Clinical, Biostatistical, Clinical Pharmacology, Clinical Virology and CDTL Summary Review

Date	September 19, 2019
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Subject	Combined Discipline and Cross-Discipline Team Leader Summary Review
NDA/BLA # and Supplement#	NDA 209394, Supplements 7 and 8
Applicant	AbbVie
Date of Submission	March 29, 2019
PDUFA Goal Date	September 29, 2019
Proprietary Name	MAVYRET™
Established or Proper Name	glecaprevir/pibrentasvir
Dosage Form(s)	Tablets: 100 mg glecaprevir and 40 mg pibrentasvir
Applicant Proposed Indication(s)/Population(s)	*Indication (no changes proposed):* MAVYRET™ is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). *Additional Data:* Efficacy and safety data for HCV genotypes 5 and 6 and treatment-naïve HCV GT 1-6 subjects with compensated cirrhosis treated for 8 weeks
Applicant Proposed Dosing Regimen(s)	Three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food
Recommendation on Regulatory Action	Approval

Contents

Table of Tables

Table of Figures

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1. Introduction

The purpose of this combined primary Clinical, Statistical, Clinical Pharmacology, Clinical Virology, and CDTL Summary Review is to provide an overview of the submitted clinical and virologic data, summarize the findings of the FDA multi-disciplinary team of reviewers, describe the conclusions and recommendations presented by all disciplines, and provide an overall benefit-risk assessment of AbbVie's supplemental New Drug Applications (sNDAs) 209394, S-007 and S-008. Supplemental NDA 007 provides additional safety and efficacy data for the fixed dose combination of glecaprevir and pibrentasvir (GLE/PIB) treatment in subjects with genotype (GT) 5 and 6 HCV infection enrolled in ENDURANCE-5,6 (M16-126) to fulfill PMC 3246-2. Supplemental NDA 008 provides data from trial EXPEDITION-8 (M16-135) in subjects with hepatitis C (HCV) genotypes 1, 2, 3, 4, 5 or 6 infection and compensated cirrhosis who were treated with GLE/PIB for 8 weeks. The data from EXPEDITION-8 were submitted to support a shorter duration of 8 weeks of treatment for treatment-naïve subjects with compensated cirrhosis. EXPEDITION-8 initially excluded subjects with HCV GT3 infection, but the protocol was later amended to include GT3 subjects. The initial S-008 sNDA submission included data (b) (4) reflecting efficacy results from EXPEDITION-8 excluding GT3 subjects, as GT3 data were not yet complete at the time of the initial submission, but per the Division's request, data from the GT3 population that were available at the time of sNDA submission (cutoff date 2/28/2019) were summarized in a separate submission. In addition, the sponsor provided several updates of topline efficacy and resistance data from the GT3 population during the review of these efficacy supplements. The GT3 data were accepted based on the strong safety and efficacy results, as well as the importance for a clear and consistent public health message on dosing for treatment-naïve subjects across all genotypes.

Current labeling for GLE/PIB indicates treatment for pediatric patients 12 years and older or weighing at least 45 kilograms based on review of the data from DORA Part 1 (sNDA S-006). EXPEDITION-8 enrolled adults ≥18 years of age. The previously reviewed PK and safety data in adolescents from DORA Part 1 established the exposure and safety of GLE/PIB to be similar between adults and adolescents. Because the dose of GLE 100mg/PIB 40mg for the current indication remains unchanged, and because the disease and response to therapy is believed to be similar in adults and children, extension of the indication of 8-week dosing in treatment-naïve HCV patients with compensated cirrhosis is recommended for the adolescent population based on extrapolation of previously reviewed PK and safety data.

Based on review of the data provided, the benefit-risk remains favorable across all genotypes, including GT5 and GT6 which had fewer enrolled subjects than other genotypes in the original registrational trials. In addition, the data from EXPEDITION-8 support a shortened treatment duration of 8 weeks for treatment-naïve subjects with compensated cirrhosis, making this the first 8-week pan-genotypic HCV treatment for treatment-naïve patients with or without compensated cirrhosis. The clinical, statistical, clinical pharmacology and clinical virology team recommend the approval of these sNDAs.

2. Benefit Risk Framework

Benefit Risk Assessment Framework

Benefit Risk Integrated Assessment

MAVYRET is a fixed-dose combination of glecaprevir, a hepatitis C virus (HCV) NS3/4A protease inhibitor, and pibrentasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg with HCV GT1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The original MAVYRET New Drug Application (NDA) was approved on August 3, 2017. The current NDA supplements provide additional efficacy and safety data that continue to support the recommended use of GLE/PIB in patients with HCV GT5 or GT6 infection who were underrepresented in the original NDA, as well as new efficacy and safety data that support a shortened treatment duration of 8 weeks for treatment-naïve patients with compensated cirrhosis for all major HCV genotypes.

HCV infection is a serious disease, affecting an estimated 3 million people in the U.S. and over 100 million people worldwide. Although often asymptomatic in early stages, if untreated, chronic HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. The current standard of care treatments for HCV GT 1-6 infection consist of oral direct-acting antivirals (DAAs) that result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in up to 93-100% of patients.

GLE/PIB demonstrated SVR12 rates ranging from 91-100% for treatment durations recommended by the FDA review team in the original NDA submission. SVR rates varied depending on the regimen, patients' HCV GT, and patients' prior treatment history. Efficacy in the original NDA was similar in patients with or without cirrhosis, with or without HIV coinfection, and with chronic kidney disease (CKD), with or without hemodialysis. Efficacy results were similarly high in these supplements both for the HCV GT5- and GT6-infected population, which demonstrated an overall SVR12 rate of 98% (82/84), and for the population of treatment-naïve subjects with GT 1,2,3,4, 5 or 6 HCV infection and compensated cirrhosis treated for 8 weeks, which demonstrated an overall SVR12 rate of 98% (335/343). No new major safety issues were identified based on the data submitted for this review and the overall safety profile of GLE/PIB remains unchanged. However, labelling changes were made based on three separate post-marketing safety assessments: a warning regarding the risk of hepatic decompensation/failure in patients with baseline advanced liver disease, labeling in Section 7 Drug Interactions to describe the potential for safe and effective use of concomitant medications with changes in hepatic function, and labeling describing angioedema in the postmarketing section.

The previously reviewed PK and safety data in adolescents from DORA Part 1 established the exposure and safety of GLE/PIB to be similar between adults and adolescents. Because the dose of GLE 100mg/PIB 40mg for the current indication remains unchanged, and because the

disease and response to therapy is believed to be similar in adults and children, extension of the indication of 8-week dosing in treatment-naïve HCV patients with compensated cirrhosis is recommended for the adolescent population based on extrapolation of previously reviewed PK and safety data.

The multidisciplinary review team and CDTL recommend approval of these supplements in adults and adolescents 12 years and older or weighing at least 45 kilograms based on review of the available evidence of efficacy and safety submitted.

Benefit Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic hepatitis C viral infection (HCV infection) causes inflammation of the liver that can lead to long-term health problems or death. • Globally it is estimated that over 71 million people are chronically infected with HCV, including approximately 2.4 million people in the United States (U.S.). • Reported cases of acute HCV increased about 3.5-fold from 2010 through 2016 -Incidence reflects new infections associated with rising rates of injection-drug use • 41,200 new HCV infections occurred in 2016 - 80% people who inject drugs (PWIDS) • New infections are increasingly common in women, children and in younger patients in rural and vulnerable urban settings with less access to specialist providers. • There are six major HCV genotypes (GTs). Most common among U.S. patients is GT 1 (72%), followed by GT 2 (11%), GT 3 (9%), and GT 4 (6%). GTs 5 and 6 occur uncommonly (< 1%) in the U.S. but may predominate in other parts of the world. Less common genotypes have been less well represented in clinical studies given the difficulties of recruiting and enrolling those patients with rare genotypes. • HCV infection is typically asymptomatic in its early stages. However, if left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the U.S.	• If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population. Patients can experience symptoms that are severe and debilitating and can transmit the infection to others. HCV infection is a significant and growing public health concern particularly in the context of an ongoing HCV-Opioid co-epidemic.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The current standard-of-care treatments for chronic HCV infection are interferon-free, all-oral DAA regimens, with high SVR rates. Treatment options vary based on disease status and other patient characteristics, including HCV GT and prior treatment history. GLE/PIB currently provides the first pangenotypic 8-week treatment option for treatment-naïve patients without cirrhosis; patients with cirrhosis currently are prescribed 12 or more weeks of therapy. • Currently, there are three available treatment options for adolescents with HCV. Ledipasvir/sofosbuvir, sofosbuvir and ribavirin and GLE/PIB are approved for use in adolescents 12 years and older.	• Given potential complex drug interactions and challenges with adherence associated with longer durations of therapy, a shorter pangenotypic regimen for patients with cirrhosis is of therapeutic benefit, particularly in the context of the HCV-Opioid epidemic. This may also eliminate the need for HCV genotype testing for treatment-naïve patients and may facilitate a "test and treat" • Extension of the 8-week dosing duration in treatment-naïve HCV adolescents with compensated cirrhosis is supported based on extrapolation of previously reviewed PK and safety data. • response to the epidemic, implementable by non-specialist providers regardless of cirrhosis status (in patients without decompensated liver disease).
Benefit	• In the original approval, the efficacy and safety of GLE/PIB was established in nine Phase 2 and 3 clinical trials which cumulatively evaluated 2,369 subjects who received GLE/PIB for 8, 12 or 16 weeks duration. The trial populations varied based on HCV GT, cirrhosis status, treatment experience and renal disease. • As in the original NDA, the primary efficacy endpoint was the proportion of subject who achieved SVR12, which is considered a virologic cure. • Efficacy was similarly high in these supplements both for the HCV GT5 and GT6 population, which demonstrated an overall SVR12 rate of 98% (82/84), and for the population of treatment-naïve subjects with GT 1,2,3,4, 5 or 6 HCV infection with compensated cirrhosis, that demonstrated an overall SVR12 rate of 98% (335/343). • Although the numbers of subjects with HCV GT 5 and 6 and compensated cirrhosis treated for 8 weeks were small in EXPEDITION-8 (GT 5 N=1, GT 6 N=9), the 8 week treatment duration for these genotypes is also supported by consistently high efficacy with this duration of treatment across all	• Nine clinical registrational trials and other trials conducted in specific populations previously provide substantial evidence of effectiveness of GLE/PIB for treatment of chronic HCV infection GT1-6. • Limited data from GT5 and 6 infected patients in the registrational trials were available at the time of the Original NDA review to support the recommended treatments for patients with these genotypes. Additional data from ENDURANCE- 5,6 continue to support the use of GLE/PIB for patients with HCV GTs 5 and 6. • Results from EXPEDITION-8 support a shortened treatment duration of 8 weeks for treatment-naïve patients with compensated cirrhosis, regardless of HCV genotype.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	genotypes in EXPEDITION-8, including GT3, which traditionally has been considered harder to treat with DAA regimens. In addition, the results of ENDURANCE-5,6, indicate that efficacy in HCV GT 5 and 6 patients do not differ from that of other genotypes treated with GLE/PIB for the same durations.	• Additionally, available data from the sponsor and others indicate most patients who fail treatment with GLE/PIB can be retreated successfully with either GLE/PIB + sofosbuvir + ribavirin or sofosbuvir/velpatasvir/voxilaprevir.
Risk and Risk Management	• No new safety signals were detected in the review of ENDURANCE-5,6 and EXPEDITION-8 • Labeling changes were made based on the following post-marketing assessments: o New Warning and Precautions in Section 5.2 describing the risk of hepatic decompensation in patients with evidence of baseline advanced liver disease o Labeling in Section 7 Drug Interactions to describe the potential for safe and effective use of concomitant medications with changes in hepatic function o New Section 7.4 describing drug interactions with Medication Assisted Treatment for Opioid Use Disorder, and o Angioedema was added to Section 6.2 Postmarketing Experience	• Safety concerns associated with GLE and PIB are adequately addressed in product labelling

3. Background

According to World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) estimates, chronic HCV infection affects approximately 71 million people worldwide, and 2.4 million people in the United States. Reported cases of acute HCV increased about 3.5-fold from 2010 through 2016. The increasing incidence reflects new infections associated with rising rates of injection-drug use; 41,200 new HCV infections occurred in 2016 - 80% people who inject drugs (PWIDS). New infections are increasingly common in women, children and in younger patients particularly in rural and vulnerable urban settings with less access to specialist providers, highlighting the need for short, safe and easily administrable regimens with clear, consistent and simple dosing regimens.

Over years, chronic HCV infection can lead to liver-related complications such as cirrhosis, liver failure, and hepatocellular carcinoma (HCC)[1]. In the United States, chronic HCV infection is the second most common etiology of liver disease leading to liver transplantation and development of HCC and is responsible for more annual deaths than HIV and 59 other infectious diseases combined[2].

Virologic cure is measured by the lack of quantifiable HCV RNA in the blood at certain time points after completion of HCV therapy, known as sustained virologic response (SVR). SVR at 12 weeks post-treatment (SVR12) is the standard measure of virologic cure.

MAVYRET is a fixed-dose combination of glecaprevir (GLE), an HCV NS3/4A protease inhibitor, and pibrentasvir (PIB), an HCV NS5A inhibitor, and is indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A). MAVYRET is also indicated for the treatment of adult and pediatric patients 12 years and older or weighing at least 45 kg with HCV GT1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. The original MAVYRET New Drug Application (NDA) was approved on August 4, 2017. GLE/PIB was the first regimen indicated to treat all major HCV genotypes (1-6) including patients with advanced renal disease and for those requiring hemodialysis.

sNDA 209394 Supplement-7 (S-007) provides additional efficacy and safety results from clinical trial ENDURANCE-5,6 (M16-126) that continue to support the recommended use of GLE/PIB in patients with HCV GT5 or GT6 infection and to fulfill PMC3246-2, which was requested given the limited data from subjects with HCV GT5 or GT6 infection in the original application. sNDA S-008 provides efficacy and safety data from clinical trial EXPEDITION-8 (M16-135), which support a shortened treatment duration of 8 weeks for treatment-naïve patients with compensated cirrhosis for all major HCV genotypes.

4. Product Quality

No new product quality information was included in these sNDAs. The commercial GLE/PIB drug product is an immediate release fixed-dose combination bilayer tablet containing 100 mg of glecaprevir in one layer and 40 mg of pibrentasvir in the other layer for once daily oral administration. The dosing regimen consists of a total daily dose of glecaprevir/pibrentasvir 300 mg/120 mg (or three 100 mg/40 mg tablets daily).

Please refer to the Office of Product Quality (OPQ) reviews in the original NDA by Dr. Danuta Gromek-Woods, Dr. Balajee Shanmugam, Dr. Raymond Frankewich, Dr. Kasturi Srinivasachar, Dr. Ying Wang and Dr. Upinder Atwal for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for GLE/PIB.

5. Nonclinical Pharmacology/Toxicology

This section provides a brief review of key outcomes of the pharmacology/toxicology program. No new toxicology data were reviewed for these supplements. Please see the original NDA submission primary nonclinical review by Ilona Bebenek for complete details.

No clinically relevant adverse effects were observed in pivotal repeat-dose general toxicology studies for GLE or PIB. Clinically relevant non-adverse effects included elevated ALT and GGT levels in GLE dog studies.

Both GLE and PIB were not considered genotoxic based on negative results in the in vitro bacterial mutation assay, in vitro mammalian chromosome aberration assay, and in vivo rat micronucleus assay

There were no clinically relevant adverse effects on male or female fertility, embryofetal development, or pre/post-natal development in rats for either GLE or PIB.

6. Clinical Pharmacology

6.1. Conclusions

The clinical pharmacology review team recommends approval of these sNDAs. Clinical pharmacology related items of these sNDAs are discussed below.

6.2. Labeling Recommendations

No clinical pharmacology related labeling updates are recommended based on the results of the two submitted clinical trials; ENDURANCE-5,6 (sNDA 209394, S-007) and EXPEDITION-8 (sNDA 209394, S-008).

Due to the current opioid and HCV syndemic in the US, the following new subsection was proposed to highlight and emphasize important drug-drug interaction information important to providers.

> **7 . 4 Medication-Assisted Treatment (MAT) for Opioid Use Disorder**
> No buprenorphine/naloxone or methadone dosage adjustment is required when used concomitantly with MAVYRET. There is insufficient information to make a recommendation regarding the concomitant use of naltrexone with MAVYRET.

6.3. Clinical Trial ENDURANCE-5,6

Only clinical pharmacology related results are discussed in this section.

The applicant provided a summary of GLE and PIB plasma concentrations by binned time interval and treatment arm (Appears this way on original

Table 1 and Table 2).

Table 1 GLE Plasma Concentrations by Binned Time Interval and Treatment Arm

Treatment Arm	Binned Time Interval (h)	Number of Samples	Median (Mean, SD)	
			Time from Previous GLE Dose (h)	GLE Concentration (ng/mL)
Arm A (Non-Cirrhotic)	1 to 3	10	2.24 (2.21, 0.41)	772 (1150, 1110)
	3 to 6	7	3.68 (3.62, 0.45)	2840 (3010, 1300)
	6 to 10	8	8.06 (7.78, 0.65)	45.3 (489, 1250)
	10 to 22	59	20.3 (18.0, 4.05)	27.1 (71.3, 93.4)
	22 to 26	167	24.3 (24.2, 1.12)	9.38 (24.9, 65.1)
	> 26	47	27.2 (36.4, 49.4)	8.64 (34.5, 113)
Arm B (Cirrhotic)	10 to 22	6	19.6 (19.9, 0.92)	15.4 (19.4, 14.5)
	22 to 26	36	24.0 (24.0, 0.78)	22.7 (25.9, 18.2)
	> 26	3	26.2 (26.3, 0.32)	30.5 (29.6, 14.9)

GLE = glecaprevir; h = hour; SD = standard deviation
Source: Clinical Study Report, P. 98

Table 2 PIB Plasma Concentrations by Binned Time Interval and Treatment Arm

Treatment Arm	Binned Time Interval (h)	Number of Samples	Median (Mean, SD)	
			Time from Previous PIB Dose (h)	PIB Concentration (ng/mL)
Arm A (Non-Cirrhotic)	1 to 3	10	2.24 (2.21, 0.41)	130 (127, 83.2)
	3 to 6	7	3.68 (3.62, 0.45)	153 (192, 99.8)
	6 to 10	8	8.06 (7.78, 0.65)	68.1 (113, 78.6)
	10 to 22	59	20.3 (18.0, 4.05)	30.8 (45.4, 33.9)
	22 to 26	167	24.3 (24.2, 1.12)	25.2 (30.3, 20.9)
	> 26	47	27.2 (36.4, 49.4)	25.5 (29.2, 25.9)
Arm B (Cirrhotic)	10 to 22	6	19.6 (19.9, 0.92)	27.4 (29.1, 13.3)
	22 to 26	36	24.0 (24.0, 0.78)	26.6 (27.3, 14.3)
	> 26	3	26.2 (26.3, 0.32)	22.4 (20.5, 4.69)

h = hour; PIB = pibrentasvir; SD = standard deviation
Source: Clinical Study Report, P. 99

Results

The median $C_{22\text{-}26}$ of GLE and PIB were about 2.4-fold higher and similar, respectively, in subjects with compensated cirrhosis vs. subjects without cirrhosis (Tables 1 and 2). Of note, GLE AUC and Cmax values increased by ~ 2-fold in subjects with cirrhosis vs. those without cirrhosis, while PIB AUC and Cmax values were comparable between subjects with cirrhosis vs. those without cirrhosis (Please see the USPI and Report RD 160234 in the original NDA for more details).

6.4. Clinical Trial EXPEDITION-8

Only clinical pharmacology related results are discussed in this section.

The applicant provided a summary of GLE and PIB concentrations following administration of GLE/PIB 300/120 mg QD to treatment-naïve adults with chronic HCV Genotype 1,2,4,5 and 6 infection and compensated cirrhosis as shown in (

Appears this way on original

Table 3 and Table 4).

