discrepancies in the spelling of physicians' names within this list versus that found in the statistical tables.