



Effectiveness of 8-Week Glecaprevir/Pibrentasvir for Treatment-Naïve, Compensated Cirrhotic Patients with Chronic Hepatitis C Infection

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ABSTRACT

Introduction: Glecaprevir/pibrentasvir (G/P) was approved on 26 September 2019 by the US Food and Drug Administration for 8-week duration in treatment-naïve (TN) hepatitis C virus (HCV)-infected patients with compensated cirrhosis (CC). Evidence from the EXPEDITION-8 study demonstrated that 8 weeks of G/P achieved a 98% intent-to-treat (ITT) sustained virologic response rate 12 weeks post treatment (SVR12) in 343 TN/CC patients. The

aim of this study is to demonstrate the first US real-world effectiveness of G/P 8-week treatment in genotype 1–6 TN/CC HCV patients.

Methods: Data from 73 TN/CC patients who initiated 8 weeks of G/P treatment between August 2017 and November 2018 were collected electronically from providers and specialty pharmacies of the Trio Health network and analyzed. Cirrhosis was determined by FIB-4 > 5.2 or was physician reported. The primary outcome was Per Protocol (PP) SVR12.

Results: The majority (60%) of patients were male, with (mean values): age 59 years, body mass index (BMI) of 30, aspartate aminotransferase (AST) 105, and alanine aminotransferase (ALT) 101 IU/ml. HCV genotypes (GT) were: GT1 81% (59/73), GT2 10% (7/73), GT3 5% (4/73), GT4 3% (2/73), and GT6 1% (1/73). Eight percent (6/73) of patients had concurrent proton pump inhibitor (PPI) use, and 15% (11/72) had a baseline viral load > 6 MM IU/ml. Zero patients discontinued, two patients were reported as lost to follow-up, and there was one virologic failure. PP sustained virologic response at 12 weeks (SVR12) rate was 99% (70/71), and the intent-to-treat (ITT) SVR12 rate was 96% (70/73).

Conclusions: Early real-world experience indicates high effectiveness of the 8-week G/P regimen in a diverse treatment-naïve, compensated cirrhotic US population.

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Key Summary Points

Why carry out this study?

Expedition-8 is the first phase 3b trial to demonstrate a 98% (335/343) intent-to-treat (ITT) sustained virologic response rate 12 weeks post treatment (SVR12) in 343 treatment-naïve (TN) compensated cirrhosis (CC) patients after 8 weeks of glecaprevir/pibrentasvir (G/P).

Subsequently, G/P was approved on 26 September 2019 by the US Food and Drug Administration for an 8-week duration in TN hepatitis C virus (HCV)-infected patients with CC.

To date, there are no published US real-world studies of G/P with 8-week duration in TN/CC HCV patients.

What was learned from this study?

Early real-world experience indicates high effectiveness of an 8-week G/P regimen in a diverse treatment-naïve, compensated cirrhotic US population.

Results showed a high SVR12 rate of 96% (70/73 by ITT analysis) and 99% [70/71 by per protocol (PP) analysis], similar to the results of the EXPEDITION-8 registration study.

cause of death in the US compared with the next 60 reportable chronic infectious diseases combined in 2013 [2]. Patients living with HCV exhibit significantly greater risks for extra-hepatic manifestations and higher medical costs. Treatment of hepatitis C significantly mitigates this economic burden from HCV/hepatic complications and extrahepatic manifestations [3]. However, only about 19% of the HCV ribonucleic acid (RNA)-positive patients were treated for HCV in the US in 2016 [4]. While eliminating HCV may be extremely challenging, the World Health Organization (WHO) and multiple public policy advocacy groups have established goals to eliminate HCV by 2030 [5].

Glecaprevir/pibrentasvir (G/P) was initially approved in August 2017 for an 8-week duration in treatment-naïve (TN) non-cirrhotic (NC) patients with chronic HCV infection and for a 12-week duration in TN-compensated cirrhotic (CC) patients across genotypes (GT) 1–6. In September 2019, the US Food and Drug Administration (USFDA) approved a shorter 8-week treatment duration for G/P in GT 1–6 TN CC patients. FDA approval was based on the EXPEDITION-8 trial, which demonstrated 98% sustained virologic response at 12 weeks post treatment (SVR12) in 343 TN/CC patients with chronic HCV GT 1–6 infection [6]. A previous real-world study in 560 HCV TN/NC patients in the US with GT 1–6 infection demonstrated similar efficacy of an 8-week G/P treatment duration compared with registration trials [7]. The aim of this study is to provide the first US real-world effectiveness data of G/P 8-week treatment duration in TN/CC HCV patients.