Table 3 GLE Plasma Concentrations During the Treatment Period and Time from Previous Dose

Treatment	Binned Time Interval (h)	Number of Samples	Median (Mean, SD)	
			Time from Previous GLE Dose[a] (h)	GLE Concentration (ng/mL)
GLE/PIB 300 mg/120 mg QD	0 to 1	10	0.79 (0.67, 0.35)	64.2 (356, 611)
	1 to 3	32	2.21 (2.15, 0.59)	859 (1550, 2020)
	3 to 6	25	3.83 (4.19, 0.91)	717 (1030, 1100)
	6 to 10	7	6.83 (6.82, 0.30)	865 (755, 289)
	10 to 22	274	20.1 (18.9, 3.1)	102 (290, 515)
	22 to 26	625	23.8 (23.8, 1.0)	34.4 (225, 769)
	> 26	103	26.8 (27.9, 4.0)	27.0 (270, 796)

eCRF = electronic case report form; h = hour; QD = once daily; SD = standard deviation

a. Calculated on the basis of the date and time of the previous dose recorded in the eCRF at the time of the blood draw.

Source: Clinical Study Report, P. 104

Table 4 PIB Plasma Concentrations During the Treatment Period and Time from Previous Dose

Treatment	Binned Time Interval (h)	Number of Samples	Median (Mean, SD)	
			Time from Previous PIB Dose[a] (h)	PIB Concentration (ng/mL)
GLE/PIB 300 mg/120 mg QD	0 to 1	10	0.79 (0.67, 0.35)	16.3 (27.1, 28.5)
	1 to 3	32	2.21 (2.15, 0.59)	62.8 (77.2, 60.9)
	3 to 6	25	3.83 (4.19, 0.91)	84.3 (125, 94.0)
	6 to 10	7	6.83 (6.82, 0.30)	98.2 (107, 70.0)
	10 to 22	274	20.1 (18.9, 3.1)	36.0 (44.3, 34.4)
	22 to 26	625	23.8 (23.8, 1.0)	26.0 (39.3, 39.8)
	> 26	103	26.8 (27.9, 4.0)	22.7 (42.9, 52.3)

eCRF = electronic case report form; h = hour; QD = once daily; SD = standard deviation

a. Calculated on the basis of the date and time of the previous dose recorded in the eCRF at the time of the blood draw.

Source: Clinical Study Report, P. 105

7. Clinical Virology

7.1 Clinical Virology Conclusions and Summary of Labeling Recommendations

NDA 209394 efficacy supplements S-007 and S-008 are approvable from a Clinical Virology perspective.

Results from clinical trial ENDURANCE-5,6 (M16-126) showed a high SVR12 rate of 98% (82/84) among subjects infected with HCV GT5 (n=23) or GT6 (n=61), confirming that GLE/PIB is highly effective for the treatment of HCV GT5 and GT6 infection. One GT5a infected subject and one GT6f infected subject experienced virologic failure in ENDURANCE-5,6. HCV subtype 6f, which appears to be extremely uncommon in the U.S., may be particularly difficult to treat as this subtype has been reported to have reduced susceptibility to NS5A inhibitors.

In clinical trial EXPEDITION-8 (M16-135), a total of 280 treatment-naïve, HCV non-GT3 infected subjects with compensated cirrhosis were initially enrolled to receive GLE/PIB for 8 weeks. The intent-to-treat SVR12 rate in this population was 98% (274/280), with no cases of virologic failure. Topline SVR12 results from GT3 infected subjects who enrolled later in the trial showed similarly high efficacy, with an intent-to-treat SVR12 rate of 95% (60/63) and only a single case of virologic failure. Baseline NS5A resistance-associated polymorphisms did not affect treatment outcomes in this trial. Of note, baseline NS5A A30K and Y93H polymorphisms each were detected in 5% (3/62) and 6% (4/62) of GT3 infected subjects, respectively, none of whom experienced virologic failure. The one GT3 infected subject who

experienced virologic failure had treatment-emergent NS5A A30K+Y93H detected at the time of failure (relapse). Overall, these results from clinical trial EXPEDITION-8 indicate the GLE/PIB 8-week duration was highly effective in treatment-naïve, compensated cirrhotic subjects across all major HCV genotypes, including GT3.

The Clinical Virology Reviewer recommends updating product labeling to (1) incorporate efficacy results from GT5 and GT6 infected subjects in clinical trial ENDURANCE-5,6 into Section 14, and (2) recommend an 8-week GLE/PIB treatment duration for treatment-naïve, compensated cirrhotic patients across all major HCV genotypes (1-6), with key supporting resistance and efficacy data from EXPEDITION-8 summarized in Sections 12.4 and 14, respectively.

7.2 Nonclinical Virology

No new nonclinical virology information was reported or reviewed for these applications.

7.3 Clinical Virology

7.3.1 Methodology

The Clinical Virology review included independent analyses of HCV RNA and drug resistance data from clinical trials ENDURANCE-5,6 and EXPEDITION-8. For both trials, plasma HCV RNA levels were determined by a central laboratory using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0, which has a lower limit of quantification (LLOQ) of 15 IU/mL regardless of HCV genotype. The primary efficacy endpoint was sustained virologic response at Post-Treatment Week 12 (SVR12), defined as HCV RNA <LLOQ 12 weeks after the last actual dose of study drug.

HCV genotype and subtype were assessed at Screening using the Versant® HCV Genotype Inno-LiPA Assay, Version 2.0 or higher (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY) by the central laboratory. If the LiPA assay was unable to genotype a sample, its genotype and subtype was to be determined by a Sanger sequencing assay the NS5B gene, also conducted by the central laboratory. HCV subtypes were further refined retrospectively by phylogenetic analysis of baseline NS3/4A or NS5A amino acid sequences. For the purposes of this review, HCV subtype determination was based on the same algorithm used by the sponsor, which was based primarily on phylogenetic analysis. If phylogenetic analysis results were not available, HCV subtype was based on NS5B sequence analysis; if NS5B subtype was not available, LiPA assay results were used. Across both trials 99% (359/364) of subjects had subtype data available based on phylogenetic analysis.

For resistance analyses, next generation sequencing (NGS) analyses of HCV NS3/4A and NS5A genes were conducted for baseline samples from all subjects, and appropriate post-baseline samples for any subjects who experienced virologic failure. Amino acid changes were reported in datasets relative to subtype-specific prototypic reference sequences. The sponsor confirmed in SDNs 389/390 that the reference sequences in datasets AXRFNS3 and AXRFNS5A in the Original NDA are applicable for the resistance analyses for these sNDAs. Resistance data were provided in a vertical analysis dataset structure, and all amino acids

detected at a frequency of ≥2% (technical cutoff) were reported. For analyses of baseline polymorphisms, only those detected at a frequency of ≥15% of the viral population were considered, as lower frequency variants generally have not been found to be clinically significant, at least in DAA-naïve subjects. More in-depth analyses were conducted specifically for subjects who experienced virologic failure.

The sponsor's resistance analyses considered two sets of amino acid positions for each drug target, including one broad list of positions and one narrow "Key Subset" list of positions. This reviewer's independent analysis considered the same set of positions in the sponsor's "Key Subset" list, with the exception that position 56 was added to the NS3 list, as substitutions at this position have been associated with resistance to GLE and other newer generation NS3/4A protease inhibitors. The following amino acid positions were considered in the independent analyses:

- NS3: 56, 155, 156, 168
- NS5A: 24, 28, 30, 31, 58, 92, 93

7.3.2 Clinical Trial ENDURANCE-5,6 (M16-126) (S-007, GT5/6)

A total of 84 subjects were enrolled in ENDURANCE-5,6, including 23 subjects with HCV GT5 infection, and 61 subjects with HCV GT6 infection. Independent Clinical Virology analyses of the sponsor's HCV RNA dataset confirmed the sponsor's efficacy analyses. The overall SVR12 rate was 98% (82/84). SVR12 results according to HCV genotype and cirrhosis status are summarized in Table 5 (FDA analysis).

Table 5 ENDURANCE-5,6 SVR12 results (intent-to-treat analysis) according to HCV genotype and cirrhosis status

	Non-Cirrhotic + Cirrhotic	Non-Cirrhotic (GLE/PIB 8W)	Cirrhotic (GLE/PIB 12W)
All Subjects	98% (82/84)	99% (74/75)	89% (8/9)
GT5 Subjects	96% (22/23)	95% (19/20)	100% (3/3)
GT6 Subjects	98% (60/61)	100% (55/55)	83% (5/6)

There is only a single confirmed GT5 subtype (GT5a), while GT6 is extremely genetically diverse with at least 29 subtypes (6a-6xf) (ICTV-June 2017). HCV GT5 is primarily found in Southern Africa, and GT6 is primarily found in Southeast Asia; both genotypes are uncommon in the U.S., accounting for ≤1% of U.S. infections (Gower et al., 2014; Messina et al., 2015). No GT5 infected subjects were enrolled at a U.S. study site. At least 15 different HCV GT6 subtypes were represented in the trial, although subtypes 6a and 6e were most common, consistent with previous DAA trials. A total of 15 HCV GT6 infected subjects were enrolled at U.S. study sites and included subjects with subtypes 6a (n=7), 6e (n=3), 6j (n=1), 6p (n=2) or 6c-l/undetermined (n=2).

Table 6 (FDA analysis) shows a breakdown of HCV GT5 and GT6 subtypes and SVR12 results.

Table 6 ENDURANCE-5,6 SVR12 results (intent-to-treat analysis) according to HCV subtype

HCV Subtype	SVR12 Rate
5a	22/23 (96%)
6a	26/26 (100%)
6b/6xd	1/1 (100%)
6c	1/1 (100%)
6c-l*	1/1 (100%)
6e	12/12 (100%)
6f	0/1 (0%)
6h	1/1 (100%)
6j	1/1 (100%)
6k	3/3 (100%)
6l	4/4 (100%)
6m	1/1 (100%)
6n	3/3 (100%)
6o	1/1 (100%)
6p	2/2 (100%)
6q	1/1 (100%)
6r	1/1 (100%)
6-unassigned subtype	1/1 (100%)

*GT6c-l based on LiPA assay; all other reported subtypes based on phylogenetic analysis

The two subjects who did not achieve SVR12 experienced virologic failure. Subject (b) (6) (GT5a, Non-Cirrhotic, Tx-Naïve, GLE/PIB 8W) experienced virologic relapse between Post-Treatment Weeks 4 and 12, and Subject (b) (6) (GT6f, Cirrhosis, Tx-Naïve, GLE/PIB 12W) experienced virologic breakthrough at Treatment Week 12.

Overall, baseline NS3 and NS5A resistance-associated polymorphisms were detected in 19% (15/79) and 48% (39/81) of subjects, respectively. Table 7 (FDA analysis) summarizes the specific NS3 and NS5A polymorphisms of interest.

Table 7 HCV amino acid polymorphisms detected at resistance-associated positions in GT5 and GT6 infected subjects in ENDURANCE-5,6 (≥15% frequency, polymorphisms reported relative to indicated subtype-specific reference strains). Blank cell indicates same amino acid as reference.

		NS3 Polymorphisms					NS5A Polymorphisms							
HCV Subtype	**Ref.**	**56**	**155**	**156**	**168**	**Any NS3**	**24**	**28**	**30**	**31**	**58**	**92**	**93**	**Any NS5A**
5a (n=23, both targets)	SA13	F	R	A	D	13 (57%)	Q	L	Q	L	P	A	T	3 (13%)
					E(13)				L(1)		S(1)	S(1)		
6a (n=25, both targets)	EUHK2	Y	R	A	D	1 (4%)	Q	F	R	L	T	A	T	17 (68%)
					E(1)		K(3)	L(17)		M(1)				
6b/6xd (n=1, both targets)	L394 (6xd)	Y	R	A	D	1 (100%)	K	F	R	L	P	A	T	1 (100%)
		F(1)			E(1)			Y(1)			S(1)			
6c (n=1, NS5A only)	TH846	Y	R	A	D	n/a	K	V	A	L	G	P	T	1 (100%)
	(no data available)											A(1)		
6e (n=12, both targets)	GX004	Y	R	A	D	0 (0%)	K	V	S	L	P	A	T	7 (58%)
							R(5)	M(6)		I(1)				
6f (n=1, both targets)	C-0044	Y	R	A	D	0 (0%)	K	A	S	L	S	A	T	0 (0%)
6h (n=1, both targets)	VN004	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	1 (100%)
											S(1)			
6j (n=1, both targets)	TH553	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	1 (100%)
											A(1)			
6k (n=2 NS3, n=3 NS5A*)	KM41	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	0 (0%)
6l (n=4, both targets)	537796	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	2 (50%)
									T(1)	I(1), M(1)				
6m (n=1, both targets)	C-0185	Y	R	A	D	0 (0%)	K	V	S	L	T	A	S	0 (0%)
6n (n=3, both targets)	KM42	Y	R	A	D	0 (0%)	K	V	S	L	T	A	S	1 (33%)
									A(1)					
6o (n=1, both targets)	QC227	Y	R	A	D	0 (0%)	K	L	A	L	A	A	S	1 (100%)
													T(1)	
6p (n=2, both targets)	QC216	Y	R	A	D	0 (0%)	K	V	S	L	P	A	T	2 (100%)
								M(1)					S(1)	
6q (n=1, both targets)	QC99	Y	R	A	D	0 (0%)	K	V	S	L	P	A	T	1 (100%)
													S(1)	
6r (n=1, both targets)	QC245	F	R	A	D	0 (0%)	K	G	A	L	P	A	T	1 (100%)
								A(1)						

The primary baseline polymorphism of interest in HCV GT5a infected subjects is NS3 D168E, although it is challenging to draw firm conclusions on the impact of this polymorphism based on a single case of virologic failure among 13 subjects with this polymorphism. Position NS3 D168 is a key GLE resistance-associated position, and D168E is a relatively common polymorphism in GT5a. In an HCV GT5a-based replicon, an NS3 D168E substitution conferred a relatively modest 4.2-fold decrease in GLE anti-HCV activity (Clinical Virology Review Addendum for Original NDA 209394). In ENDURANCE-5,6, NS3 D168E was detected in 57% (13/23) of GT5a subjects, including Subjec (b) (6) who experienced virologic relapse following GLE/PIB 8-week treatment. The other 12 GT5a infected subjects with NS3 D168E achieved SVR12, including 10 non-cirrhotic subjects treated for 8 weeks and 2 cirrhotic subjects treated for 12 weeks, reflecting an overall SVR12 rate of 92% (12/13) for GT5a infected subjects with NS3 D168E. Baseline NS5A resistance-associated polymorphisms were infrequent in GT5a infected subjects (n=3) and none were detected in Subject (b) (6)

For GT6 infected subjects, as expected, there was extensive amino acid heterogeneity at NS5A resistance-associated positions both within and between subtypes. Again, with only a single case of virologic failure among GT6 infected subjects it is not possible to draw any conclusions on the impact of GT6 subtypes and baseline NS5A polymorphisms on treatment efficacy. Nevertheless, it is noted that the single GT6 virologic failure, Subject (b) (6), was also the only subject with subtype 6f infection. No subjects with subtype 6f were included in the Original NDA dataset (Clinical Virology review of Original NDA 209394). Subject (b) (6) did not have any reported NS3 or NS5A baseline amino acid polymorphisms at resistance-associated positions relative to the C-0044 GT6f reference strain. Baseline NS3 resistance-associated polymorphisms were infrequent in GT6 infected subjects (n=2) precluding any conclusion about their impact on efficacy.

Data from other DAA programs indicate that HCV subtype 6f may be particularly challenging to treat. According to the Clinical Virology review of sofosbuvir/velpatasvir (Epclusa®) by Dr. Lisa Naeger, an HCV replicon carrying the first 100 amino acids of NS5A from a GT6f clinical isolate had 432- and 13,631-fold reduced susceptibility to the NS5A inhibitors velpatasvir and ledipasvir, respectively, relative to a subtype 1a laboratory strain. An A28M site-directed amino acid substitution (to wild-type AA in GT1a) restored velpatasvir anti-HCV activity against this clinical isolate. This reviewer is not aware of any data on the cell culture antiviral activity of PIB against HCV GT6f. A published clinical study showed that elbasvir/grazoprevir (NS5A inhibitor + NS3/4A protease inhibitor) had poor efficacy in a small group of subjects with GT6f infection, with 5 of 6 subjects (83%) experiencing on-treatment virologic failure (George et al., 2018). Presumably HCV subtype 6f is extremely uncommon in the U.S., as any GT6 subtype is uncommon in the U.S.; the single GT6f GLE/PIB failure subject was from Australia, and the 6 GT6f subjects from the elbasvir/grazoprevir study were all from Thailand.

Table 8 (FDA analysis) summarizes all of the reported amino acid changes detected at any frequency ≥2% (assay technical cutoff) relative to subtype-specific references, both at baseline and at the time of virologic failure for Subjects (b) (6) and (b) (6), considering the full NS3 protease domain (amino acids 1-181) and NS5A amino acids 1-100, which encompass all of the known key resistance-associated positions for NS3/4A protease inhibitors and NS5A inhibitors, respectively.

Table 8 HCV amino acid polymorphisms/substitutions detected in ENDURANCE-5,6 virologic failure subjects (b) (6) and (b) (6). The table includes any amino acid change detected at a ≥2% frequency in the NS3 protease domain [aa 1-181] or NS5A amino acids 1-100 relative to subtype-specific reference strains.

USUBJID	Visit	Target	AA Substitution	AA Frequency (%)	Tx-Emergent?	Tx-Enriched?	Key Resist. Position?
(b) (6)	BASELINE	NS3/4A	I18V	99.83			
			K26R#	6.59			
			C47S	16.42			
			A61S	99.26			
			T87S	99.49			
			S93*#	2.06			
			V114I	99.73			
			R117H	97.67			
			R117N#	2.02			
			T122A#	83.56			
			T122S#	11.21			
			R123S#	2.09			
			L167I	99.91			
			D168E	97.94			Y
			F169L#	2.15			
			I170V	99.73			
			S181*#	2.13			
		NS5A	A7I	98.71			
			V34L	99.9			
			R44K	88.35			
			V46A	98.77			
			R48N	98.96			
			I63L#	5.41			
			H66N#	2.21			
			P77S#	2.98			
	POST-TREATMENT WEEK 12	NS3/4A	I18V	99.942			
			C47S	99.935		Y	
			A61S	99.912			
			T87S	99.85			
			V114I	99.899			
			R117H	99.314			
			T122G	99.696	Y		
			L167I	99.856			
			D168E	99.567			Y
			I170V	99.878			
		NS5A	A7I	99.677			
			V34L	99.928			
			R44K	99.545			
			V46A	99.791			
			R48N	99.79			
(b) (6)	BASELINE	NS3/4A	L52M	99.87			
			T98A	80.52			
			V107I#	20.93			
			I143V#	97.25			
			I153L	99			
		NS5A	D18Y#	2.29			
			I34V#	2.73			
			S58P	2.4			
			V75I	98.83			
			K78R	94.35			
	POST-TREATMENT WEEK 4	NS3/4A	L52M	99.965			
			T98A	99.735			
			I153L	99.571			
			A156M	99.595	Y		Y
		NS5A	W47*	5.253	Y		
			S58P	3.081			
			V75I	99.845			
			K78R	99.518			
			T93A	99.846	Y		Y

#Polymorphism no longer detected (<2%) at failure; *Stop codon (possibly due to an assay error)

For GT5a Subject (b) (4), other than the NS3 D168E baseline polymorphism, no other suspected NS3 or NS5A resistance-associated substitutions were detected at the time of virologic failure. An NS3 C47S polymorphism was enriched in the viral population at the time of failure, although this polymorphism was also detected at a relatively high frequency at baseline (16.42%), and this reviewer is not aware of this position being associated with NS3/4A protease inhibitors. A treatment-emergent NS3 A/S122G (or T122G relative to reference) substitution was also observed. While substitutions at NS3 position 122 have been considered to be associated with resistance to some earlier generation NS3/4A protease inhibitors (Lontok et al., 2015), this position is highly polymorphic, and T122A, T122G or T122S were detected at baseline in 35% (8/23) of GT5a subjects. No NS5A resistance-associated polymorphisms or treatment-emergent substitutions were detected at any time in this subject.

