1. Abstract

Title

Drug use results survey for GLE/PIB in patients diagnosed with hepatitis C virus genotype 1-6

Keywords

Hepatitis C Virus, Direct-acting Antiviral Agent, Glecaprevir/pibrentasvir, Maviret, real world, Japan

Rationale and Background

Glecaprevir/pibrentasvir (GLE/PIB) approval in Japan was anticipated September 2017 with market launch in November 2017. GLE/PIB is the first pangenotypic IFN-free regimen in Japan. The Pharmaceuticals and Medical Devices Agency (PMDA) requests pharmaceutical companies to collect data on the safety and effectiveness in daily practice for new drugs.

M15-594 and M15-828 Phase III studies with GLE/PIB have been conducted in Japan for patients infected with HCV genotypes 1-6. This PMOS was designed to collect data on the safety and effectiveness of GLE/PIB in daily practice. This study addressed the evaluation of the appropriate use of the GLE/PIB regimen and the monitoring of risks with the regimen as described in the J-RMP.

Research Questions and Objectives

What is the real-world safety and effectiveness data of GLE/PIB in Japan
Therefore the objective of this study is to evaluate the safety and effectiveness of GLE/PIB in patients infected with hepatitis C virus genotype 1-6 in daily practice as mandated by the Japanese authorities.

Primary endpoints

- SVR_{12}

Secondary endpoints

✓ Safety endpoints

- Adverse events and clinical laboratory tests.

- ✓ Effectiveness endpoints
  - SVR4, 8, 24
  - On-treatment virologic failure (breakthrough)
  - After-treatment virologic failure (relapse)

Study Design

This was a prospective, non-randomized, unblinded, non-comparative, non-interventional, multi center Post-Marketing Observational Study (PMOS).

For each individual patient, the observation period of this study started with the enrollment at the beginning of the treatment with GLE/PIB. The observational period consisted of treatment period (8 or 12 weeks) and follow-up period (24 weeks).

Setting

Study Period

- ✓ Registration period
  - From the 27 Dec 2017 to 31 Oct 2018
- ✓ Study period
  - From the 27 Dec 2017 to 21 Aug 2019

Investigative Sites

About 300 sites for gastroenterology and hepatology, mainly.

After a Medical Representative (MR) explained in detail the purpose and methods of the study to participating physicians in medical institutions where GLE/PIB would be used, a written agreement was finalized between AbbVie and each participating institution.

Study medication

AbbVie does not provide any study medication.

The GLE/PIB used in daily medical care was used. The GLE/PIB was prescribed to patients as per Japan label by a physician with sufficient knowledge and experience in the treatment of hepatic viral disease, including HCV.

The recommended oral dose in adults is three tablets (300 mg glecaprevir and 120 mg pibrentasvir) of GLE/PIB once daily after a meal for 8 or 12 weeks.

In case of serogroup 1 (GT1) or serogroup 2 (GT2) chronic hepatitis C
The usual treatment period for adults and children 12 years of age and older is 8 weeks. The duration of treatment may be 12 weeks, depending on the history of prior treatment for chronic hepatitis C.

In case of GT1 or GT2 chronic hepatitis C patients with compensated cirrhosis
The usual treatment period in adults and children aged 12 years or older is 12 weeks.

In case of chronic hepatitis C or compensated cirrhosis that is neither GT1 nor GT2
The usual treatment period in adults and children aged 12 years or older is 12 weeks.

Observation Period

For each patient, the observation for safety and effectiveness evaluation started from the enrollment which is beginning of the treatment with GLE/PIB. And the observation period consisted of the treatment period and the follow-up period, which was 32 weeks or 36 weeks from the day of the first dose of GLE/PIB. The treatment period was as follows and the follow-up period was 24 weeks from the date of discontinuation/completion of treatment.

- ✓ Chronic hepatitis C with serogroup 1 [genotype 1 (GT1)] or serogroup 2 [genotype 2 (GT2)]: 8 weeks (12 weeks can be set according to previous treatment for chronic hepatitis C)
- ✓ Compensated cirrhosis C with serogroup 1 (GT1) or serogroup 2 (GT2): 12 weeks
- ✓ Chronic hepatitis C or compensated cirrhosis that is neither serogroup 1 (GT1) nor serogroup 2 (GT2): 12 weeks

Subjects and Study Size, Including Dropouts

Subjects

The subjects were the 1,000 patients that met the following criteria.

Inclusion Criteria

- ✓ Patients with chronic HCV infection treated with GLE/PIB in daily practice.

Exclusion Criteria

- ✓ Patients treated with GLE/PIB previously.

Study Size

1,000 patients

Variables and Data Sources

Variables

1) Patient demographics and characteristics
2) Treatment with GLE/PIB
3) Completion status of GLE/PIB Treatment
4) Completion status of this study
5) Concomitant therapies
6) Clinical laboratory tests
7) EQ-5D
8) HCV resistance test
9) Adverse events

Data Sources

The original data source for this study was medical records retained by medical institutions participating in this study. Physicians completed registration form and case report form prepared by AbbVie.

If the event fulfills the serious criterion (Serious Adverse Event), the "Serious Adverse Event Report" form was to be completed additionally.

For some survey questions, such as those listed below, the information provided in CRF was the original data source.

- ✓ observations
- ✓ assessments

Results

171 sites were contracted with AbbVie GK to conduct this study, and 165 sites of these sites enrolled patients into the study. Recruitment period was from 27 Dec 2017 to 31 Oct 2018.

A total of 1095 patients were enrolled, and 1093 patients for whom the CRF were collected.

Of the 1093 CRFs, 2 patients were excluded from the safety analysis set, patients who did not meet any of the exclusion criteria, and 1091 patients were included in the final safety analysis set.

Of the 1091 patients in the safety analysis set, 148 were excluded from the effectiveness analysis set, and 943 patients were included in the final effectiveness analysis set.

Effectiveness

The SVR12 rates were 98.41% (928/943), no response rate was 0.00% (0/943), partial response rates were 0.11% (1/943), breakthrough rates were 0.42% (4/943) and relapse rate was 0.85% (8/943), respectively.

The SVR12 rates from clinical trials for approval (M15-594[1)], M15-828[2)]) were 97.9% (325/332), and the SVR12 rates in this study was comparable with the previous clinical trials.

Safety

The cumulative rates of AEs were 19.80% (216/1091), and the cumulative rates of ADRs were 14.39% (157/1091).

The cumulative rates of SAEs were 3.85% (42/1091), and the cumulative rates of serious ADRs were 0.82% (9/1091).

The SOCs with the most frequently reported ADRs (≥2% of patients) were Skin and subcutaneous tissue disorders and Investigations. The frequently reported ADRs (≥1% of patients) were Pruritus and Blood bilirubin increased.

The rates of ADRs from clinical trials for approval (M15-594[1)], M15-828[2)]) were 23.49% (78/332), and the rates of ADRs in this study was lower than the rates of ADRs in the previous clinical trials.

As for the occurrence status of ADRs in this study, compared to the occurrence status at the time of approval, there was no notable difference in the occurrence tendency.

Discussion

The results of this observational study support the safety and effectiveness of GLE/PIB used for patients with hepatitis C virus genotype 1-6 in routine daily practice in Japan. The safety results of this study were consistent to the currently documented safety profile of the product, as described in the label and periodic safety update reports. GLE/PIB used for chronic hepatitis C virus genotype 1-6 has been shown to be highly effective in the real world.

Marketing Authorisation Holder(s)

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Names and Affiliations of Principal Investigators

Not applicable