METHODS

Real-world data from 73 TN/CC patients who initiated 8 weeks of G/P treatment between August 2017 and November 2018 were collected electronically from providers and specialty pharmacies of the Trio Health network and analyzed. The Trio Health network is a platform designed as a portal for specialty pharmacies and physicians to collaborate on efforts to improve patient care. Data were entered into the TRIO Health's proprietary Innervation

INTRODUCTION

The National Health and Nutrition Examination Survey (NHANES) estimated that there are 2.4 million hepatitis C virus (HCV) patients in the USA [1]. Chronic HCV infection is a leading cause of liver fibrosis that may progress to liver cirrhosis, hepatocellular carcinoma or hepatic decompensation. Hepatitis C is the leading

Platform through nightly file feeds and manual user data entry. This portal provides applied proprietary logic to identify and prompt users of input errors and missing data. Where mandated by state law, patients signed an electronic informed consent allowing specialty pharmacies to collect the data. Each participating clinician and specialty pharmacy signs an agreement attesting to compliance with all rules and regulations regarding the disclosure of patient information to a shared prescription database. FDA-mandated reporting of deaths and/or adverse events was assumed to be completed at the time of the event. The causes and outcomes of individual events were not known. TRIO Health Analytics was provided with de-identified, HIPAA-compliant patient information from the platform. A letter of exemption from the Western Institutional Review Board was received since this is a retrospective review of existing data recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects. The primary outcome measure in this study is an HCV plasma RNA below the limit of quantification obtained 12 weeks after the end of G/P treatment (SVR12). A window of 10–26 weeks post treatment was acceptable for the primary outcome measure. The primary end point of this study is the per protocol (PP) SVR12 rate in GT1–6 TN/CC HCV patients defined as adult patients who have received 8 weeks of G/P therapy and with an HCV RNA viral load measurement 10–26 weeks post treatment. The secondary end point is the intent-to-treat (ITT) SVR12 rate defined as all adult patients who initiated 8 weeks of G/P therapy.

Patients were included if they were TN/CC, > 18 years of age, initiated 8-week G/P (drug dispensed to patient), genotype 1–6, and had sufficient follow-up time in the database to obtain an SVR12 assessment. Patients were excluded if they were currently enrolled in a clinical trial; received initial prescription for > 8 weeks of G/P; had decompensated cirrhosis; current hepatocellular carcinoma (HCC) (previously treated HCC was permitted); had prior HCV

treatment; had missing age, missing fibrosis staging, missing prior HCV treatment status, missing or mixed genotype; and/or had a liver transplant.

Treatment-naïve was defined as no prior HCV treatment, reported by the treating physician. Cirrhosis was defined as a FIB-4 score > 5.2 [4] or was physician reported. Decompensated cirrhosis was defined as no current or past clinical evidence of Child-Pugh B or C classification or clinical history of liver decompensation including ascites, bleeding esophageal varices, or hepatic encephalopathy. Compensated cirrhosis was defined as cirrhosis with no prior history of liver decompensation.

Virologic failures were physician reported and defined as the first HCV viral load anytime post G/P 8-week treatment where the provider indicates a detectable level of HCV or the actual measure is above the lower level of quantification. Treatment start and end dates are defined by pharmacy dispensing records.

Baseline demographic and clinical characteristics consisted of information obtained closest to the start of therapy. These included: age, ethnicity, body mass index (BMI), and gender; laboratory values including alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets, hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), and hepatitis C virus ribonucleic acid (HCV RNA); comorbidities including human immunodeficiency virus (HIV), hepatitis B virus (HBV), anxiety, depression, chronic kidney disease (CKD), hyperlipidemia, and hypertension; genotype/subtype; concurrent proton pump inhibitor (PPI) use during HCV treatment; physician practice site; payer type (commercial, Medicare, Medicaid, other); and practice type (academic, community). Academic centers are defined as tertiary care centers or clinics affiliated with academic centers. Any other practice (solo or group) is characterized as a community site.