For GT6f Subject (b) (4), no obvious resistance-associated polymorphisms were detected at baseline relative to the 6f reference strain, although NS3 A156M and NS5A T93A substitutions, which occurred at key NS3 and NS5A resistance-associated positions, emerged and were detected in >99.5% of the viral population at the time of failure.

7.3.3 Clinical Trial EXPEDITION-8 (M16-135) (S-008, GLE/PIB 8W in Subjects w/Compensated Cirrhosis)

A total of 280 treatment-naïve, non-GT3 subjects with compensated cirrhosis were enrolled in EXPEDITION-8 to receive GLE/PIB for 8 weeks. Independent Clinical Virology analyses of the sponsor's HCV RNA dataset confirmed the sponsor's efficacy analyses. The overall SVR12 rate was 98% (274/280). SVR12 results according to HCV genotype and subtype are summarized in Table 9 (FDA analysis).

Although the major HCV genotypes (other than GT3 initially) were represented in the trial, most subjects had HCV GT1 infection, with relatively limited data for HCV GT4 (n=13), GT5 (n=1) and GT6 (n=9). Nevertheless, the favorable SVR12 data subsequently reported for HCV GT3 infected subjects (see Section 7.3.4), which generally has been the most difficult to treat HCV genotype, provide further confidence that GLE/PIB for 8 weeks is highly effective in treatment-naïve subjects with compensated cirrhosis across all major HCV genotypes.

Table 9 EXPEDITION-8 SVR12 results (intent-to-treat analysis) overall, and according to HCV genotype and subtype (non-GT3 subjects)

HCV Genotype/Subtype	GLE/PIB 8W SVR12
All Subjects	98% (274/280)
Genotype 1	97% (225/231)
1a*	96% (91/95)
1b*	99% (134/136)
Genotype 2	100% (26/26)
2a	100% (12/12)
2b	100% (9/9)
2c	100% (5/5)
Genotype 4	100% (13/13)
4a	100% (4/4)
4c	100% (1/1)
4d	100% (7/7)
4r	100% (1/1)
Genotype 5	100% (1/1)
5a	100% (1/1)
Genotype 6	100% (9/9)
6a	100% (4/4)
6c-l*	100% (1/1)
6e	100% (1/1)
6h	100% (2/2)
6l	100% (1/1)

*2 GT1a, 1 GT1b, and 1 GT6c-l subtypes based on LiPA assay, all others based on phylogenetic analysis

Among the 6 non-GT3 subjects who did not achieve SVR12 (intent-to-treat analysis), none were due to virologic failure. Five of the 6 subjects had missing SVR12 data but had HCV RNA Target Not Detected at the last available timepoint (Treatment Week 8 through Post-Treatment Week 4), and the sixth subject (Subject (b) (6)) received only 17 days of treatment and had only a baseline HCV RNA result reported. Note that it appears one of the non-SVR12 subjects was later found to have achieved SVR12 according to updated efficacy results provided in SDN 464, with an intent-to-treat SVR12 rate of 98% (275/280) for non-GT3 subjects.

Overall, baseline NS3 and NS5A resistance-associated polymorphisms were detected in 15% (42/273) and 36% (99/275) of subjects, respectively, similar to previous HCV DAA studies. Table 10 (FDA analysis) summarizes the specific NS3 and NS5A polymorphisms of interest. Baseline resistance-associated polymorphisms did not impact treatment outcomes in non-GT3 infected subjects in this trial, as no subjects experienced virologic failure.

Table 10 HCV amino acid polymorphisms detected in non-GT3 infected subjects at resistance-associated positions in EXPEDITION-8 (≥15% frequency, polymorphisms reported relative to indicated subtype-specific reference strains)

HCV Subtype	Ref.	NS3 Polymorphisms					NS5A Polymorphisms							
		56	155	156	168	Any NS3	24	28	30	31	58	92	93	Any NS5A
1a (n=92 NS3, n=93 NS5A)	H77	Y	R	A	D	1 (1%)	K	M	Q	L	H	A	Y	18 (19%)
			K(1)				Q(1),R(2)	T(1), V(3)	H(2)	M(4)	P(7),Y(1)		C(1), H(2)	
1b (n=134, both targets)	Con1	Y	R	A	D	33 (25%)	Q	L	R	L	P	A	Y	47 (35%)
		F(32)			E(1)			M(3)	K(1), Q(8)	M(6)	A(2), L(1), Q(2), R(2), S(4), T(3), V(1)	T(5), V(1)	H(20)	
2a (n=12, both targets)	JFH-1	Y	R	A	D	5 (42%)	T	F	K	L	P	C	Y	11 (92%)
		F(5)					A(1)			M(11)				
2b (n=9, both targets)	HC-J8	Y	R	A	D	2 (22%)	S	L	K	M	P	C	Y	6 (67%)
		F(2)								L(6)		S(1)		
2c (n=5, both targets)	BEBE1	F	R	A	D	0 (0%)	S	F	R	L	P	C	Y	5 (100%)
								C(2)	K(5)	M(1)				
4a (n=4, both targets)	ED43	Y	R	A	D	0 (0%)	K	L	L	M	P	A	Y	1 (25%)
									R(1)					
4c (n=1, both targets)	QC381	Y	R	A	D	0 (0%)	K	L	R	M	P	A	Y	1 (100%)
										L(1)	T(1)			
4d (n=7, both targets)	QC382	Y	R	A	D	0 (0%)	K	L	R	M	T	A	Y	7 (100%)
											P(7)			
4r (n=1, both targets)	QC384	Y	R	A	D	0 (0%)	K	I	R	L	P	A	Y	1 (100%)
								V(1)						
5a (n=1, both targets)	SA13	F	R	A	D	1 (100%)	Q	L	Q	L	P	A	T	0 (0%)
					E(1)									
6a (n=3 NS3, n=4 NS5A)	EUHK2	Y	R	A	D	0 (0%)	Q	F	R	L	T	A	T	2 (50%)
								L(2)					S(1)	
6e (n=1, both targets)	GX004	Y	R	A	D	0 (0%)	K	V	S	L	P	A	T	0 (0%)
6h (n=2, both targets)	VN004	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	0 (0%)
6l (n=1, both targets)	537796	Y	R	A	D	0 (0%)	K	V	A	L	P	A	T	0 (0%)

7.3.4 Topline Efficacy and Resistance Results from EXPEDITION-8 GT3-Infected Subjects (S-008 4-Month Safety Update and SDNs 448, 464)

EXPEDITION-8 initially excluded subjects with HCV GT3 infection, but the protocol was later amended to include GT3 subjects (see Clinical Virology review of IND 127416 SDN 136). The initial S-008 sNDA submission included data (b) (4) reflecting efficacy results from EXPEDITION-8 excluding GT3 subjects, as GT3 data were not yet complete at the time, but per the Division's request data from the GT3 population that were available at the time of sNDA submission (cutoff date 2/28/2019) were summarized in a separate report (EXPEDITION-8 GT3 and Retreatment Report). In addition, the sponsor provided several updates of topline efficacy and resistance data from the GT3 population during the review of these efficacy supplements.

Topline SVR12 results were reported for all HCV GT3-infected subjects in SDN 464, received 8/22/2019. The intent-to-treat SVR12 rate was 95% (60/63), with only a single case (1.6%) of virologic failure. All 63 subjects had a subtype 3a infection. Other GT3 subtypes are uncommon in the US infected population.

Key resistance results from GT3 infected subjects (n=62 with available data) were summarized in SDN 448, received 7/26/2019. Baseline resistance-associated polymorphisms were reported using a 15% next generation sequencing sensitivity threshold. The key baseline polymorphisms of interest are NS5A A30K and Y93H, which were detected in 5% (3/62) and 6% (4/62) of GT3 infected subjects, respectively. No subjects had combined A30K + Y93H detected. Other potential NS5A resistance-associated polymorphisms detected in individual subjects included A30T (A30K also detected in this subject), A30L/V, A30R, P58A, P58R, and P58S. Two subjects had an NS5A S24A polymorphism.

No HCV GT3 infected subjects with Baseline NS5A resistance-associated polymorphisms experienced virologic failure. Although it is challenging to draw firm conclusions on the impact of baseline NS5A resistance-associated polymorphisms due to the limited data, these results are consistent with those from non-GT3 infected subjects (Section 7.3.3).

The one subject ((b) (6)) who experienced virologic failure had a virologic relapse detected at Post-Treatment Week 4. This subject did not have any baseline polymorphisms detected at signature resistance-associated positions in NS3 or NS5A. At the time of failure, treatment-emergent NS5A A30K and Y93H substitutions were detected, while no treatment-emergent, resistance-associated substitutions were detected in NS3. The A30K and Y93H treatment-emergent substitutions have been observed previously in GT3 infected subjects and this is described in the current GLE/PIB prescribing information.

Collectively, the results from GT3-infected subjects summarized here, along with the non-GT3 results summarized in Section 7.3.3, indicate the GLPE/PIB 8-week duration was highly effective in treatment-naïve, compensated cirrhotic subjects across all major HCV genotypes, including GT3.

7.3.5 Summary of Available Efficacy Data from GLE/PIB-Experienced Subjects (S-008)

In response to a request from the review team, the sponsor summarized available SVR12 retreatment data from AbbVie Studies MAGELLAN-3 (M15-942) and M13-576, and from other data sources, for subjects who failed treatment with GLE/PIB, based on data available as of 2/28/2019.

MAGELLAN-3 is an ongoing study evaluating GLE/PIB in combination with sofosbuvir (SOF) and ribavirin (RBV) in subjects who have experienced virologic failure while participating in an AbbVie HCV Parent Study. Non-cirrhotic subjects with HCV GT1, 2, 4, 5 or 6 infection and no NS3/4A protease inhibitor or NS5A inhibitor treatment experience prior to the AbbVie Parent Study are to receive GLE/PIB + SOF + RBV for 12 weeks, while all other subjects are to receive GLE/PIB + SOF + RBV for 16 weeks.

Preliminary efficacy results from MAGELLAN-3 are summarized in Table 11

(b) (4)

(b) (4)

Study M13-576 is an ongoing, long-term follow-up study of DAA resistance and SVR durability among subjects who received GLE and/or PIB in Phase 2 or Phase 3 studies. No investigational products are being administered as part of this study. Subjects who were virologic failures could participate in Study M13-576 and be re-treated at any time. (b) (4)

(b) (4)

(b) (4)

From a literature/abstract search, the sponsor identified two studies summarizing retreatment data for subjects who had previously failed GLE/PIB treatment. The sponsor noted one abstract summarizing a study of 14 subjects who failed GLE/PIB and were subsequently retreated with 12 weeks of SOF/VEL/VOX. Presumably these data are included in a more recent journal publication by the same author(s) (Pearlman et al., 2019). According to the publication, of 31 subjects who previously failed GLE/PIB, 29 (94%) achieved SVR12 with SOF/VEL/VOX treatment, including 26/28 (93%) with baseline resistance-associated substitutions detected. SVR12 rates were 12/13 (92%) and 17/18 (94%) for GT1 and GT3 infected subjects, respectively. One GT1a subject with cirrhosis had a Y93x (unspecified) substitution detected prior to retreatment, and L31M and Y93x (unspecified) detected at relapse. The other virologic failure subject had GT3 infection, was non-cirrhotic, and had an NS5A A30K substitution detected prior to retreatment and again at relapse.

The second publication identified by the sponsor was from a study of SOF/VEL + RBV in Japan. One subject with an unspecified HCV GT (all subjects in the study had GT1 or GT2) who had prior GLE/PIB treatment experience was successfully retreated with SOF/VEL + RBV for 12 weeks (Izumi et al., 2018).

(b) (4)

8. Clinical/Statistical- Efficacy

Table 12 List of Clinical Trials Included in Efficacy Review

Appears this way on original

VQ #	Wuldo#LG #	G hvljq#	Sdwlhqw Srsxodwlrq#	Wuhdwp hqw&Vdp sdn#Vl}h##	Hqgsrlqw# #
007	ENDURANCE 5,6 (M16-126)	single arm, NR, OL, MC	HCV GT5 or GT6, without cirrhosis or with compensated cirrhosis, TN or TE with IFN or pegIFN with or without RBV or treatment-experienced with SOF plus RBV with or without pegIFN	8-week treatment for non-cirrhotic subjects and 12-week treatment for cirrhotic subjects HCV GT5 subjects n=23, including n=20 for non-cirrhotic subjects, and n=3 for cirrhotic subjects HCV GT6 infected subjects n=61, including n=55 for cirrhotic subjects and n=6 for non-cirrhotic subjects	SVR12 rate
008	EXPEDITION-8 (M16-135)	single arm, NR, OL, MC	HCV GT1 to GT6 infection, compensated cirrhosis, TN	8-week treatment total n=280, including n=231 for HCV GT1 infection, n=26 for HCV GT2 infection, n=13 for HCV GT4 infection, n=1 for HCV GT5 infection,	SVR12 rate

				n=9 for HCV GT6 infection	

NR: non-randomized, OL: open-label, MC: multicenter

DATA QUALITY

The complete submission for SN 007 is located at the following EDR location: \\CDSESUB1\evsprod\NDA209394\0094; and the complete submission for SN 008 is located at the following EDR location: \\CDSESUB1\evsprod\NDA209394\0095. The quality of the data in this NDA are good, and the statistical reviewer did not have any concerns.

TRIAL DESIGN CHARACTERISTICS COMMON TO BOTH TRIALS

Trial Endpoints

The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after the last dose of the study drug. Both studies utilized two secondary efficacy endpoints: on-treatment virologic failure and post-treatment relapse. On-treatment virologic failure was defined by the applicant as 1) confirmed HCV RNA measurements of > 1 $\log_{10}$ IU/mL above nadir during treatment; 2) confirmed HCV RNA measurements ≥ 100 IU/mL after HCV RNA < LLOQ during treatment; or 3) HCV RNA ≥ LLOQ at the end of treatment with at least six weeks of treatment. Post-treatment relapse was defined as confirmed HCV RNA measurements ≥ LLOQ between the end of treatment and 12 weeks after the last dose of study drug in subjects with HCV RNA < LLOQ and who completed treatment as planned. Subjects were considered to have completed the study drug if their actual treatment duration was at least 52 days for those who were assigned to receive eight weeks of treatment and at least 77 days for those who were assigned to receive 12 weeks of treatment. Subjects who were re-infected with HCV were not considered to have experienced post-treatment relapse.

Handling of Missing Values

Both studies used a backward imputation approach in analysis of SVR, when necessary. If the nearest HCV RNA value after the SVR window was undetectable or unquantifiable, then that value was imputed as the HCV RNA value in the SVR window.

If the subject was still missing an HCV RNA value in the SVR window after backward imputation, then the HCV RNA value in the SVR window was imputed based on the HCV RNA value obtained from a local laboratory if present. Otherwise, the HCV RNA value was considered missing. In both studies, missing was treated as a failure in the primary analysis of SVR12. If HCV RNA values from the central lab were missing, then the values obtained from a local laboratory were imputed, if available, to assess on-treatment virologic failure and post-treatment relapse.

Calculation of Confidence Intervals

For the primary efficacy analysis in each trial, a two-sided 95% confidence interval (CI) based on the Wilson score method was calculated. The same approach was also applied to generate

the 95% CIs in subgroup analyses for the subgroups with at least 10 subjects. The Wilson score method is not as conservative as exact methods of calculating intervals (Wilson, 1927). The 95% CIs in sections below are based on the Wilson score method unless specified otherwise.

STATISTICAL ISSUES

Lack of Concurrent Active Control Arm in Trials

Both trials were single arm studies without a control arm. There was no formal hypothesis testing pre-specified for EUDURANCE-5,6. EXPEDITION-8 aimed to compare the SVR12 rate of 8-week GLE/PIB treatment to the thresholds obtained based on the historical control regimen of 12-week GLE/PIB. The distribution of baseline characteristics of the patient population enrolled in the study may be different from the populations used to generate the historical SVR12 rate. Therefore, lack of a randomized control arm in a clinical trial can impact the interpretability of the findings and can potentially bias the evidence of efficacy of a treatment. However, considering the objective virologic primary endpoint and the high virological success rates observed for the 12-week GLE/PIB, we accept the use of single-arm trials, as stated in the FDA guidance "Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment."

EFFICACY: ENDURANCE–5, 6

ENDURANCE-5,6 was a Phase 3b, open-label, multicenter study evaluating the efficacy and safety of GLE/PIB in adults with chronic HCV GT5 or GT6 infection, without cirrhosis or with compensated cirrhosis, who were either treatment-naïve or treatment-experienced with IFN or pegIFN with or without RBV or treatment-experienced with SOF plus RBV with or without pegIFN. The study consisted of treatment and post-treatment periods. In the treatment period, non-cirrhotic subjects received GLE/PIB 300 mg/120 mg daily for eight weeks (Arm A), the subjects with compensated cirrhosis were treated with GLE/PIB 300 mg/120 mg daily for 12 weeks (Arm B). Per protocol, all subjects administered at least one dose of study drug were followed for 24 weeks after treatment to monitor safety, HCV RNA, and the emergence and/or persistence of resistance-associated viral variants.

Subject Disposition

In total, 84 subjects enrolled in the study, including 23 (27%) subjects infected with HCV GT5 and 61 (73%) subjects infected with HCV GT6. Seventy-five subjects were non-cirrhotic and assigned to eight weeks of treatment; and nine subjects were cirrhotic and assigned to 12 weeks of treatment. All subjects completed the study drug.

Subject Demographics and Baseline Characteristics

More than half of the HCV GT5 and HCV GT6 infected subjects were females. The majority of HCV GT5 infected subjects were white (91%), and the majority of HCV GT6 infected

subjects were Asian (92%). The mean (SD) age was 61 years old (16.2) for the GT5 infected subjects, and 55 years old (11.4) for the GT6 infected subjects.

The majority subjects were non-cirrhotic (87% of HCV GT5 infected subjects and 90% of HCV GT6 infected subjects). The numbers of cirrhotic subjects were small for both genotypes. Also, 83% of HCV GT5 infected subjects and 90% of HCV GT6 infected subjects were treatment-naïve. Approximately 30% of HCV GT5 infected subjects were with IL28B CC genotype and 76% HCV GT6 infected subjects were with CC genotype. Among either HCV GT5 or GT6 infected subjects, approximately 87% subjects had HCV viral load ≥ 1,000,000 IU/mL at baseline.

Table 13 Subject Demographics in ENDURANCE-5,6

	HCV GT5 (N=23)	HCV GT6 (N=61)	All (N=84)
Gender			
Female	13 (56.5%)	32 (52.5%)	45 (53.6%)
Male	10 (43.5%)	29 (47.5%)	39 (46.4%)
Race			
Asian	1 (4.3%)	56 (91.8%)	58 (69.0%)
Black or African American	1 (4.3%)	0	1 (1.2%)
White	21 (91.3%)	4 (6.6%)	25 (29.8%)
Other[1]	0	1 (1.6%)	1 (1.2%)
Ethnicity			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	23 (100%)	61 (100%)	84 (100%)
Age (year)			
Mean (SD)	61 (16.2)	55 (11.4)	57 (13.0)
Median (Min, Max)	68 (24, 76)	54 (30, 79)	59 (24, 79)
Country			
Australia	0	8 (13.1%)	8 (9.5%)
Belgium	8 (34.8%)	0	8 (9.5%)
Canada	0	13 (21.3%)	13 (15.5%)
France	11 (47.8%)	5 (8.2%)	16 (19.0%)
New Zealand	1 (4.3%)	3 (4.9%)	4 (4.8%)

Source: Table 7 in ENDURANCE-5,6 clinical study report
[1]Other included multi-race.

Table 14 Baseline Disease Characteristics in ENDURANCE-5,6

	HCV GT5 (N=23)	HCV GT6 (N=61)	All (N=84)
Cirrhotic status			
Cirrhotic	3 (13.0%)	6 (9.8%)	9 (10.7%)
Non-cirrhotic	20 (87.0%)	55 (90.2%)	75 (89.3%)
Prior HCV treatment history			
Treatment-naïve	19 (82.6%)	57 (93.4%)	76 (90.5%)
Treatment-experienced	4 (17.4%)	4 (6.6%)	8 (9.5%)
IFN-based	4 (17.4%)	4 (6.6%)	8 (9.5%)
SOF-based	0	0	0
IL28B genotype			
CC	9 (39.1%)	46 (76.4%)	55 (65.5%)
CT	8 (34.8%)	14 (23.0%)	22 (26.2%)
TT	6 (26.1%)	1 (1.6%)	7 (8.3%)
Baseline HCV RNA level (log_{10}IU/mL)			
Mean (SD)	6.52 (0.53)	6.64 (0.74)	6.61 (0.69)
Median (Min, Max)	6.55 (4.98, 7.42)	6.89 (4.35, 7.49)	6.80 (4.35, 7.49)
< 1,000,000 IU/mL	3 (13.0%)	8 (13.1%)	11 (13.1%)
≥ 1,000,000 IU/mL	20 (87.0%)	53 (86.9%)	73 (86.9%)
Baseline Child-Pugh Score			
5	3 (13.0%)	5 (8.2%)	8 (9.5%)
6	0	1 (1.6%)	1 (1.2%)
Baseline fibrosis stage			
F0 – F1	17 (73.9%)	45 (73.8%)	62 (73.8%)
F2	3 (13.0%)	1 (1.6%)	4 (4.8%)
F3	0	9 (14.8%)	9 (10.7%)
F4	3 (13.0%)	6 (9.8%)	9 (10.7%)

Source: Tables 9 and 14.1_3.1 in ENDURANCE-5,6 clinical study report
[1]other included multi-race.

Statistical Methods

Efficacy analysis was performed in the ITT population which included the subjects who received at least one dose of study drug. The number and percentage of subjects achieved SVR12 were summarized by genotypes. Additionally, the applicant summarized the percentage of subjects who experienced 1) on-treatment virologic failure, and 2) post-treatment relapse among subjects who complete the subjects with HCV RNA < LLOQ at final treatment visit who completed treatment.

Efficacy Findings

The SVR12 rate was 96% (95% CI: 79.0%, 99.2%) in HCV GT5 infected subjects and 98% (95% CI: 91.3%, 99.7%) in HCV GT6 infected subjects (Table 15). Only two subjects did not achieve SVR12. One HCV GT5 infected subject without cirrhosis experienced virologic relapse, and one HCV GT6 infected subject with compensated cirrhosis had on-treatment

virologic failure. The non-cirrhotic subjects received GLE/PIB for eight weeks and cirrhotic subjects received GLE/PIB for 12 weeks. The SVR12 rate by treatment duration (or cirrhotic status) is presented in Table 16. The statistical reviewer confirmed the applicant's results.

Table 15 Virologic Outcome at Post-Treatment Week 12 by Genotype in ENDURANCE-5,6 (ITT)

	GLE/PIB	
	HCV GT5 (N=23)	**HCV GT6 (N=61)**
SVR12 rate (95% CI)	95.7% (22/23) (79.0%, 99.2%)	98.4% (60/61) (91.3%, 99.7%)
Not achieving SVR12		
On-treatment virologic failure	0% (0/23)	1.6% (1/61)
Relapse	4.3% (1/23)	0% (0/60)
Other	0% (0/23)	0% (0/61)

Source: Table 11 in ENDURANCE-5,6 clinical study report

Table 16 SVR12 by Genotype and Treatment Duration in ENDURANCE-5,6 (ITT)

	HCV GT5 (N=23)	**HCV GT6 (N=61)**
Non-cirrhosis (8-week treatment) [95% CI]	95.0% (19/20) [76.4%, 99.1%]	100% (55/55) [93.5%, 100%]
Cirrhosis (12-week treatment)	100% (3/3)	83.3% (5/6)

Source: Table 16 in ENDURANCE-5,6 clinical study report

Subgroup Analyses

Overall only two subjects did not achieve SVR12. The high SVR12 rate precludes meaningful interpretation of subgroup analyses.

EFFICACY: EXPEDITION-8

EXPEDITION-8 was a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of eight weeks of GLE/PIB in HCV treatment-naïve adult subjects with chronic HCV infection and compensated cirrhosis. Eligible subjects were enrolled to receive 8 weeks of GLE/PIB 300 mg/120 mg daily. In the post-treatment period, all subjects administered at least one dose of study drug are to be monitored for 24 weeks following the last dose of study drug for safety, HCV viral load, and the emergence and/or persistence of resistance-associated viral variants.

The study was initially designed to enroll subjects with HCV GT 1, 2, 4, 5 or 6 infection. The protocol was then amended to enroll patients with HCV GT3 infection following completion of enrollment of subjects with HCV GT1, 2, 4, 5, or 6 infection. The initial submission included the results and datasets for all the non-HCV GT3 infected subjects. In response to the review team's information request (IR), the applicant provided a topline summary of the key SVR12 efficacy results for all the enrolled HCV GT3 infected on August 22, 2019 (\\CDSESUB1\evsprod\NDA209394\0125\m1\us\111-information-amendment). As the

applicant did not submit datasets for the HCV GT3 infected subjects, the statistical reviewer could not confirm their results for HCV GT3 infected or all subjects. Only a single virologic failure was reported and no HCV GT3 infected subjects with Baseline NS5A resistance-associated polymorphisms experienced virologic failure (see further discussion in the Clinical Virology Section 7.3.3). The tables in next few sections display the results of the non-HCV GT3, the HCV GT3 and all subjects separately where appropriate.

Subject Disposition

The study recruited a total of 343 treatment-naïve cirrhotic subjects, including 280 non-GT3 HCV subjects and 63 HCV GT3 subjects. All of these subjects received at least one dose of GLE/PIB. Only one subject was discontinued from the study drug. This subject received only one dose of study drug before he/she was lost to follow-up.

Table 17 Subject Disposition in EXPEDITION-8

	8-week GLE/PIB		
	Non-HCV GT3	**HCV GT3**	**All**
Enrolled	280	63	343
Treated	280 (100%)	63 (100%)	343 (100%)
Completed study drug	279 (99.6%)	63 (100%)	342 (99.7%)
Not completed study drug	1 (0.4%)	0	1 (0.3%)
Lost to follow-up	1 (0.4%)	0	1 (0.3%)

Sources: Table 6 in Study EXPEDITION-8 clinical study report and Table 14.1__1.1 in the applicant's responses to IR submitted on August 22, 2019

Subject Demographics and Characteristics

Majority of subjects were male (63%) and white (83%). The mean (±SD) age was approximately 58 (±11) years. Approximately half of the subjects were recruited in Europe. Majority of the subjects had HCV GT1 infection (82%). Only one subject was infected with HCV GT5 and nine subjects were infected with HCV GT6. The mean (±SD) HCV RNA at baseline was 6.12 (±0.72) $\log_{10}$ IU/mL.

Table 18 Subject Demographics in EXPEDITION-8 (ITT)

	8-week GLE/PIB		
	Non-HCV GT3 (N=280)	**HCV GT3 (N=63)**	**All (N=343)**
Gender			
Female	112 (40.0%)	14 (22.2%)	126 (36.7%)
Male	168 (60.0%)	49 (77.8%)	217 (63.3%)
Race			
Asian	28 (10.0%)	0	28 (8.2%)
Black or African American	27 (9.6%)	1 (1.6%)	28 (8.2%)
White	223 (79.6%)	62 (98.4%)	285 (83.1%)
Other	2 (0.7%)	0	2 (0.6%)

(to be continued)

Table 19 Subject Demographics in EXPEDITION-8 (ITT) (continued)

	8-week GLE/PIB		
	Non-HCV GT3 (N=280)	**HCV GT3 (N=63)**	**All (N=343)**
Ethnicity			
Hispanic or Latino	35 (12.5%)	8 (12.7%)	43 (12.5%)
Not Hispanic or Latino	245 (87.5%)	55 (87.3%)	300 (87.5%)
Age			
Mean (SD)	59.1 (10.3)	50.9 (9.4)	57.6 (10.6)
Median (Min, Max)	60 (34, 88)	52 (32, 83)	58 (32, 88)
Region			
Europe	143 (51.1%)	43 (68.3%)	186 (54.2%)
North/Central America[1]	102 (36.4%)	15 (23.8%)	117 (34.1%)
Rest of world[1]	35 (12.5%)	5 (7.9%)	40 (11.7%)

Source: Table 9 in EXPENDITION-8 clinical study report and table 14.1_2.1 in applicant's responses to IR submitted on August 22, 2019
[1]North/Central America included USA, Canada and Puerto Rico, and rest of world included Israel, Taiwan and Vietnam.

Table 20 Baseline Disease Characteristics in EXPENDITION-8 (ITT)

	8-week GLE/PIB		
	Non-HCV GT3 (N=280)	**HCV GT3 (N=63)**	**All (N=343)**
HCV genotype			
1	229 (81.8%)	0	229 (66.8%)
2	28 (10.0%)	0	28 (8.2%)
3	0	63 (100%)	63 (18.4%)
4	13 (4.6%)	0	13 (3.8%)
5	1 (0.4%)	0	1 (0.3%)
6	9 (3.2%)	0	9 (2.6%)
IL28B genotype[1]			
CC	90 (32.1%)	24 (38.1%)	114 (33.2%)
CT	127 (45.4%)	29 (46.0%)	156 (45.5%)
TT	54 (19.3%)	6 (9.5%)	60 (17.5%)
Missing	9 (3.2%)	4 (6.3%)	13 (3.8%)
Baseline HCV viral load (log_{10} IU/mL)			
Mean (SD)	6.13 (0.72)	6.12 (0.73)	6.12 (0.72)
Median (Min, Max)	6.30 (3.36, 7.51)	6.22 (4.08, 7.43)	6.27 (3.36, 7.51)
< 1,000,000 IU/mL	90 (32.1%)	22 (34.9%)	112 (32.7%)
≥ 1,000,000 IU/mL	190 (67.9%)	41 (65.1%)	231 (67.3%)
Baseline Child-Pugh score			
5	252 (90.0%)	55 (87.3%)	307 (89.5%)
6	25 (8.9%)	8 (12.7%)	33 (9.6%)
> 6	3 (1.1%)	0	3 (0.9%)

Source: Table 10 in EXPEDITION-8 clinical study report and Tables 14.1_3.1 and 14 1_3.2 in applicant's responses to IR submitted on August 22, 2019
[1]The percentages were generated by the statistical reviewer.

Statistical Methods

Three analyses were planned to be conducted in EXPEDITION-8. The first analysis was to be performed after all non-HCV GT3 infected subjects completed the post-treatment Week 12

visit or prematurely discontinued study. The second analysis would occur after all HCV GT3 infected subjects had completed their post-treatment Week 12 visit or prematurely discontinued study. The final analysis would be carried out after all subjects have completed post-treatment Week 24 or prematurely discontinued study. Of note, the initial submission included the results and the datasets for the first analysis; the topline summary of efficacy results for the second analysis were submitted as the applicant's response to IR on August 22, 2019.

There were two hypothesis tests for the primary efficacy endpoint of SVR12 rate. The first test was the SVR12 rate for the 8-week GLE/PIB treatment was better than 94% in the per-protocol (PP) population. The PP population included all enrolled subjects who received at least one dose of study drug, except for the subjects who experienced breakthrough, or prematurely discontinued treatment prior to Week 8, or had no HCV RNA value in the SVR12 visit window or later. The second hypothesis test was the SVR12 rate for the 8-week GLT/PIB treatment was better than 93% in the ITT population which was defined as all enrolled subjects who received at least one dose of study drug.

Reviewer Comments*: During the review for the study protocol submitted in an IND, the statistical reviewer, Dr. Fraser Smith, conveyed a comment to the applicant that "the primary analysis should be conducted using the ITT population." The statistical reviewer agrees with Dr. Smith. However, the applicant did not incorporate Dr. Smith's comment. The protocol-specified PP analysis focused only on relapse and neglected on-treatment virologic failure or early discontinuation of study drug due to any reason. Therefore, the analysis would result in 100% SVR12 rate if no subjects experienced relapse.*

Efficacy Findings

In the first ITT analysis, that excludes HCV GT3 infected subjects, the SVR12 rate was approximately 98% (CI: 96.7%, 99.6%) (Table 20). In the second ITT analysis, that includes HCV GT3 infected subjects, the SVR12 rate was 98% (CI: 96.1%, 99.3%) (Table 21). Both analyses showed that the SVR12 rates were significantly better than the prespecified threshold of 93% in the ITT population since the lower bound of its 95% CI was greater than 93%.

No subjects experienced on-treatment virologic failure. One HCV GT3 infected subject relapsed at post-treatment Week 4. The main reason for not achieving SVR12 was missing data. Of the four non-GT3 infected subjects with missing SVR12 data, none of them had HCV detected at their last visits with HCV RNA available. The last visits were either at the end of treatment or post-treatment Week 4.

The SVR12 rates by HCV genotype are displayed in Table 23. The SVR12 rate was 97% for HCV GT1 infected subjects, 95% for HCV GT3 infected subjects, and 100% for HCV GT2, 4, 5 and 6 infected subjects. However, the sample sizes for HCV GT5 or GT6 infected subjects were very limited as mentioned earlier.

Table 21 Virologic Outcome at Post-Treatment Week 12 for Non-HCV GT3 Subjects (in EXPEDITION-8 (ITT)

	8-week GLE/PIB (N=280)
SVR12 rate[1]	98.2% (275/280)
[95% CI]	[96.7%, 99.8%]
Not achieving SVR12[1]	1.8% (5/280)
On-treatment virologic failure	0%
Relapse	0%
Other	
Premature study drug discontinuation	0.4% (1/280)
Missing SVR12 data[1]	1.4% (4/280)

Source: Table 1 in applicant's response to IR submitted on August 22, 2019
[1]In the initial submission, the SVR12 rate was 97.9% (274/280), the percent of not achieving SVR12 was 2.1% (6/280), and the percent of missing SVR12 data was 1.7% (5/280). This was because one GT1 infected subject had missing SVR12 data initially and the data was available when the applicant responded to IR.

Table 22 Virologic Outcome at Post-Treatment Week 12 for All subjects in EXPEDITION-8 (ITT)

	8-week GLE/PIB (N=343)
SVR12 rate	97.7% (335/343)
[95% CI]	[96.1%, 99.3%]
Not achieving SVR12	2.3% (8/343)
On-treatment virologic failure	0%
Relapse	0.3% (1/336)
Other	
Premature study drug discontinuation	0.3% (1/343)
Missing SVR12 data	1.7% (6/343)

Source: Table 2 in applicant's response to IR submitted on August 22, 2019

Table 23 Virologic Outcome at Post-Treatment Week 12 by Genotype in EXPEDITION-8 (ITT)

	8-week GLE/PIB					
	HCV GT1 (N=231)	**HCV GT2 (N=26)**	**HCV GT3 (N=63)**	**HCV GT4 (N=13)**	**HCV GT5 (N=1)**	**HCV GT6 (N=9)**
SVR12 rate	97.8%[1] (226/231)	100% (26/26)	95.2% (60/63)	100% (13/13)	100% (1/1)	100% (9/9)
[95% CI]	[95.0%, 99.1%]	[87.1%, 100%]	[86.9%, 98.4%]	[77.2%, 100%]	n/a	n/a
Not achieving SVR12	0% (0/231)	0% (0/26)	0% (0/63)	0% (0/13)	0% (0/1)	0% (0/9)
On-trt VF[2]	0% (0/225)	0% (0/26)	1.6% (1/62)	0% (0/13)	0% (0/1)	0% (0/9)
Relapse	2.2% (5/231)[1]	0% (0/26)	3.2% (2/63)	0% (0/13)	0% (0/1)	0% (0/9)
Other						

Source: Tables 14.2_1.2 in EXPEDITION-8 clinical study report and Table 14.2_1.2 in applicant's response to IR submitted on August 22, 2019
[1]In the initial submission, the SVR12 rate for HCV GT1 infected subjects was 97.4% (225/231), and the percent of missing SVR12 data was 2.6% (6/231). This was because one GT1 infected subject had missing SVR12 data initially and the data was available when the applicant responded to IR.
[2]On-trt VF = On-treatment virologic failure

Subgroup Analysis

The applicant did not submit the results or datasets for subgroup analyses for HCV GT3 infected subjects in their responses to IR. The subgroup analysis results discussed in this section were based on those in the initial submission for non-HCV GT3 infected subjects. Since only a few non-HCV GT3 subjects did not achieve SVR12, the SVR12 rate among the various subgroups was greater than 95%. The results of selected subgroup analyses are presented in Table 37 in Section 16 Appendix.

Efficacy Conclusion

The evidence of efficacy supporting sNDAs 007 and 008 primarily comes from two studies, EUDURANCE-5,6 and EXPEDITION-8. ENDURANCE-5,6 assessed GLE/PIB in the HCV GT5 or GT6 infected subjects who were either treatment-naïve or treatment-experienced with SOF plus RBV with or without pegIFN. The treatment duration was eight weeks for the non-cirrhotic subjects and 12 weeks for the cirrhotic subjects. A total of 75 non-cirrhotic subjects received eight weeks treatment of GLE/PIB, including 20 infected with HCV GT5 and 55 infected with HCV GT6. The SVR12 rate was 95% (95% CI: 76.4%, 99.1%) for HCV GT5 infected subjects and 100% (95% CI: 93.5%, 100%) for HCV GT6 infected subjects. Meanwhile, the number of cirrhotic subjects who received 12 weeks of treatment was very limited. Although there were only nine cirrhotic subjects including three HCV GT5 infected and six HCV GT6 infected subjects, the SVR12 rate was 100% for the three HCV GT5 infected subjects and 83.3% for the six HCV GT6 infected subjects, which was consistent with what was observed in EXPEDITION-1 in the original NDA.

EXPEDITION-8 evaluated eight weeks treatment with GLE/PIB in treatment-naïve cirrhotic subjects. The study enrolled and treated 343 subjects. The SVR12 rate was 98% (95% CI: 96.1%, 99.3%), which was significantly higher than the prespecified threshold of 93% as the lower bound of the 95% CI was greater than 93%. The evidence from EXPEDITION-8 and strong results across all major genotypes in previous registrational trials in treatment-naïve subjects without cirrhosis and treatment-naïve subjects with cirrhosis treated for 12 weeks also supports the approval of eight-week treatment duration for treatment-naïve cirrhotic subjects.

9. Safety

This section presents a summary of the analysis of safety data from ENDURANCE- 5,6 and EXPEDITION-8. Safety data for sNDA S-007 and S-008 were submitted by AbbVie primarily as Clinical Study Reports (CSRs) and electronic datasets. The safety analysis set was used for all analyses unless otherwise specified. Treatment-emergent events were defined as any AE with onset dates on or after study drug start date and no later than 30 days after permanent study drug discontinuation, as well as any AEs leading to premature discontinuation of study drug. Safety data was reported according to MedDRA version 21.1. The FDA data analyses were performed using JMP Clinical, and JReview data analysis tools.

Safety data for EXPEDITION-8 GT3 are presented separately in sub-section 9.30, as efficacy and safety results and data were submitted after the initial submission and review of Supplement 8, which included the study EXPEDITION-8 genotypes 1,2,4,5 and 6, as described in Section 1.

9.1 Exposure – ENDURANCE-5,6

The 84 enrolled subjects who received at least one dose of study drug were included in the Safety Analysis Set. All subjects in the safety population took a full course of study drug (8 weeks for the 75 subjects without cirrhosis and 12 weeks for the 9 subjects with compensated cirrhosis).

9.2 Overall Adverse Events – ENDURANCE-5,6

Treatment emergent adverse events (TEAEs), both those considered related and not related, were overall proportionally lower in GT 5 and 6 infected subjects enrolled in ENDURANCE 5,6 than in the Phase 2/3 Trials in the original NDA. Serious adverse events overall were proportionally equivalent to those seen in cirrhotic subjects in the original NDA. However, none of the serious events in ENDURANCE-5,6 were considered related to GLE/PIB.