For patient disposition, lost to follow-up is defined as patients who were unreachable either during or after completion of treatment. SVR12 rates are calculated by dividing the number of HCV patients that achieved an SVR12 by the total number of patients in the study.

RESULTS

The majority (60%) of HCV patients were male, with a mean age of 59 years of age, BMI of 30, AST 105, and ALT 101 IU/ml. HCV genotypes (GT) were: GT1 81% (59/73), GT2 10% (7/73), GT3 5% (4/73), GT4 3% (2/73), and GT6 1% (1/73). Eight percent (6/73) of patients had concurrent PPI use, and 15% (11/72) had a baseline viral load > 6 million international units (IU)/milliliter (ml) (Table 1). No patients discontinued G/P therapy, two patients were reported as lost to follow-up, and there was one virologic failure (Fig. 1). The PP SVR12 rate was 99% (70/71), and the ITT SVR12 rate was 96% (70/73) (Table 2). The two patients that were lost to follow-up were both from community practices. One was a 65-year-old male with GT1b infection, 820,000 IU/ml baseline viral load, and concomitant PPI use. The second patient was a 73-year-old female with GT1 infection, 1,600,000 IU/ml baseline viral load. One patient with virologic failure relapsed after treatment. This patient was a male, 51 years old, with GT6 infection and a baseline viral load of 50,000,000 IU/ml, on Medicaid, and from a community practice (Table 3).

DISCUSSION

G/P was recently approved by the US Food and Drug Administration for use with a shortened treatment duration of 8 weeks in TN/CC patients with chronic HCV genotype 1–6 infection [8]. Here we report the first real-world effectiveness data of G/P 8-week treatment in HCV TN/CC patients from the US TRIO health community and academic healthcare providers who choose to utilize an 8-week treatment duration for TN/CC patients prior to FDA approval of the 8-week treatment duration. There are very limited ex-US real-world data on the 8-week effectiveness of glecaprevir/pibrentasvir in TN/CC HCV patients, and none of these studies have assessed more than ten HCV TN/CC patients [9–11]. In this limited sample, our results showed a high SVR12 rate of 96% (70/73 by ITT analysis) and 99% (70/71 by PP analysis), similar to the results of the

Table 1 Demographics and baseline characteristics

Characteristics	n/total (%)
Community practice	63/73 (86)
Payer type	
Commercial	19/73 (26)
Medicaid	22/73 (30)
Medicare	31/73 (42)
Other	1/73 (1)
Male	44/73 (60)
BMI, median (range)	30 (19–53)
Age, median (range)	59 (31–76)
Ethnicity	
White	20/73 (27)
Black	7/73 (10)
Asian	2/73 (3)
Hispanic or Latinx	4/73 (5)
Other or unspecified	40/73 (55)
Concurrent PPI use	6/73 (8)
Chronic kidney disease stage	
No CKD	40/67 (61)
1–3	25/67 (37)
4–5	1/67 (1)
Comorbidities	
Anxiety	12/73 (16)
Depression	13/73 (18)
Diabetes	12/73 (16)
Hypertension	33/73 (45)
Hyperlipidemia	5/73 (7)
HIV co-infection	1/73 (1)
HBV co-infection	2/73 (3)
Baseline laboratory	
ALT U/l, mean (SD) <i>n</i> = 73	101 (125)
AST U/l, mean (SD) <i>n</i> = 70	105 (184)
eGFR < 30 ml/min	1/67 (1)
HCV RNA > 6,000,000 IU/ml	11/73 (15)

Table 1 continued

Characteristics	n/total (%)
HCV genotype	
1a	41/73 (56)
1b	16/73 (22)
1 (subtype unspecified)	2/73 (3)
2	7/73 (10)
3	4/73 (5)
4	2/73 (3)
6	1/73 (1)

EXPEDITION-8 registration study with an ITT SVR12 rate of 98% (335/343) and PP SVR12 rate of 99.7% (334/335) [6]. Real-world evidence in addition to clinical trial results provides additional confidence and insights for healthcare providers. G/P is now the first and only 8-week treatment approved for GT1-6 chronic HCV infection in treatment-naïve patients without cirrhosis, or with compensated cirrhosis. This shorter duration offers an added benefit of simplifying treatment and has the potential to reduce costs, which will be important as the world moves towards eliminating HCV. Epidemiology estimates of the US HCV population suggest that as many as 98% of all TN HCV patients could be treated with an 8-week regimen [12].