Table 24 Overall Summary of Adverse Events with 8 or 12 Weeks of GLE/PIB ENDURANCE -5,6 (sNDA S-007) and Phase 2/3 Data from the Original NDA 209394

	GLE/PIB 8 or 12 weeks GT 5,6 No Cirrhosis (n=75) Cirrhosis (n=9)	GLE/PIB 12 weeks Phase 2/3 Safety Dataset 209394 No Cirrhosis (n=1070)	GLE/PIB 12 weeks Phase 2/3 Safety Dataset 209394 Cirrhosis (n=225)
Number (%) of Subjects Experiencing Any:			
Adverse Event (AE)	**46 (54%)**	735(69%)	166 (74%)
Treatment-Related AE	**26 (31%)**	454(42%)	98 (43%)
Serious Adverse Event (SAE)	**5 (6%)**	16(1.5%)	13 (6%)
Treatment-Related SAE	**0**	1(<1%)	0
Grade 3 and 4 AEs	**3 (3.6%)**	25(2.3%)	14 (6%)
Treatment-Related Grade 3 and 4 AEs	**0**	3(<1%)	0
AE Leading to Permanent Discontinuation of GLE/PIB	**0**	7 (<1%)	0
Death	**0**	2(<1%)	1(<1%)

Source: NDA 209394, Supplement 7 ADSL, ADAE

Reviewer Comment: Overall proportionally less AEs were reported for subjects in ENDURANCE-5,6 than were seen in the original NDA, and there is no evidence to suggest

that subjects with GT5 or 6 infection should have a higher proportion of adverse events. Proportionally, Serious Adverse Events in ENDURANCE -5,6 approximated those seen in the cirrhotic population in the original NDA, but none of the SAEs in ENDURANCE-5,6 were considered drug related and the numbers of reported events in this trial were very small, which limits the ability to draw meaningful conclusions.

9.3 Deaths – ENDURANCE-5,6
There were no reported deaths for ENDURANCE-5,6.

9.4 Non-fatal Serious Adverse Events -ENDURANCE-5,6
Five subjects (6%) experienced one or more SAEs, all considered by the investigator to be not related to study drug (Table 24). All subjects with serious events were non-cirrhotic, treated for 8 weeks and all but one subject experienced SAEs that were infectious in nature or sequalae of infection. There were no hepatic serious adverse events. No subject interrupted or discontinued study drug because of a serious event.

Table 25 Subjects with Treatment Emergent Serious Adverse Events – ENDURANCE-5, 6

Unique Subject Identifier	Age-Sex-Race	MedDRA Preferred Term	Toxicity Grade	Causality	Reason Considered a SAE
(b) (6)	66-F-ASIAN	Viral infection	2	No reasonable possibility	Hospitalization
	59-M-ASIAN	Pulmonary tuberculosis	2	No reasonable possibility	Important medical or surgical intervention
	69-M-ASIAN	Anaemia	3	No reasonable possibility	Hospitalization
		Gastric ulcer helicobacter	3	No reasonable possibility	Hospitalization
	73-F-WHITE	Escherichia pyelonephritis	3	No reasonable possibility	Hospitalization
	75-F-WHITE	Giardiasis	2	No reasonable possibility	Hospitalization
		Major depression	3	No reasonable possibility	Hospitalization

Source: NDA 209394, Supplement 7 ADSL, ADAE

Reviewer Comment: The majority of SAEs were infections or results of infections and are unlikely to be related to GLE/PIB. The only noninfectious SAE was major depression, which did not appear to be associated with treatment with GLE/PIB in this case or in the original NDA. In this case of major depression, subject (b) (6)*, had a past medical history of depression and started the study on several medications for depression and psychosis (Lithium, Clomipramine, Venlafaxine).*

Subject (b) (6) *with pyelonephritis also experienced an isolated Grade 2 increase in bilirubin (over 2 days). However, this did not require intervention and did not appear to be*

related to the SAE, although it overlapped with this subject's SAE (at that time the subject was started on amoxicillin and a short course of Glucion, glucose monohydrate with lactic acid,).

9.5 Other non-serious Grade 3 and 4 Clinical Adverse Events-ENDURANCE-5,6
Three subjects experienced AEs of Grade 3 in severity (events of anemia and Helicobacter pylori gastric ulcer for 1 subject and events of Escherichia coli pyelonephritis and major depression for 1 subject each). All 3 subjects required hospitalization for treatment of the Grade 3 AE(s) and are therefore, also considered SAEs and are described above.

9.6 Discontinuations – ENDURANCE-5,6
At the time of submission, 1 subject discontinued the study, 71 completed the study and 12 were ongoing in the post treatment period. All subjects completed therapy without discontinuations. No subject discontinued or interrupted therapy due to adverse events.

9.7 Common Adverse Events and Reactions -ENDURANCE-5,6
Table 26 summarizes the common adverse events and adverse drug reactions in ENDURANCE – 5, 6 in more than 2 subjects (≥2%). All common events were non-serious and either Grade 1 or 2. The most common adverse drug reactions (≥ 10% of subjects) experienced in ENDURANCE – 5, 6 were fatigue (11.9%) and headache (10.7%).

Table 26 Common Adverse Events and/or Adverse Drug Reactions Greater than or equal to 2% with GLE/PIB in ENDURANCE-5,6

MedDRA Preferred Term	Adverse Events N=280	Adverse Drug Reactions N=280
Headache	11 (13.1%)	9 (10.7%)
Fatigue	11 (13.1%)	10 (11.9%)
Dizziness	6 (7.1%)	3 (3.6%)
Insomnia	5 (6.0%)	2 (2.4%)
Nausea	5 (6.0%)	4 (4.8%)
Diarrhoea	4 (4.8%)	2 (2.4%)
Abdominal distension	4 (4.8%)	2 (2.4%)
Arthralgia	3 (3.6%)	0 (0.0%)
Abdominal pain	3 (3.6%)	1 (1.2%)
Pruritus	3 (3.6%)	3 (3.6%)
Vomiting	2 (2.4%)	2 (2.4%)
Constipation	2 (2.4%)	0 (0.0%)
Chills	2 (2.4%)	2 (2.4%)
Decreased appetite	2 (2.4%)	1 (1.2%)
Rhinitis allergic	2 (2.4%)	0 (0.0%)
Abdominal pain upper	2 (2.4%)	1 (1.2%)
Hyperhidrosis	2 (2.4%)	0 (0.0%)
Urinary tract infection	2 (2.4%)	0 (0.0%)
Vertigo	2 (2.4%)	0 (0.0%)

Source: NDA 209394, Supplement 7 ADSL, ADAE

Reviewer Comment: Common adverse events and adverse drug reactions in this population were similar in proportion and nature to those seen in the original NDA. In the NDA 209394 Phase 2/3 dataset, the adverse drug reactions of headache (13%), fatigue (11%) and nausea (8%) were seen in ≥5% of subjects. No labelling changes are recommended, based on these data.

9.8 Laboratory Abnormalities- ENDURANCE-5,6

The tables in this section display treatment-emergent graded laboratory abnormalities for hematology and chemistry parameters in ENDURANCE-5,6 in comparison to the pooled Phase 2/3 dataset from the original NDA 209394. These analyses represent the worst change from baseline per subject. Abnormalities for most parameters occurred infrequently and at a similar rate as seen in the original NDA 209394 submission.

Hematology

Table 27 presents treatment-emergent graded laboratory abnormalities for hematology parameters in ENDURANCE -5,6 in comparison to the pooled Phase 2/3 dataset from the original NDA 209394. These analyses represent the worst change from baseline per subject. For most hematology parameters, abnormalities occurred infrequently and at a similar rate as seen in the original NDA 209394 submission.

Table 27 Hematology Maximum Post-Baseline Toxicity Grade Analysis for GLE/PIB-ENDURANCE-5,6 and Phase 2/3 Data from Original NDA209394

	ENDURANCE-5,6		Phase 2/3 Data	
Post-baseline Maximum Standard Toxicity Grade *	**No Cirrhosis N=75**	**Cirrhosis N=9**	**No Cirrhosis N=1,977**	**Cirrhosis N=288**
HEMOGLOBIN				
Grade 1 (< LLN – 100 g/L)	1 (1%)	1 (11%)	66 (3%)	17 (6%)
Grade 2(< 100 – 80 g/L)	2 (3%)	0	3 (<1%)	1(<1%)
Grade 3 (< 80 g/L)	1 (1%)	0	1 (<1%)	1(<1%)
LEUKOCYTES				
Grade 1 (< LLN to 3000/mm3)	2 (3%)	0	93 (5%)	16 (6%)
Grade 2 (< 3000 to 2000/mm3)	1(1%)	0	22 (1%)	11 (4%)
Grade 3 (< 2000 to 1000/mm3)	0	0	1 (<1%)	0
NEUTROPHILS				
Grade 1 (< LLN – 1.5 × 10^9/L)	2 (3%)	0	130 (7%)	26 (9%)
Grade 2 (< 1.5 – 1.0 × 10^9/L)	4 (5%)	0	52 (3%)	12 (4%)
Grade 3 (<50.0 -25.0 x 10^9/L)	0	0	10 (<1%)	1 (<1%)
PLATELETS				
Grade 1 (LLN – 75.0 × 10^9/L)	2 (3%)		78 (4%)	24 (8%)

	ENDURANCE-5,6		Phase 2/3 Data	
Post-baseline Maximum Standard Toxicity Grade *	**No Cirrhosis N=75**	**Cirrhosis N=9**	**No Cirrhosis N=1,977**	**Cirrhosis N=288**
Grade 2 (75.0 – 50.0 × 10^9/L)	0	1 (11%)	2 (<1%)	21 (7%)
Grade 3 (< 50.0 – 25.0 × 10^9/L)	0	0	0	4(1%)

**Indicates the post-baseline toxicity grades that were more clinically extreme than the toxicity grade corresponding to the baseline.*
Source: Supplement 7 and NDA 209394, ADLBGRD

Chemistry
Table 28 presents treatment-emergent graded laboratory abnormalities for select chemistry parameters in EXPEDITION-2 in comparison to the pooled Phase 2/3 dataset from the original NDA 209394. These analyses represent the worst change from baseline per subject. For most chemistry parameters, abnormalities occurred infrequently and at a similar rate as seen in the original NDA 209394 submission.

Table 28 Select Chemistry Maximum Post-Baseline Toxicity Analysis by Cirrhosis Status for GLE/PIB - ENDURANCE-5,6 and Phase 2/3 Data from Original NDA209394

	EXPEDITION-2		Phase 2/3 Data	
Post-baseline Maximum Toxicity Grade*	**No Cirrhosis N=75**	**Cirrhosis N=9**	**No Cirrhosis N=1,977**	**Cirrhosis N=288**
Alanine Aminotransferase				
Grade 1 (> ULN to 3.0 x ULN)	0	0	20 (1%)	1 (<1%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	0	0	3 (2%)	2 (<1%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	0	0	2 (<1%)	0
Alkaline Phosphatase				
Grade 1 (> ULN to 2.5 x ULN)	7 (9%)	0	154 (8%)	32 (11%)
Aspartate Aminotransferase				
Grade 1 (> ULN to 3.0 x ULN)	1 (1%)	0	35 (2%)	1 (<1%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	0	0	1 (<1%)	4 (1%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	0	0	6 (<1%)	0

	EXPEDITION-2		Phase 2/3 Data	
Bilirubin				
Grade 1 (> ULN to 1.5 x ULN)	3 (4%)	0	115 (6%)	39 (14%)
Grade 2 (> 1.5 to 3.0 × ULN)	1 (1%)	0	41 (2%)	10 (4%)
Grade 3 (> 3.0 to 10 x ULN)	0	0	6 (<1%)	2 (<1%)
Prothrombin Intl. Normalized Ratio				
Grade 1 (> 1 to 1.5 x ULN)	1 (1%)	1 (1%)	146 (7%)	42 (15%)
Grade 2 (> 1.5 to 2.5 x ULN)	0	0	12 (<1%)	2 (<1%)
Grade 3 (> 2.5 x ULN)	0	0	9 (<1%)	0

**Indicates the post-baseline toxicity grades that were more clinically extreme than the toxicity grade corresponding to the baseline.*
Source: Supplement 7 and NDA 209394, ADLBGRD

Reviewer Comment: Overall both hematology and chemistry laboratory abnormalities were Grade 1-2, transient, not associated with significant AEs or clinical symptoms and were consistent with findings in the original NDA. Changes in creatinine clearance (not shown) were also transient in nature and similar to those seen with the original NDA submission. No labelling changes recommended based on these laboratory data.

9.9 Vital Signs – ENDURANCE-5,6
No new clinically important trends in vital signs were observed.

9.10 Electrocardiograms (ECGs)- ENDURANCE-5,6
No subjects had clinically significant abnormal ECG findings during the study. One subject ([redacted] (b) (6)) experienced a prolonged QT on day 1 prior to the first dose; screening and post treatment studies were normal. This event is of unknown significance. There are no other ECGs and the subject appeared to tolerate treatment well and achieved SVR 12.

9.11 Pregnancy-ENDURANCE-5,6
No pregnancies were reported during the study.

9.12 Safety Issues of Interest: Hepatotoxicity- ENDURANCE-5,6
No subject met the criteria for the hepatic laboratory abnormalities of interest listed below:

- Confirmed post-nadir ALT value > 5 × ULN
- Post-nadir increase in ALT to ALT value > 3 × ULN and a concurrent total bilirubin > 2 × ULN with direct bilirubin/total bilirubin ratio > 0.4

One subject ([redacted] (b) (6) -with the SAE of pyelonephritis) had an elevation of total bilirubin on Day 45 to 2 times the upper limit of normal, which was higher than baseline. Subsequent values were within reference range.

No subject experienced hepatic decompensation or hepatic failure PMQ by MEDDRA system or class and preferred term. Treatment-emergent hepatic decompensation/hepatic failure events identified using the AbbVie PMQ for hepatic decompensation/hepatic failure included the preferred terms of ascites, hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis. No post-baseline HCC event was identified

9.13 Safety Profile Differences by Baseline Demographics -ENDURANCE-5,6
Subjects were compared by age under or over 65 years, race, and gender for frequency of safety events. These safety events included the proportions of TEAEs, treatment-related AEs, Grade 3 and 4 TEAEs, Grade 3 or 4 laboratory toxicity values, and SAEs. With the caveat that small sample sizes in the specific subgroups limit these comparisons, no clear difference in safety events was detected based on age, race, and gender.

Reviewer Comment: Available data do not support additional relevant labeling.

Reviewer Comment: Summary of Safety Findings – ENDURANCE-5,6
In summary, review of adverse events, laboratory abnormalities, ECG findings, and vital signs did not reveal any novel safety findings in this population of GT 5 and 6 infected subjects.

9.14 Four-month Safety Update-ENDURANCE-5,6
No new SAEs, deaths, Grade ≥ 3 AEs, AEs leading to discontinuation of study drug, AEs leading to interruption of study drug, or postbaseline HCC events were reported since the primary analysis database lock for the sNDA submission and through the end of the study. With the exception of a mean reduction from baseline in alanine aminotransferase (ALT) associated with clearance of HCV infection, no clinically meaningful mean changes in hematology, chemistry, or urinalysis parameters from baseline to each study visit were observed in the sNDA. No pregnancies were reported since the primary analysis database lock for the sNDA submission and through the end of the study. No clinically significant ECG findings or trends in vital signs associated with study drug were observed since the primary analysis database lock for the sNDA submission and through the end of the study.

Reviewer Comment: The safety conclusions were unchanged from the Post-Treatment Week 12 Primary Analysis CSR to the Final CSR for ENDURANCE-5,6.

9.15 Exposure - EXPEDITION-8-GT 1,2,4,5,6
All 280 GT1, 2, 4, 5 and 6-infected subjects in the safety population of EXPEDITION-8, except for2 subjects, were administered a full 8-week course of study drug(one discontinued study drug prematurely due to loss of follow-up; one received treatment for 51 days and achieved SVR12).

9.16 Overall Adverse Events – EXPEDITION-8-GT 1,2,4,5,6
Approximately 48% of subjects experienced at least 1 AE (Table 29). Most subjects experienced AEs with a maximum severity of Grade 1 (mild). No subjects experienced a

study drug-related AE of Grade ≥ 3, a study drug-related SAE, discontinued treatment due to an AE, or died during the study.

Treatment emergent adverse events (TEAEs), both those considered related and not related, were overall substantially proportionally lower in the cirrhotic subjects treated for 8 weeks in EXPEDITION-8 than both in the cirrhotic and non-cirrhotic populations included in the Phase 2/3 Trials in the original NDA. Serious adverse events were proportionally lower by two thirds than those seen in cirrhotic subjects in the original NDA and none were considered related to GLE/PIB.

Table 29 Overall Summary of Adverse Events with 8 Weeks of GLE/PIB - EXPEDITION-8 (sNDA S-008) and in the Original NDA 209394

	EXPEDITION-8	**Phase 2/3 Data**	
	8 weeks Cirrhosis n=280 (%)	8-12 weeks No Cirrhosis n=1070 (%)	12 weeks Cirrhosis n=225 (%)
Number (%) of Subjects Experiencing Any:			
Adverse Event (AE)	**134 (48%)**	735(69%)	166 (74%)
Treatment-Related AE	**74 (26%)**	454(42%)	98 (43%)
Serious Adverse Event (SAE)	**6 (2%)**	16(1.5%)	13 (6%)
Treatment-Related SAE	**0**	1(<1%)	0
Grade 3 and 4 AEs	**9 (3%)**	25(2.3%)	14 (6%)
Treatment-Related Grade 3 and 4 AEs	**0**	3(<1%)	0
AE Leading to Permanent Discontinuation of GLE/PIB	**0**	7 (<1%)	0
Death	**0**	2(<1%)	1(<1%)

Source: NDA 209394, Supplement 8 ADSL, ADAE

Reviewer Comment: Overall proportionally substantially less AEs were reported for compensated cirrhotic subjects in EXPEDITION-8 as compared to the cirrhotic subjects included in the original NDA, suggesting that 8 weeks of treatment may better tolerated than 12 weeks of treatment, in a cirrhotic population. Alternatively, the shorter duration in EXPEDITION-8 may explain the overall lower proportion of subjects reporting events. Regardless, the numbers of events are relatively small, and this study lacks a comparative arm, thus data should be interpreted with caution.

9.17 Deaths – EXPEDITION-8-GT 1,2,4,5,6

There were no deaths in EXPEDITION-8.

9.18 Non-fatal Treatment Emergent Serious Adverse Events- EXPEDITION-8-GT 1,2,4,5,6

Six subjects experienced ≥ 1 SAE, none of which were considered related to study drug or led to treatment discontinuation. All but one event, the event of pneumonia, occurred in subjects with a baseline Child Pugh score of 5. There were no hepatobiliary serious adverse events.

Table 30 Subjects with Treatment Emergent Serious Adverse Events – EXPEDITION-8-GT 1,2,4,5,6

Unique Subject Identifier	Age/Sex/Race	Baseline Child Pugh Score	Baseline Fibroscan Score	MedDRA Preferred Term	Toxicity Grade	Causality	Reason Serious
(b) (6)	68-M-WHITE	5	12.7	Duodenal ulcer haemorrhage	3	No reasonable possibility	HOS, IMP, PSD, LT
	68-M-WHITE	5	12.7	Adenocarcinoma gastric	2	No reasonable possibility	HOS, IMP, PSD, LT
	61-F-WHITE	5	17.3	Pyelonephritis	3	No reasonable possibility	HOS
	58-M-BLACK OR AFRICAN AMERICAN	8	26.3	Pneumonia	2	No reasonable possibility	HOS
	54-F-WHITE	5	17	Bronchitis	3	No reasonable possibility	HOS
	69-F-WHITE	5	17.3	Cardiac failure	3	No reasonable possibility	HOS, IMP, LT
	69-F-WHITE	5	17.3	Atrial fibrillation	2	No reasonable possibility	HOS, IMP,
	47-M-WHITE	5	33.1	Oedema peripheral	3	No reasonable possibility	HOS

HOS = hospitalization or prolonged hospitalization; IMP = important medical or surgical intervention; LT = life-threatening; PSD = persistent or significant disability.
Source: NDA 209394, Supplement 8ADSL, ADAE

Reviewer Comment: Narratives were requested for SAEs as narratives for SAEs were not included in the sNDA. All narratives were reviewed. This reviewer concurs with the Sponsor that these events, although temporarily related to the administration of GLE/PIB, do not appear to be related to treatment with GLE/PIB. Three of the events were infections, no similar SAEs occurred in the Phase 2/3 data with GLE/PIB in the original NDA. The events of Atrial Fibrillation and Cardiac Failure occurred in a subject with a history of previous

cerebrovascular accident, hypertension and thyroid disease. Valvular disease was also found on echocardiography.

There were no cases of hepatobiliary events related to drug toxicity with GLE/PIB. The event of duodenal ulcer hemorrhage occurred in the context of a gastric carcinoma. The subject with peripheral edema, had a past medical history which included hypertension, and nonalcoholic fatty liver disease, presented after self-discontinuation of furosemide. It is unclear why he was on furosemide (heart or liver disease) but pre-treatment he had similar episodes for which he was also hospitalized. The subject's CT of the abdomen did reveal evidence of portal hypertension, but the subject's bilirubin remained normal and ALT and AST improved over the course of treatment. This event did not appear to represent a worsening of his baseline liver disease or liver failure.

9.19 Treatment Emergent Grade 3 and 4 Clinical Adverse Events-EXPEDITION-8-GT 1,2,4,5,6

Approximately 3% of subjects (9/280) experienced an AE of Grade ≥ 3 in severity, none of which were considered related to study drug (Table 30). Seven of these events were also in subjects with SAEs, which are described above (Grade ≥ 3 SAEs also highlighted in the below table). No trend in the type and frequency of Grade ≥ 3 AEs was observed. The only event occurring in more than one subject was Grade 3 hypertension, which occurred in 2 subjects. No Grade 3 or higher event was considered related to study drug.

Table 31 Treatment-Emergent Grade 3* Clinical Adverse Events-EXPEDITION-8-GT1,2,4,5,6

Unique Subject Identifier	MedDRA Preferred Term	Serious Event	Study Day of Start of Adverse Event	Study Day of End of Adverse Event
(b) (6)	Hypertension	N	8	Ongoing
	Hypertension	N	8	Ongoing
	Dermatitis contact	N	13	14
	Paraesthesia	N	13	14
	Swelling face	N	13	14
	Influenza	N	26	28
	Duodenal ulcer haemorrhage	Y	60	61
	Varices oesophageal	N	60	.
	Pyelonephritis	Y	32	83
	Bronchitis	Y	15	22
	Cardiac failure	Y	72	77
	Oedema peripheral	Y	34	41

Source: NDA 209394, Supplement 8 ADSL, ADAE
*There were no Grade 4 events

Reviewer comment: There were two non-serious Grade 3 events of hypertension, both occurring on Study Day 8, both thought by the investigator to be unrelated to GLE/PIB. Subject (b) (6) *is 66-year-old Asian male with compensated cirrhosis and a Childs Pugh Score of 6 at baseline, and a past medical history of degenerative spine and prostate disease, who had a screening blood pressure of 135/85 and a baseline blood pressure of 130/80, which went up to 160/85 on Day 8 and peaked at 160/90 around Day 30. He was briefly started on valsartan and amlodipine (for 2 days), which were discontinued for unknown reasons. His blood pressure trended downward over treatment to 150/80 at the end of treatment and 140/90 after the end of treatment. While it appeared that his systolic blood-pressure was slightly higher on GLE/PIB it is difficult to determine if this was related to study drug or if this represented unmasking of preexisting hypertension. No alternative etiology was given; however, narratives were not available for non-serious Grade 3 events.*

Subject (b) (6) *is a 56-year-old male with a Childs Pugh score of 5 with a history of hypertension, on amlodipine 5mg, doxazocin 4mg and enalapril at baseline, who had a screening blood pressure of 141/89. One day prior to treatment start, enalapril was discontinued (for unknown reasons) and his baseline blood pressure was 152/96. His blood pressure was highest on Day 8 at 169/105 (off enalapril) and mostly trended downward on treatment, after restarting enalapril on Day 8. On Day 58 this was switched to an enalapril/hydrochlorothiazide fixed-dose combination. In this case, it was also not clear if the subject's blood pressure increased on GLE/PIB, but it is more likely related the discontinuation of enalapril before treatment initiation.*

There was also one non-serious event of contact dermatitis, paresthesia and facial swelling reported in a single subject ((b) (6) *). The events occurred in a 56-year-old Black or African American Male with a relevant history of chronic rash (lichen simplex chronicus and prurigo nodules) and acne. All events occurred over a single day and resolved without discontinuation of study drug. However, the subject was started and remained on diphenhydramine until study Day 134. At the time of the event the subject was also reported to be taking tramadol, coroval, fluocinonide, adapoli, minocycline, ergocalciferol and sumatriptan. Although temporally related, given this history, these events are unlikely related to study drug. However, given other reported post-marketing cases of angioedema (with most cases occurring with concomitant lisinopril), labelling for angioedema/facial swelling will be added in the post-marketing section of the label (see Section 14 for discussion of further details).*

The subject with esophageal varices (b) (6) *) had duodenal ulcer hemorrhage in the context of a gastric carcinoma (as described above in section on SAEs) and is unlikely to be related to study drug (the varices were an incidental finding and were not bleeding/or the cause of the subject's GI bleed*

9.20 Discontinuations-EXPEDITION-8-GT 1,2,4,5,6

No subject discontinued treatment due to an AE. Two subjects had treatment interruptions due to AEs. Subject (b) (6) is a 69-year white old male with pyrexia thought to be unrelated to study drug experienced a 4-day interruption of GLE/PIB. Subject (b) (6) 54-year-old white female experienced nausea thought to be reasonably related to GLE/PIB. Her treatment was interrupted for 1 day. Both subjects completed treatment and achieved SVR 12.

9.21 Common Adverse Events and Reactions -EXPEDITION-8-GT 1,2,4,5,6

The most frequently reported AEs (≥ 5.0% of subjects) were pruritus, fatigue, headache, and nausea (Table 32). Only pruritis met the 10% AE cutoff (with rounding). Study-drug related AEs (Adverse Drug Reactions (ADRs) were experienced by ≥ 5.0% of subjects were fatigue (7.5%), pruritus (7.5%), and headache (5.7%).

Table 32 Common Adverse Events and/or Adverse Drug Reactions Greater than or equal to 2% (with rounding) - EXPEDITION-8-GT 1,2,4,5,6

MedDRA Preferred Term	Adverse Events N=280	Adverse Drug Reactions N=280
Pruritus	27 (9.6%)	21 (7.5%)
Fatigue	24 (8.6%)	21 (7.5%)
Headache	23 (8.2%)	16 (5.7%)
Nausea	18 (6.4%)	12 (4.3%)
Upper respiratory tract infection	9 (3.2%)	0 (0.0%)
Asthenia	8 (2.9%)	6 (2.1%)
Hypertension	8 (2.9%)	1 (0.4%)
Abdominal pain upper	8 (2.9%)	1 (0.4%)
Diarrhoea	7 (2.5%)	5 (1.8%)
Nasopharyngitis	6 (2.1%)	0 (0.0%)
Influenza	6 (2.1%)	0 (0.0%)
Dizziness	6 (2.1%)	4 (1.4%)
Dry mouth	5 (1.8%)	4 (1.4%)
Pyrexia	5 (1.8%)	2 (0.7%)
Vomiting	5 (1.8%)	3 (1.1%)
Back pain	5 (1.8%)	1 (0.4%)
Rash	5 (1.8%)	2 (0.7%)
Abdominal pain	5 (1.8%)	2 (0.7%)

Source: NDA 209394, Supplement 8ADSL, ADAE

Reviewer Comment: Overall the types and nature of the reported adverse drug reactions were similar to those seen in cirrhotic subjects in the Phase 2/3 data in the original NDA application. In the original NDA application, cirrhotic subjects treated across all durations (12 -16 weeks) reported Fatigue (14.9%), Headache (13.5%), Nausea (8.3%), Diarrhea (5.6%) and Pruritis (5.6%), as the most common ADRS ≥ 5%. In EXPEDITION-8, subjects who were treated for 8 weeks experienced overall less AEs and ADRs, and a smaller proportion of individual ADRs ≥5%, except pruritus, which was slightly proportionally higher in EXPEDITION -8. This again suggests that 8 weeks of treatment in a cirrhotic population may be better tolerated than 12 weeks of treatment. However, numbers are relatively small and this study lacks a comparative arm, thus data should be interpreted with caution.

9.22 Laboratory Abnormalities – EXPEDITION-8-GT 1,2,4,5,6

The tables in this section display treatment-emergent graded laboratory abnormalities for hematology and chemistry parameters in EXPEDITION-8 in comparison to the Phase 2/3 data from the original NDA.

Hematology
Table 33 presents treatment-emergent Graded laboratory abnormalities for hematology parameters in EXPEDITION-8 in comparison to the Phase 2/3 data from the original NDA 209394. These analyses represent the worst change from baseline per subject. Most hematology abnormalities in EXPEDITION-8 were Grade 1 or 2, occurred infrequently and at a rate similar to the Phase2/3 data from the original NDA.

Table 33 Hematology Maximum Post-Baseline Toxicity Grade for GLE/PIB - EXPEDITION-8 and Phase 2/3 Data from the Original NDA

	EXPEDITION-8	Phase 2/3 Data	
Post-baseline Maximum Standard Toxicity Grade *	**Cirrhosis N=280**	**No Cirrhosis N=1,977**	**Cirrhosis N=288**
HEMOGLOBIN			
Grade 1 (< LLN – 100 g/L)	12 (4%)	66 (3%)	17 (6%)
Grade 2(< 100 – 80 g/L)	3 (1%)	3 (<1%)	1(<1%)
Grade 3 (< 8.0 9 g/L)	0	1 (<1%)	1(<1%)
NEUTROPHILS			
Grade 1 (< LLN – 1.5 × 109/L)	26 (9%)	130 (7%)	26 (9%)
Grade 2 (< 1.5 – 1.0 × 109/L)	6 (2%)	52 (3%)	12 (4%)
Grade 3 (<50,000 - 25,000/mm3; <50.0 -25.0 x 10^9/L)	2 (<1%)	10 (<1%)	1 (<1%)
PLATELETS			
Grade 1 (LLN – 75.0 × 10^9/L)	19 (7%)	78 (4%)	24 (8%)
Grade 2 (75.0 – 50.0 ×10^9/L)	5 (2%)	2 (<1%)	21 (7%)
Grade 3 (< 50.0 – 25.0 × 10^9/L)	1 (<1%)	0	4(1%)

*Indicates the post-baseline toxicity Grades that were more clinically extreme than the baseline toxicity Grade.
Source: Supplement 8 and NDA 209394,ADLBGRD

Reviewer Comment: Most hematology abnormalities in EXPEDITION-8 were Grade 1 or 2 and seen in proportionally less or similar rates than seen in the original NDA. No labeling changes recommended.

Chemistry
Table 34 presents treatment-emergent Graded laboratory abnormalities for select chemistry parameters in EXPEDITION-8 in comparison to the Phase 2/3 dataset from the original NDA. These analyses represent the worst change from baseline per subject. Selected chemistry parameters are summarized in Table 33. Overall, the chemistry parameter abnormalities

observed in EXPEDITION-8 were Grade 1 or 2, infrequent and observed at a similar rate to the original NDA.

Table 34 Select Chemistry Maximum Post-baseline by Standard Toxicity Grade and Cirrhosis Status in EXPEDITION-8 and Phase 2/3 Data from the Original NDA 209394

	EXPEDITION-8	Phase 2/3 Data	
Post-baseline Maximum Standard Toxicity Grade*	**Cirrhosis N=280**	**No Cirrhosis N=1,977**	**Cirrhosis N=288**
Alanine Aminotransferase			
Grade 1 (> ULN to 3.0 x ULN)	0	20 (1%)	1 (<1%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	0	3 (2%)	2 (<1%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	0	2 (<1%)	0
Alkaline Phosphatase			
Grade 1 (> ULN to 2.5 x ULN)	17 (6.1%)	154 (8%)	32 (11%)
Aspartate Aminotransferase			
Grade 1 (> ULN to 3.0 x ULN)	0	35 (2%)	1 (<1%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	0	1 (<1%)	4(1%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	0	6 (<1%)	0
Bilirubin			
Grade 1 (> ULN to 1.5 x ULN)	30 (11%)	115 (6%)	39(14%)
Grade 2 (> 1.5 to 3.0 × ULN)	17 (6%)	41 (2%)	10 (4%)
Grade 3 (> 3.0 to 10 x ULN)	0	6 (<1%)	2 (<1%)
Prothrombin Intl. Normalized Ratio			
Grade 1 (> 1 to 1.5 x ULN)	22 (8%)	146 (7%)	42 (15%)
Grade 2 (> 1.5 to 2.5 x ULN)	0	12 (<1%)	2 (<1%)
Grade 3 (> 2.5 x ULN)	0	9 (<1%)	0
Creatinine Clearance			
Grade 1 (< LLN – 60 mL/min)	25 (9%)	NA	NA
Grade 2 (< 60 – 30 mL/min)	9 (3.2%)	NA	NA

**Indicates the post-baseline toxicity Grades that were more clinically extreme than the toxicity Grade corresponding to the baseline.*
Source: EXPEDITION-8 Lab Toxicity Grade Analysis Dataset (ADLBGRD) and NDA 209394

Reviewer Comment: Chemistry laboratory abnormalities were mostly Grade 1-2, transient, not associated with significant AE or clinical symptoms and were consistent with findings in the original NDA. As in the original NDA, Grade 1 and Grade 2 bilirubin elevations occurred in more than 10% of subjects (17% in EXPEDITION-8 and 17% in cirrhotic subjects in the original NDA). However, only 4 subjects (1%) had Bilirubin values ≥2 X ULN. Most of these elevations were transient, peaking before 20 days, not associated with transaminase elevations or clinical symptoms associated with liver failure and in most cases resolved or trended down while still taking GLE/PIB (See also Hepatotoxicity section 9.26). One of these subjects, a 59-

year-old white female with a baseline Childs Pugh score of 5 did develop peripheral swelling on day 40 , thought to be related to GLE/PIB and was started briefly on spironolactone. However, study drug was not interrupted, liver parameters did not worsen and bilirubin improved post treatment. In addition, one subject each developed ocular icterus (b) (6)) or had hyperbilirubinemia (b) (6) or blood bilirubin (b) (6)) increased reported as an AE; in these cases study drug was not interrupted. The subject with ocular icterus had missing SVR12 data but no HCV RNA detected at Post-Treatment Day 29; the other subjects achieved SVR12.

Changes in creatinine clearance were also transient in nature without a distinct pattern associated with GLE/PIB use, and similar to abnormalities observed in the original NDA.

No labelling changes are recommended based on the laboratory data observed in EXPEDITION-8.

9.23 Vital Signs- EXPEDITION-8-GT 1,2,4,5,6
No clinically important trends in vital signs were observed.

9.24 Electrocardiograms (ECGs)- EXPEDITION-8-GT 1,2,4,5,6
Seven subjects had clinically significant abnormal ECG findings. Five subjects (Subjects (b) (6)) had an abnormal ECG finding prior to the first dose of study drug (i.e., during screening and/or at baseline, prior to the administration of study drug).

Subject (b) (6), with a medical history of atrial fibrillation, had a clinically significant abnormal ECG finding of atrial fibrillation at baseline (Day 1) and was also noted during treatment (Day 53); this event was assumed to be related to a preexisting abnormality.

Subject (b) (6), with a medical history of hypertension, cerebrovascular accident and thyroid disorder, had 2 clinically significant abnormal ECG findings of atrial fibrillation during treatment (Day 12 and Day 51). This subject had a corresponding Grade 2 AE of atrial fibrillation that was assessed as serious and not considered by the investigator to be related to study drug; the event was considered by the Sponsor to be more likely related to a history of hypertension, alcohol use and advanced age. The subject continued in the study and subsequently completed study drug without interruption/discontinuation.

9.25 Pregnancy-EXPEDITION-8-GT 1,2,4,5,6
No pregnancies were reported.

9.26 Safety Issues of Special Interest: Hepatotoxicity and Liver Related Events- EXPEDITION-8-GT 1,2,4,5,6
Data from EXPEDITION-8 were evaluated to identify treatment-emergent hepatic decompensation/hepatic failure events, defined as ascites, hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis.

One subject (Subject (b) (6)) met the criteria for having a hepatic decompensation event. This subject experienced an event of worsening of ascites (Grade 1) on Day 8 that was not considered by the investigator to be related to study drug and did not meet serious criteria. This subject was enrolled in the study in violation of the protocol exclusion criteria due to a prior history of decompensated cirrhosis with a baseline Child Pugh Score of 8.

Additionally, there was one subject with 2 separate reported events of encephalopathy thought to be unrelated to GLE/PIB; Grade 2; Days 34-41 and Grade 1; Days 77-100 . The subject is a 66-year-old male with a baseline Childs-Pugh score of 5 and a fibroscan of 20 kPa, with a medical history of seizure disorder, anxiety and gastritis/esophagitis and past injection drug and alcohol use. Additionally, the subject's post baseline liver transaminases and bilirubin measurements fluctuated minorly but were within the upper limits of normal and he did not exhibit any other clinical signs or symptoms of liver failure.

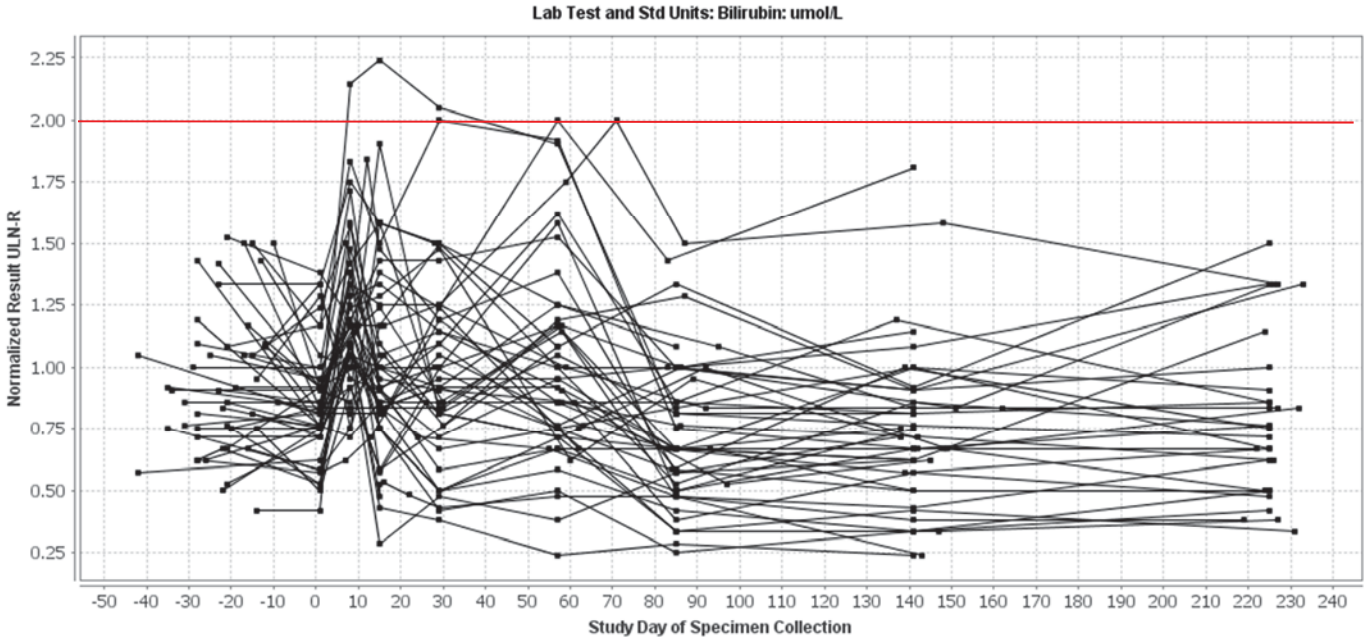
Postbaseline events of hepatocellular carcinoma (HCC) were identified using the preferred terms of hepatocellular carcinoma, hepatic neoplasm, hepatic cancer, hepatic cancer metastatic, and hepatic cancer recurrent. No cases of postbaseline HCC were identified.