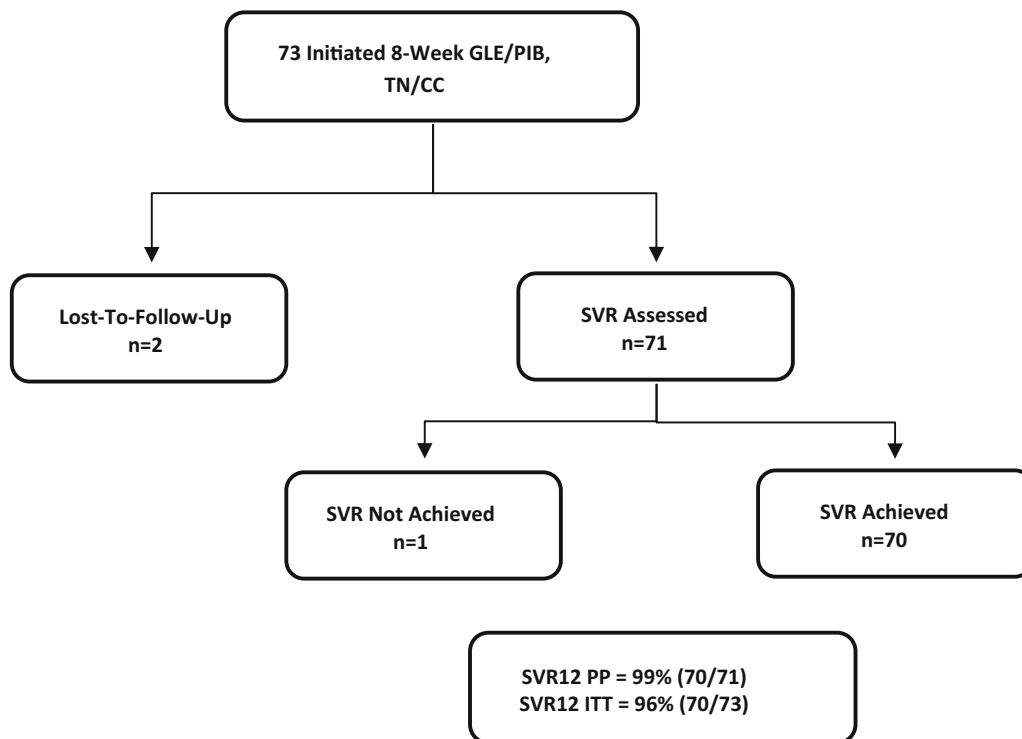


Fig. 1 HCV patient disposition

Table 2 SVR12 rates by genotype

Genotype	GT1	GT2	GT3	GT4	GT6	Total
SVR12 PP	100% (57/57)	100% (7/7)	100% (4/4)	100% (2/2)	0% (0/1)	99% (70/71)
SVR12 ITT	97% (57/59)	100% (7/7)	100% (4/4)	100% (2/2)	0% (0/1)	96% (70/73)