No subject met the criteria for hepatic laboratory abnormalities of interest below:
- Confirmed post-nadir ALT > 5 × ULN
- Post-nadir ALT > 3 × ULN and a concurrent total bilirubin > 2 × ULN with direct/total bilirubin ratio > 0.4

As stated above, and as in the original NDA, Grade 1 and Grade 2 post baseline bilirubin elevations occurred in a significant number of subjects [17% (n=47/280) in EXPEDITION-8 compared to 17% (49/288) in cirrhotic subjects in the original NDA].

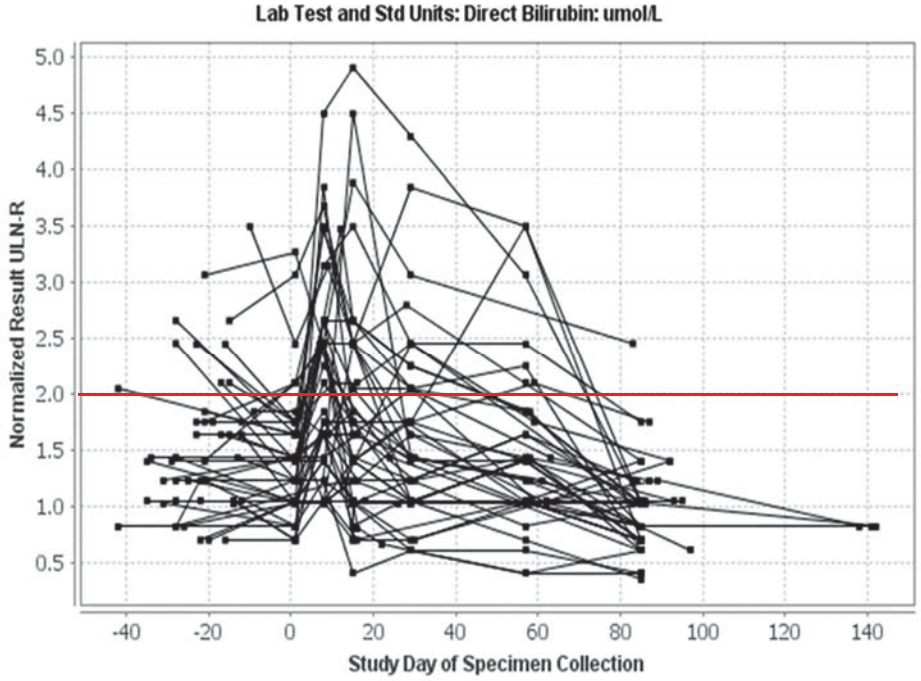
However, in EXPEDITION-8, only 4 subjects within the subset of those with postbaseline Grade 1 or 2 total bilirubin elevations had total bilirubin values ≥2 X ULN (see Figure 1). In addition, most of the postbaseline total bilirubin elevations were transient, associated with a direct bilirubinemia (see Figure 2), peaked before 20 days, and were not associated with transaminase elevations or clinical symptoms associated with liver failure. There was a downward trend in liver enzymes and in most cases, the bilirubin elevations resolved or trended down while the subject was still taking GLE/PIB (see Figure 3 and Figure 4). Subjects with transiently elevated bilirubin did not proportionally experience more SAEs or Grade 3 or higher adverse events, and appeared to tolerate therapy, as well as subjects without bilirubin elevations.

Figure 1 Total Bilirubin (xULN from Baseline) by Study Day in Select Subjects (N=47) with a Post-baseline Elevation of Total Bilirubin -EXPEDITION -8



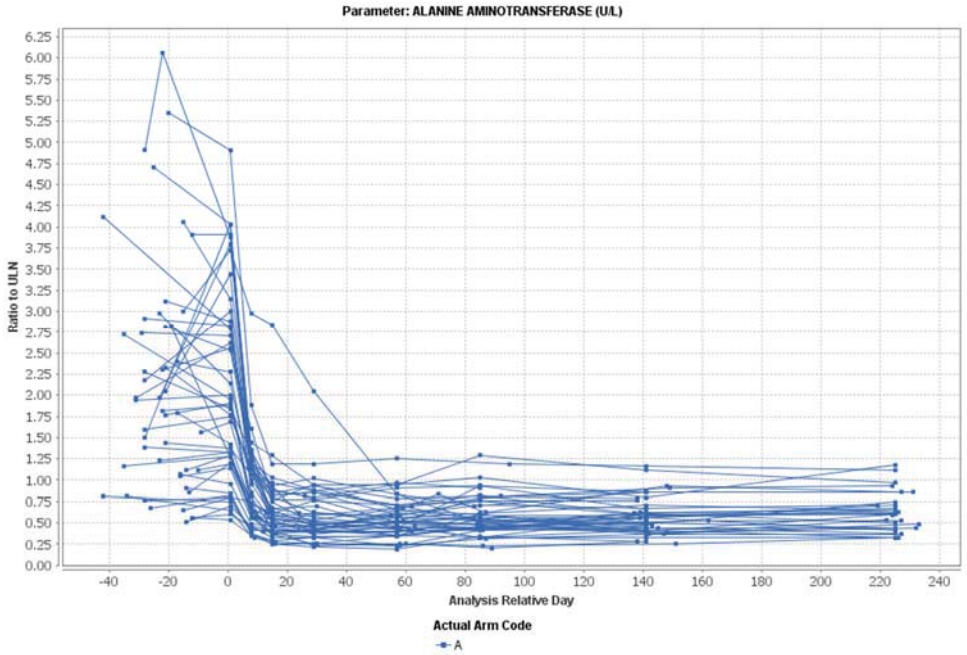
Source: EXPEDITION-8 Lab Toxicity Grade Analysis Dataset (ADLBHY)

Figure 2 Direct Bilirubin (xULN from Baseline) by Study Day in Select Subjects (N=47) with a Post-baseline Elevation of Total Bilirubin -EXPEDITION -8



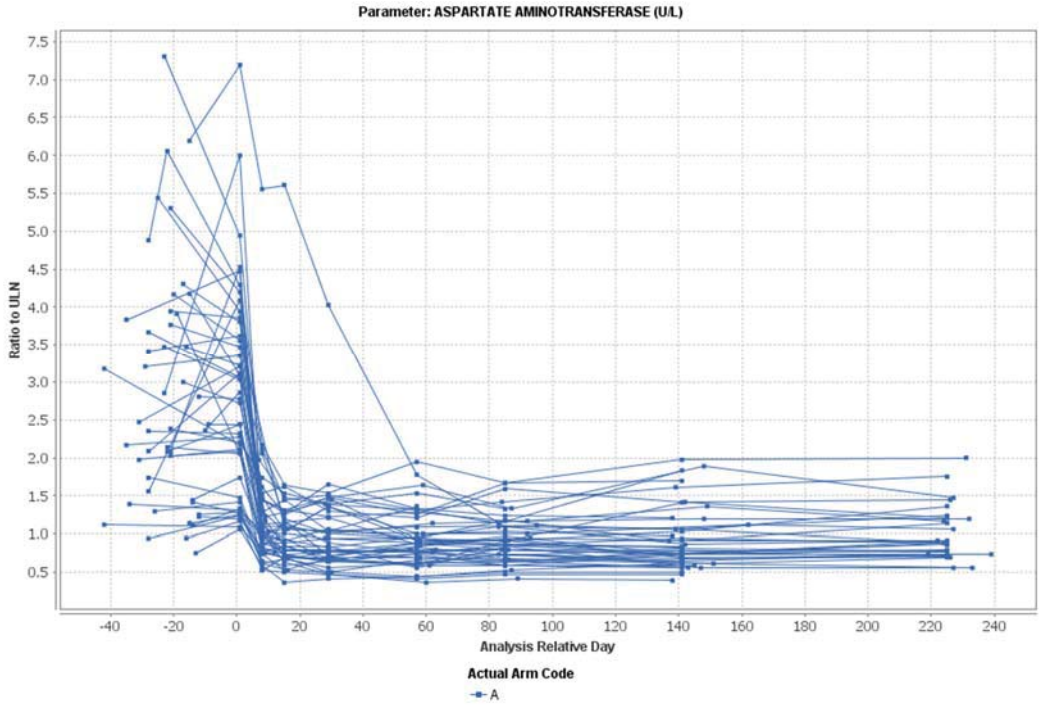
Source: EXPEDITION-8 Lab Toxicity Grade Analysis Dataset (ADLBHY)

Figure 3 ALT Trends in Select Subjects (N=47) with a Post-baseline Elevation of Bilirubin -EXPEDITION -8



Source: EXPEDITION-8 Lab Toxicity Grade Analysis Dataset (ADLBHY)

Figure 4 AST Trends in Select Subjects (N=47) with a Post-baseline Elevation of Bilirubin -EXPEDITION -8



Source: EXPEDITION-8 Lab Toxicity Grade Analysis Dataset (ADLBHY)

Reviewer Comment: Overall, the liver safety data in EXPEDITION-8 is consistent with the data in the original NDA in both cirrhotic and noncirrhotic subjects and does not support changes in labeling (other than the addition of data). Transient increases in bilirubin could represent adaptation and/or a reflection of OATPB1B3 saturation, of which GLE/PIB is a substrate, resulting in a transient "Rotor like-syndrome" in some subjects on GLE/PIB; this is the primary medical reviewer's theory.

Rotor syndrome is a rare, relatively benign autosomal recessive bilirubin disorder associated with increases in direct/conjugated bilirubin. SLCO1B1 and SLCO1B3 genes, which are mutated in Rotor syndrome, encode OATP1B1 OATP1B3. The proteins/receptors transport bilirubin and other compounds from the blood into the liver so that they can be cleared. Without the function of either transport protein, bilirubin is less efficiently taken up by the liver and removed from the body. The buildup of this substance leads to jaundice in people with Rotor syndrome.

It is unclear why some, but not all, subjects on GLE/PIB experience transient increases in bilirubin. However, subjects with cirrhosis appear to have increased susceptibility to this phenomenon, possibly because of decreased OATP1B3 receptor availability. In addition, common concomitant medications including statins, ARBs and ACE inhibitors are co-substrates for OATP1B3 and could cause a buildup of bilirubin via competitive inhibition.

Therefore, in the context of clinical trials, it appears that for subjects with compensated cirrhosis, hepatotoxicity and progression to liver decompensation are extremely rare, despite some transient isolated increases in bilirubin. However, it is important to contextualize that compensated cirrhotic subjects in clinical trials may be a distinct population from the broader compensated cirrhosis population. Indeed, most subjects with compensated cirrhosis in both EXPEDITION -8 and in the Phase 2/3 data in the original NDA had Child Pugh Scores of 5 [90%(252/280) in EXPEDITION-8 and 87% (251/288) in the Phase 2/3 data]. Additionally, as part of a clinical trial, subjects are provided with frequent monitoring and follow-ups throughout the clinical trial. While the subjects with compensated cirrhosis and baseline Child Pugh scores of 6 did not appear to do worse in clinical trials from a safety standpoint, the numbers of subjects are small and the trials were not powered to detect specific safety signals at this level of granularity.

Like most other HCV regimens containing protease inhibitors, GLE/PIB is contraindicated in Childs Pugh C cirrhosis based on clinically-significant elevated drug exposures of the protease inhibitor. Since the original approval, GLE/PIB has been not recommended for treatment of subjects with Childs Pugh B cirrhosis because safety and efficacy were not studied in this population.

In the postmarketing setting, albeit with unknown denominator in the context of a widely used drug, cases of documented liver decompensation temporally associated with GLE/PIB have been reported. In most cases, patients had evidence of advanced liver disease or prior hepatic decompensation (Childs Pugh B or C) and/or indicators of advanced liver disease (for example ascites, hepatic encephalopathy, variceal hemorrhage, evidence of portal hypertension, changes in coagulation parameters, thrombocytopenia, alcoholic liver disease,

hepatocellular carcinoma, or history of liver lobectomy or other significant medical or surgical treatments for liver disease). Some cases were misclassified as having less severe liver impairment (Child-Pugh A) at baseline.

During the review of these supplements, the Division of Pharmacovigilance completed a review of postmarketing reports of hepatic decompensation/failure associated with the use of HCV DAA treatment regimens containing protease inhibitors, including GLE/PIB. On August 28, 2019 a DSC was issued describing the safety findings and underscoring the intended treatment population. The DSC also provides a recommendation that providers should frequently monitor patients with cirrhosis or those who have indicators of advanced liver disease, who are taking these regimens. Based on postmarketing safety findings, the label will now contraindicate patients with Child Pugh B hepatic impairment and will include a warning describing the risk of hepatic decompensation/failure in patients with evidence of advanced liver disease. Further detailed discussion of this issue is included in Section 14 of this review.

9.27 Safety Profile Differences by Baseline Demographics

Subjects were compared by age under or over 65 years, race, and gender for frequency of safety events. These safety events included the proportions of TEAEs, treatment-related AEs, Grade 3 or greater TEAEs, Grade 3 or greater laboratory toxicity values, and SAEs. With the caveat that small sample sizes in the specific subgroups limit these comparisons, no clear or meaningful difference in type or frequency of safety events was detected based on age, race, and gender.

9.28 Summary of Safety Findings – EXPEDITION-8-GT 1,2,4,5,6

In summary, review of adverse events, laboratory abnormalities, ECG findings, and vital signs did not reveal any novel safety findings in this population of subjects with HCV GT 1,2,4,5 and 6 infection with compensated cirrhosis treated for 8 weeks. See below Section 9.29 for the four-month safety update and Section 9.30 for a summary of safety findings including GT3 safety data, which was submitted later in the review cycle, as discussed in Section 1. In addition, see Section 14 for a detailed discussion of post-marketing tracked safety issues that resulted in labeling concurrent with this Supplement.

9.29 Four-month Safety Update -EXPEDITION-8-GT 1,2,4,5,6

At the time of the 4-month safety update all subjects had either completed the study or discontinued the study. Since the primary analysis database lock and through the data cutoff date for the 4-month safety update, 3 additional subjects discontinued from the study: 1 subject discontinued due to an AE of gastric carcinoma and 2 subjects were lost to follow-up. In total, 272 subjects have completed the study, and 8 subjects have prematurely discontinued from the study.

No new treatment-emergent SAEs, deaths, AEs leading to study drug discontinuation, or AEs of special interest (treatment-emergent hepatic decompensation/hepatic failure events and postbaseline events of HCC) were reported as of the data cutoff date for this 4-month safety update. There were no other clinically relevant updates to the analysis of clinical laboratory data or trends in vital signs for this safety update. No pregnancies were reported through the data cutoff date for this update.

Reviewer Comment: The safety conclusions were unchanged from the Post-Treatment Week 12 Primary Analysis CSR to the Final CSR for EXPEDITION-8.

9.30 Overall Safety Data and Analysis- EXPEDITION-8- GT 1,2,3,4, 5 and 6
Due to staggered enrollment of subjects with GT3 infection secondary to a protocol amendment, as described in Section 1, partial efficacy and safety data were submitted for the 63 subjects with GT-3 infections on July 25, 2019 at the time of the 4-month safety update (SDN 115). Complete SVR12 efficacy and safety data, as well as final efficacy and safety data across all genotypes were submitted for GT-3 data on August 22, 2019 (SDN 125). No SAEs, deaths, AEs leading to discontinuation of study drug, or AEs of special interest were reported in the HCV GT3-infected subjects.

Across all genotypes, including GT3, common (≥ 5%) adverse events, regardless of relationship to study drug, were fatigue (9%), pruritus (8%), headache (8%), and nausea (6%). Serious adverse events occurred in 2% of patients, and none were related to glecaprevir/pibrentasvir. No adverse event led to study drug discontinuation, and no deaths were reported. No post-baseline hepatocellular carcinoma (HCC) events were reported. No subject met criteria for hepatic laboratory abnormalities of potential interest (alanine aminotransferase (ALT) > 3 × ULN and Total Bilirubin > 2 × ULN with Direct: Total Bilirubin Ratio > 0.4; or confirmed ALT > 5 × ULN).

Reviewer Comment: The GT3 safety data presented here do not alter the safety conclusions reached above in consideration of this sNDA. However, labeled safety data may differ slightly numerically or proportionally from the analysis presented in other sections above (based on GTs 1,2,4,5,6) given the addition of GT-3 data to the label.

10. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

11. Pediatrics

Current labeling for GLE/PIB indicates treatment for pediatric patients 12 years and older or weighing at least 45 kilograms based on review of the data from DORA Part 1 (sNDA S-006). ENDURANCE-5,6 and EXPEDITION-8 enrolled adults ≥18 years of age.

Supplement 7, which includes the data from ENDURACE-5,6, did not trigger PREA because the indication was not changed and there are no new dosing recommendations based on the submission of the additional data in GT5 and 6. Supplement 8 includes the data from EXPEDITION-8 and triggers PREA due to a new dosing recommendation (shorter duration of treatment for treatment-naïve subjects with compensated cirrhosis from 12 to 8 weeks). Previously reviewed PK and safety data in adolescents established the exposure and safety of GLE/PIB to be similar between adults and adolescents. Because the dose of GLE 100mg/PIB 40mg) for the current indication remains unchanged, and because the disease and response to therapy is believed to be similar in adults and children, extension of the indication of 8-week

dosing in treatment-naïve HCV patients with compensated cirrhosis is recommended for the adolescent population based on extrapolation of previously reviewed PK and safety data. The assessment for the adolescent population was completed and reviewed by the FDA Pediatric Review Committee (PeRC). Consistent with the original approval, a partial waiver was granted for pediatric patients 3 years and under, because subjects under age 3 may clear hepatitis C without treatment. A deferral was requested and granted for pediatric patients 3 years to less than 12 years of age. Currently, a clinical trial is ongoing for pediatric patients 3 to 12 years of age, however few subjects with compensated cirrhosis are expected to enroll given the very low prevalence of cirrhosis in patients in this age group.

12. Other Relevant Regulatory Issues

Post-Marketing Commitment (PMC) Fulfillment:
PMC 3246-2 is fulfilled by the data presented in this sNDA.

Description of PMC 3246-2: Submit the final report and datasets, including drug resistance datasets, for the ongoing clinical trial M16-126, evaluating glecaprevir/pibrentasvir in patients with HCV genotype 5 or 6 infection.

Trial Completion: August 1, 2018
Final Report Submission: March 31, 2019

Financial Disclosures
For ENDURANCE-5,6 , among 122 investigators, 3 had disclosable financial interests (category b significant payments of other sorts). For EXPEDITION-8, among 471 investigators, 13 (category b significant payments of other sorts) had disclosable financial interests (See Section 16).

AbbVie has taken steps to minimize potential bias of all clinical investigators from financial interests and arrangements by utilizing proper study design and the primary endpoint for all of the covered studies included an objective laboratory endpoint of HCV RNA. There were no investigators with a certification of due diligence.

Site Inspections
The Division decided that no further site inspections were needed for this sNDA given recent inspections for the original NDA 209394.

13. Labeling

Significant updates to the original approved label were made to the following sections:

2.0 Dosage and Administration: Table 1was updated to reflect an 8-week treatment duration for GTs 1,2,3,4,5 and 6 for treatment-naïve subjects with compensated cirrhosis

4.0 Contraindications: Language added contraindicating GLE/PIB in patients with moderate hepatic impairment (Child-Pugh B) or those with any history of prior hepatic decompensation, based on post marketing data.

5.2 Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease: This section was added to describe rare postmarket cases of hepatic decompensation in patients with evidence of advanced liver disease at baseline and provides recommendations for monitoring. (Language related to this change was made consistent throughout the label where appropriate)

6.1 Adverse Reactions: Safety data for EXPEDITION-8 were added.

6.2 Postmarketing Experience: Angioedema and hepatic decompensation were added as rare events, based on postmarketing data.

7.0 Drug Interactions: Language was added indicating that clearance of HCV infection with direct-acting antivirals may lead to changes in hepatic function, which may impact the safe and effective use of concomitant medications, for example, altered blood glucose control resulting in serious symptomatic hypoglycemia. Appropriate laboratory monitoring and dose adjustment of concomitant medications are recommended as clinically indicated. Other text was re-arranged or moved for flow.