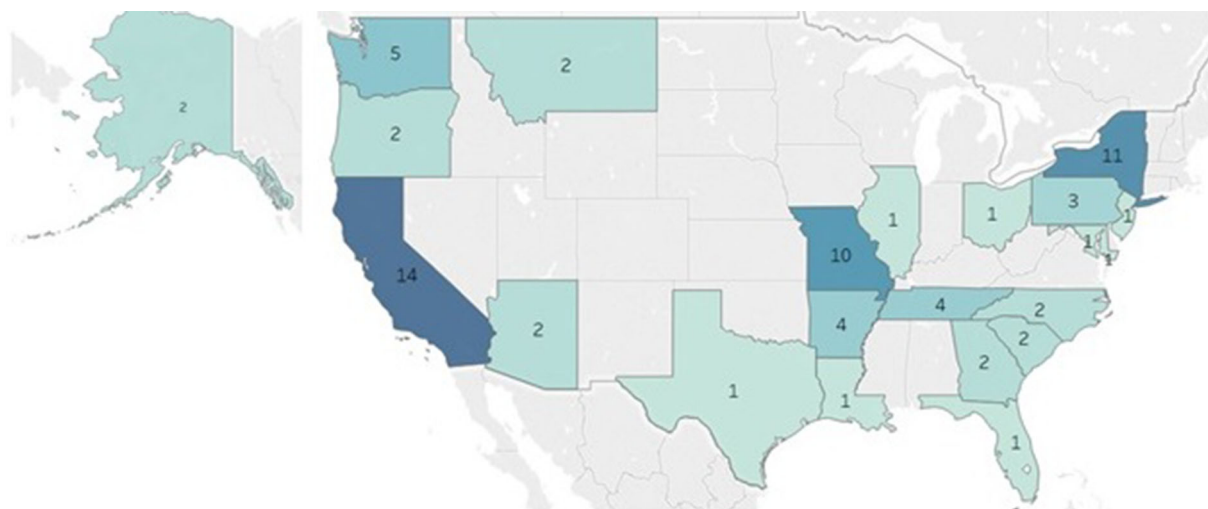


Fig. 2 Number of HCV patients, distribution by state

Table 3 Lost to follow-up and SVR12 not achieved patient characteristics

Type	Patient	Baseline VL	Genotype	Comorbidities	Concurrent PPI	Insurance	Practice type
Lost to follow-up	65, M	820,000	GT1B	None ^b	Yes	Commercial	Community
Lost to follow-up	73, F	1,600,000	GT1 ^a	CKD stage 2	No	Medicare	Community
SVR12 not achieved	51, M	50,000,000	GT6	None ^b	No	Medicaid	Community

^a Subtype mixed or unknown

^b Collected comorbidities include: anxiety, depression, hyperlipidemia, hypertension, diabetes, HIV, HBV, CKD stage

Limitations of this retrospective observational study include that the study subjects who met the study criteria were included regardless of demographics. While the data include 22 states, these results may not be generalizable to the entire US population (Fig. 2). To further inform this analysis, a complete characterization of the sample population is included in Table 1. As with all real-world studies, results may be further confounded by factors not included as covariates. Recall bias was limited to provider input into patients' charts and to patients' recollection. Therefore, the data are reflective of information recorded by the physician and would only be flawed if recorded improperly at the practice. Recall bias was not applicable to the prescription or dispensing

data, as it reflects actual transactions that occur at the pharmacy. As patients with identified decompensated Child-Pugh B or C cirrhosis are contraindicated for treatment with G/P, these patients were expressly excluded from this analysis based on a current or prior history of hepatic decompensation. Patient cirrhosis status included in the study was physician reported. While a bivariate analysis to identify associations of different variables with the outcome were planned, this was not possible, since only a single patient experienced a virologic failure.

The World Health Organization has established targets for HCV elimination by 2030; however, current rates of HCV treatment have been declining in the US, which can be

attributed to lack of patient awareness of infection as well as access barriers to treatment. To help address patient barriers to HCV treatment, the US Preventive Services Task Force and Center for Disease Control have published draft recommendations that now calls for universal screening for HCV in adults [13, 14]. Prevention can reduce the rate of new infections, as well as deaths. The availability of a simple, 8-week HCV treatment regimen that can be utilized in the broadest population with HCV infection provides a shorter time to cure and additional opportunity to encourage untreated patients to initiate HCV therapy.

Given the similar high cure rates and safety profiles of contemporary HCV regimens, HCV patients' preferences for therapy may be influenced by treatment attributes other than cure rates and tolerability. Treatments that are more convenient and require less disruption to their daily life (e.g., shorter treatment duration, no modification in PPI use, and fewer office visits when on treatment) are important to patients with HCV and should be considered when making treatment decisions [15].

CONCLUSIONS

Early real-world experience from the TRIO health network indicates high effectiveness of an 8-week G/P treatment duration for chronic HCV infection in a diverse treatment-naïve US population with compensated cirrhosis.

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Compliance with Ethics Guidelines. A letter of exemption from Western Institutional Review Board was received since this is a retrospective review of existing data that are recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available because Trio Health Analytics' data collection platform

conforms with HIPPA regulations; however, data may be available from Trio Health Analytics on reasonable request.

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