7.4 Drug Interactions: a new Section 7.4 was added describing drug interactions with Medication Assisted Treatment for Opioid Use Disorder

12.4 Microbiology: Data on the impact of baseline NS5A resistance-associated polymorphisms on GLE/PIB efficacy were updated to incorporate the results from GT3, treatment-naïve subjects with cirrhosis who received the 8-week duration in EXPEDITION-8.

14 Clinical Studies:

1) Efficacy results at post-treatment Week 12 for the 8-week duration in treatment-naïve adults with HCV GT1, 2, 3, 4, 5, or 6 infection with compensated cirrhosis obtained in EXPEDITION-8 are included.
2) Efficacy results at post-treatment Week 12 for the 8-week duration in treatment-naïve and PRS treatment-experienced adults with HCV Genotype 5 or 6 infection without cirrhosis were updated to incorporate the results obtained from ENDURANCE-5, 6.
3) Efficacy results at post-treatment Week 12 for the 12-week duration in treatment-naïve and PRS treatment-experienced adults with HCV Genotype 5 or 6 infection with compensated cirrhosis were updated to incorporate the results obtained from ENDURANCE-5,6.

14. Postmarketing Considerations

Three Tracked Safety Issues (TSIs) and one resultant Drug Safety Communication influenced labeling for this supplement. This section provides a summary of the three TSIs that resulted in labeling changes during the review of these sNDAs.

TSI 2042: Dysglycemia in HCV DAA regimens-
The Division of Pharmacovigilance II (DPV II) reviewed FAERS and published literature to evaluate submitted cases of dysglycemia associated the use of DAAs. 18 cases were included in the case series of hypoglycemia with DAA use (as of October 28, 2018). None of the cases in the FDAFAERS review were reported with use of Mavyret. Among these 18 cases, there was some evidence of an association (i.e., temporal relationship, changes in antidiabetic medication use after DAA initiation) between DAA initiations and hypoglycemic events. However, based on the small number of cases, most of which have other etiologies for hypoglycemia, the hypoglycemic events could not be solely attributed to DAA therapy.

In response to the TSI, AbbVie also submitted a cumulative review of dysglycemia events with Viekira Pak, Technivie and Mavyret use from July 26, 2017 through May 17, 2018. AbbVie concluded that "revision of each DAA Core Company Data Sheet (CCDS), and subsequent in the "Warnings and Precaution" section of the United States Package Insert (USPI), is warranted to ensure awareness among treating physicians and HCV-infected patients with diabetes regarding the need to closely monitor glucose levels for potential dysglycemia and need for dose adjustments of their diabetes medications, given the biologic plausibility of improved glucose control due to HCV clearance following DAA treatment." AbbVie's internal review of specific cases related to Mavyret, which included both hypoglycemic and hyperglycemic events with and after Mavyret administration, concluded that these specific events were not related to study drug but rather to confounding events/medications.

Medical Reviewer Comment: Given the biologic plausibility of dysglycemia secondary to improved liver function, DAVP recommended inclusion of language related to this issue in Section 7.3 of the label. This Section of the label now more broadly describes the potential for changes in hepatic function after clearance of HCV infection with DAA treatment that may affect hepatically metabolized concomitant drugs; and recommends frequent laboratory monitoring or dose adjustment of the concomitant medication, as appropriate.

Originally labeled in Section 7.1 of the MAVYRET™ label, fluctuations in INR values that may also occur in patients receiving warfarin concomitant with GLE/PIB due to changes in liver function are now also incorporated into Section 7.3.

TSI 2071: Angioedema in Anaphylaxis associated with use of Mavyret-
DPV II identified 39 postmarketing cases, including one published literature case, of angioedema in subjects on GLE/PIB. In addition, DPV II identified one case of anaphylaxis with GLE/PIB use. While 11 angioedema cases reported symptoms consistent with anaphylaxis (i.e., respiratory compromise), the events occurred 7-36 days from initiation of GLE/PIB treatment and were not acute in onset (i.e., within 24 hours); therefore, they did not meet the case definition for anaphylaxis. Based on the DPV II analysis and a limited number of anaphylaxis cases, there is insufficient evidence to support an association between anaphylaxis and the use of GLE/PIB.

In the 11 angioedema cases associated with respiratory compromise, the median time to onset was 14 days (range 7 to 36 days) after starting GLE/PIB treatment. Ten of the 11 patients were receiving at least one concomitant medication labeled for angioedema, including nine on an Angiotension Converting Enzyme Inhibitor (ACEI). Of the 11 angioedema cases associated with respiratory compromise, 10 were hospitalized, including nine that required intubation, and one resulted in an emergency room (ER) visit. Of the nine patients that required intubation, all were simultaneously receiving an ACEI (one patient was on the ACEI for five years and one for 20 years prior to GLE/PIB). Seven of these 11 cases had a positive dechallenge which included five that had simultaneous discontinuation of an ACEI.

The Sponsor also conducted a review of postmarketing cases in their global safety database and identified 15 serious and 24 non-serious cases of angioedema with GLE/PIB use. (b) (4)

Medical Reviewer Comment: While the original registrational trials and subsequent trials have not suggested a signal for angioedema, and most cases are highly confounded there is not sufficient evidence to rule out that angioedema may be a rare event associated with Mavyret or with Mavyret and concomitant ACE-inhibitors. Therefore, DAVP recommended that angioedema be added to the postmarketing section of the label, especially given the potential serious consequences including death.

<u>TSI 2046: Hepatic decompensation or hepatic failure in HCV DAA regimens containing protease inhibitors.</u>
As a part of the DPV II evaluation for hepatic decompensation in HCV DAA regimens containing protease inhibitors, the DPV II identified 63 cases of liver decompensation, including liver failure and death, associated with the use of protease containing DAAs (Mavyret (n=46), Zepatier (n=14), and Vosevi (n=3)) reported in the FAERS database and in the medical literature through January 8, 2019. Drug utilization data provides possible exposure of HCV patients treated with PI containing DAA regimens.

An estimated (b) (4) patients received dispensed prescriptions in 2018 for Mavyret, Vosevi and Zepatier. Mavyret accounted for the highest proportion (b) (4) %) of the total patients use which was consistent with the highest number of FAERS cases among the examined drugs.

Ten cases reported isolated hyperbilirubinemia and jaundice without concomitant evidence of increased transaminase levels or other hepatic decompensation events, and eight cases reported deaths.

Overall, of the 63 cases, 13 were in patients without cirrhosis, 18 with compensated cirrhosis, 21 with decompensated cirrhosis, and 11 with unknown liver function status at baseline. More than half of the cases that reported no cirrhosis or compensated cirrhosis (Child-Pugh A) at baseline were misclassified and had evidence of advanced liver disease such as decreased platelets at baseline or portal hypertension, or other pre-existing risk factors such as alcoholic liver disease, or other clinically-serious medical illnesses impacting the liver prior to receiving

treatment that may have signified or directly contributed to the development of hepatic decompensation or liver failure.

The median time to onset of a liver-related event or liver decompensation after initiating treatment was 22 days, ranging from 2 days to 16 weeks (for Mavyret the median time to event was 27 days). The most frequently reported liver-related events were hyperbilirubinemia (n=42), jaundice (n=32), ascites (n=27), and hepatic encephalopathy (n=12). Discontinuation of the drug resulted in resolution of symptoms or reduced liver biochemical values in 39 of the 63 cases, and there were two cases of recurrence of symptoms upon re-initiating treatment.

In response to the TSI, on March 3, 2019, AbbVie submitted a cumulative review of hepatic decompensation with GLE/PIB, which included non-clinical studies, clinical trials, postmarketing surveillance, real-world evidence cohorts, and published literature from July 26, 2017 (international birth date) to December 31, 2018. The Sponsor searched their global safety database using Company MedDRA Query (CMQ) Hepatic decompensation and hepatic failure and identified 42 evaluable postmarketing cases of hepatic compensation with GLE/PIB. Of the 42 cases, 13 were in patients with no evidence of decompensated liver disease at baseline, 25 were in patients with evidence of decompensated liver disease at baseline, and four were in patients with unknown liver status at baseline. The Sponsor assessed 41 out of the 42 cases as unlikely related to GLE/PIB based on alternative etiologies or identifiable risk factors for the decompensated event. One case evaluated as possibly related to GLE/PIB, was in a patient with evidence of decompensated liver disease at baseline (as per the Sponsor) that developed ascites and hyperbilirubinemia within the first two months of GLE/PIB treatment. Among the 42 cases, seven deaths were reported; three without a history of decompensation, two with a history of decompensation, and two with unknown liver status at baseline. The Sponsor indicated that all fatalities had alternative etiologies as causes of death (i.e., disseminated aspergillosis, ruptured HCC, progressive HCC, sepsis from urocutaneous fistula, post-kidney transplant with cerebral hemorrhage, pneumonia with severe sepsis, and active alcoholism with Mallory-Weiss syndrome). (b) (4)

A search of the Sponsor's clinical trial database (n=4643; 3726 non-cirrhotic and 917 cirrhotic patients) identified three cases of hepatic decompensation during treatment with GLE/PIB. Two patients had CP-A compensated cirrhosis at baseline; one experienced esophageal variceal hemorrhage on Day 22 and one experienced upper gastrointestinal hemorrhage and ascites on Day 77 and Day 86, respectively. The event of esophageal variceal hemorrhage was not considered related to GLE/PIB by either the investigator or Sponsor but rather related to the patient's current alcohol intake and history of cirrhosis and portal hypertension. The event of gastrointestinal hemorrhage was considered by the investigator as having a reasonable possibility of being related to GLE/PIB. The remaining clinical trial patient had evidence of decompensated liver disease (history of ascites) at baseline and experienced worsening of ascites on Day 8 of GLE/PIB. The event of ascites was considered by the investigator as not related to GLE/PIB treatment. (b) (4)

(b) (4)

Medical Reviewer Comment: As stated above, in response to the TSI, AbbVie submitted a review of post-marketing cases; however, cases were identified based on different methodology and slightly different, but acceptable, definition of hepatic failure that did not include isolated hyperbilirubinemia with jaundice and did not completely overlap with the DPV II review. The findings of the DPV II review were also discussed with AbbVie on a teleconference held on August 1, 2019. The Sponsor presented a sub-portion of the Mavyret cases (b) (4) *They also presented a regression analysis of claims data including chronic HCV infected patients with compensated cirrhosis who were either new users of Mavyret (n=240) or new users of a non-PI containing DAA regimen (Epclusa, Harvoni, Sovaldi, Daklinza) (n=4185). The findings of their analysis indicated no difference in decompensation rates between Mavyret and other non-protease inhibitor containing DAAs. Based on this meeting and subsequent discussion AbbVie agreed to the following additions to the label: 1) Contraindication of use in Child Pugh B Hepatic Impairment (in addition to the pre-existing contraindication for Child Pugh C) and 2) addition of Warning and Precautions Section 5.2 for risk of hepatic decompensation/failure in patients with evidence of advanced liver disease.*

Clinical monitoring of patients who may be at greater risk for liver failure/decompensation was also recommended in the Warnings and Precautions Section 5.2. It is the opinion of this reviewer that all patients with evidence of advanced liver disease (including portal hypertension, low platelets, evidence of synthetic dysfunction and/or medical illnesses impacting the liver) should be monitored closely on treatment regardless of cirrhosis status or Child-Pugh classification. In addition, this reviewer believes that all patients with Child-Pugh A liver disease should be monitored carefully clinically, including with hepatic laboratories for the following reasons. First, although cases of decompensation were rare in clinical trials, most subjects (approximately 90%) enrolled in trials with compensated cirrhosis had lower Child Pugh Scores of 5. Although there was no evidence in clinical trials that subjects with Child Pugh Scores of 6 (or even those with accidently enrolled with decompensated cirrhosis) had an increased risk of decompensation, these trials were not powered to capture these types of specific rare events. Further, an important finding of the OSE review across all DAA protease inhibitor containing regimens, was the misclassification of patients baseline liver function, which suggests that a more conservative cut-off for increased monitoring could capture patients who might have more advanced liver disease than recognized by the often non-specialist provider (also especially important given the potential reversibility of these adverse events based on the OSE analysis). Moreover, the Child Pugh Score was initially developed to risk-stratify mortality in patients with a previous variceal bleed and therefore, even those with the lowest scores may have advanced liver disease (specifically portal hypertension) by definition. Lastly, although the analysis of claims data for decompensation events conducted by AbbVie was reassuring to rule out a high increased risk of decompensation among patients with Childs Pugh A cirrhosis. However, the interpretability of

the study is limited by the small numbers of patients who received Mavyret, making it hard to determine what may be a small degree of increased risk related to these rare events.

15. Patient Experience/Patient Reported Outcomes

Table 35 and Table 36 summarize patient experience data relevant to this application.

Table 35 Patient Reported Outcomes - ENDURANCE-5,6

					The patient experience data that was submitted as part of the application, include:	Section(s) and if applicable file names where data are located and discussed in the application
	☐				Clinical outcome assessment (COA) data, such as	
			☐		Patient reported outcome (PRO)	Module 5, Section 5.3.5.2, M16-126 CSR, Section 11.2 Patient-Reported Outcomes
			☐		Observer reported outcome (ObsRO)	N/A
			☐		Clinician reported outcome (ClinRO)	N/A
			☐		Performance outcome (PerfO)	N/A
	☐				Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	N/A
	☐				Patient-focused drug development or other stakeholder meeting summary reports	N/A
	☐				Observational surveys studies designed to capture patient experience data	N/A
	☐				Natural history studies	N/A
	☐				Patient preference studies (e.g., submitted studies or scientific publications)	N/A
	☐				Other: (Please specify)	N/A

Source: Supplement 7 submission; CSR

Table 36 Patient Reported Outcomes EXPEDITION-8

☐	The patient experience data that was submitted as part of the application, include:			Section(s) and if applicable file names where data are located and discussed in the application
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	Module 5, Section 5.3.5.2, M16-135 CSR, Section 11.2 Patient-Reported Outcomes
		☐	Observer reported outcome (ObsRO)	N/A
		☐	Clinician reported outcome (ClinRO)	N/A
		☐	Performance outcome (PerfO)	N/A
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		N/A
	☐	Patient-focused drug development or other stakeholder meeting summary reports		N/A
	☐	Observational surveys studies designed to capture patient experience data		N/A
	☐	Natural history studies		N/A
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		N/A
	☐	Other: (Please specify)		N/A

Source: Supplement 8 submission; CSR

Medical Reviewer Comment: Patient reported outcomes were similar for these studies and registrational trials. No patient reported outcome data are included in labeling.

16. Appendix

Biostatistical Tables- Subgroup Analysis

Table 37 SVR12 Rates by Subject Demographics and Selected Baseline Characteristics in M16-135 (Non-HCV GT3)

	8-week GLE/PIB (N=280)	
	SVR12 Rate	**95% CI**
Gender		
Female	98.2% (110/112)	(93.7%, 99.5%)
Male	97.6% (164/168)	(94.0%, 99.1%)
Race		
Asian[2]	100% (28/28)	(87.9%, 100%)
Black or African American	100% (27/27)	(87.5%, 100%)
White	97.3% (217/223)	(94.3%, 98.8%)
Other	100% (2/2)	n/a
Ethnicity		
Hispanic or Latino	97.1% (34/35)	(85.5%, 99.5%)
Not Hispanic or Latino	98.0% (240/245)	(95.3%, 99.1%)
Age		
< 65 years	98.0% (192/196)	(94.9%, 99.2%)
≥ 65 years	97.6% (82/84)	(91.7%, 99.3%)
Region		
Europe	98.6% (141/143)	(95.0%, 99.6%)
North/Central America[1]	97.1% (99/102)	(91.7%, 99.0%)
Rest of world[1]	97.1% (34/35)	(85.5%, 99.5%)
Baseline HCV viral load		
< 1,000,000 IU/mL	96.7% (87/90)	(90.7%, 98.9%)
≥ 1,000,000 IU/mL	98.4% (187/190)	(95.5%, 99.5%)
Baseline Child-Pugh score		
5	98.0% (247/252)	(95.4%, 99.1%)
6	96.0% (24/25)	(80.5%, 99.3%)
> 6	100% (3/3)	n/a

Source: Table 14.2_4.1 in M16-135 clinical study report
[1]North/Central America included USA, Canada and Puerto Rico, and the rest of the world included Israel, Taiwan and Vietnam.

Financial Disclosures EXPEDITION- 5,6

FDA Request	AbbVie Response			
1. Total number of investigators identified in the trials (number principal investigators and sub-investigators)	Study	Total Number of Investigators	Number of Principal Investigators	Number of Sub-Investigators
	M16-126	122	27	95
	Total	**122**	**27**	**95**
2. Number of investigators who are sponsor employees (including both full-time and part-time employees)	0 in covered clinical studies			
3. Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)	3			

FDA Request	AbbVie Response
4. If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):	
a. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study	a. 0
b. Significant payments of other sorts	b. 3
c. Proprietary interest in the product tested held by investigator	c. 0
d. Significant equity interest held by investigator in sponsor of covered study	d. 0
5. Number of investigators with certification of due diligence (Form FDA 3454, box 3)	0
6. Please also provide details regarding any disclosable financial interests/ arrangements, a description of the steps taken to minimize potential bias, and an explanation for any investigators with a certification of due diligence.	As indicated in Module 1, Section 1.3.4.2.2 of the sNDA, three investigators hold disclosable financial interests/arrangements. AbbVie has taken steps to minimize potential bias of all clinical investigators from financial interests and arrangements by utilizing proper study design. There were no investigators with a certification of due diligence (Form FDA 3454, box 3).

Financial Disclosures Expedition-8

FDA Request	AbbVie Response			
1. Total number of investigators identified in the trials (number principal investigators and sub-investigators)	Study	Total Number of Investigators	Number of Principal Investigators	Number of Sub-Investigators
	M16-135	471	113	358
	Total	**471**	**113**	**358**
2. Number of investigators who are sponsor employees (including both full-time and part-time employees)	0 in covered clinical studies			
3. Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)	13			

FDA Request	AbbVie Response
4. If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):	
a. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study	a. 0
b. Significant payments of other sorts	b. 13
c. Proprietary interest in the product tested held by investigator	c. 0
d. Significant equity interest held by investigator in sponsor of covered study	d. 0
5. Number of investigators with certification of due diligence (Form FDA 3454, box 3)	0
6. Please also provide details regarding any disclosable financial interests/ arrangements, a description of the steps taken to minimize potential bias, and an explanation for any investigators with a certification of due diligence.	As indicated in Module 1, Section 1.3.4.2.2 of the sNDA, no investigators hold disclosable financial interests/arrangements. AbbVie has taken steps to minimize potential bias of all clinical investigators from financial interests and arrangements by utilizing proper study design. There were no investigators with a certification of due diligence (Form FDA 3454, box 3).

References

1. Thrift, A.P., H.B. El-Serag, and F. Kanwal, *Global epidemiology and burden of HCV infection and HCV-related disease.* Nat Rev Gastroenterol Hepatol, 2017. **14**(2): p. 122-132.
2. Carter, W., S. Connelly, and K. Struble, *Reinventing HCV Treatment: Past and Future Perspectives.* J Clin Pharmacol, 2017. **57**(3): p. 287-296.
3. *Treatment of Recurrent HCV Infection following Liver Transplantation.* Hepatitis C Online, 2018. **Module 6**.
4. Sawinski, D. and R.D. Bloom, *Novel Hepatitis C Treatment and the Impact on Kidney Transplantation.* Transplantation, 2015. **99**(12): p. 2458-66.
5. Mandorfer, M., et al., *Advances in the management of HIV/HCV coinfection.* Hepatol Int, 2016. **10**(3): p. 424-35.
6. Mehta, S.H., et al., *Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic.* AIDS, 2006. **20**(18): p. 2361-9.
7. Wilson, E. B. (1927). *Probable inference, the law of succession, and statistical inference.* Journal of the American Statistical Association. **22**: 209–212.

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/s/

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