CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209394Orig1s000

SUMMARY REVIEW

Combined Cross-Discipline Team Leader, Division Director and ODE Director Summary Review

Date	July 17, 2017
From	Wendy Carter, DO; Jeffrey Murray, MD; and Ed Cox, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	209394 000
Applicant	AbbVie Inc.
Date of Submission	December 14, 2016
PDUFA Goal Date	August 14, 2017
Proprietary Name / Non-Proprietary Name	Mavyret/glecaprevir and pibrentasvir (GLE/PIB)
Dosage form(s) / Strength(s)	Fixed dose combination tablets 100mg/40mg
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with chronic hepatitis C
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with chronic hepatitis C

1. Benefit-Risk Assessment

We concur with the overall Risk-Benefit Assessment as provided in the Clinical Review by Dr. Larissa Stabinski and Dr. Aimee Hodowanec; therefore, this section closely mirrors that found in the Clinical Review with the exception of the review team decision to support the proposed 8 week treatment duration for patients with hepatitis C genotype 5 or 6 without cirrhosis who are treatment-naïve or treatment experienced to interferon, pegylated interferon, ribavirin, or sofosbuvir (collectively abbreviated PRS). Additional data were available for this review that were not available in time for consideration in the primary review. This change, however, does not substantively impact the overall risk-benefit assessment for glecaprevir and pibrentasvir (GLE/PIB).

Benefit-Risk Summary and Assessment

Glecaprevir (GLE) is a hepatitis C virus (HCV) NS3/4A protease inhibitor and pibrentasvir (PIB) is an HCV NS5A inhibitor. GLE/PIB is a fixed-dose combination tablet with a proposed indication for treatment of chronic HCV genotypes (GTs) 1 through 6 infection in adults. Intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients including a subpopulation of those with previous exposure to Direct Acting Antiviral therapy (DAAs), patients with advanced chronic kidney disease (CKD), including those receiving hemodialysis, and patients with HCV/HIVco-infection.

HCV infection is a serious disease, affecting an estimated 3.5 million people in the U.S. and over 71 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 DAAs that result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in >90% of patients. However, a treatment gap remains for patients infected with HCV GTs 2, 3, 5 and 6 who also have CKD, including those receiving dialysis, as no IFN-sparing regimens are currently approved for this patient population. Additionally, GLE/PIB received Breakthrough Designation for treatment of HCV GT1 in subjects who previously failed a DAA treatment regimen. This particularly addresses an unmet medical need for those who have failed an NS5A inhibitor containing regimen, as there is currently no approved therapy for this subpopulation.

GLE/PIB demonstrated SVR12 rates ranging from 91-100% for treatment durations recommended by the FDA review team. SVR rates varied depending on the treatment duration, patients' HCV GT, and patients' prior treatment history. Efficacy was similar in patients with or without cirrhosis, with or without HIV coinfection, and with CKD, with or without hemodialysis. GLE/PIB represents the first DAA therapy recommended for a duration of 8 weeks for HCV GT1-6 treatment-naïve patients without cirrhosis and the first IFN-free regimen for treatment of HCV GTs 2, 3, 5 and 6 in severe CKD patients, including those receiving hemodialysis. GLE/PIB is also an effective option for HCV GT 1 infected patients with prior DAA treatment experience with NS5A inhibitors or NS3/4A protease inhibitors. Because of a high virologic failure rate, the data do not support the use of GLE/PIB in patients with prior treatment experience with both NS5A inhibitors and NS3/4A protease inhibitors.

No major safety issues specifically related to GLE/PIB were identified in this review. Headache (9%), fatigue (8%), nausea (6%), and diarrhea (5%) were the most common adverse reactions (ADRs) that occurred at greater than or equal to 5% in ENDURANCE-2, the 12 week placebo controlled study of subjects without severe renal impairment. All of the most common ADRs, except fatigue and asthenia, occurred at higher rates in the GLE/PIB arm of the placebo controlled trial. ADRs were also reported in fairly similar proportions across major clinical trials in which subjects without severe renal impairment received GLE/PIB. Most ADRs were grade 1 or 2 and mild or moderate in severity across all Phase 2 and 3 clinical trials. In subjects without severe renal impairment, there was only one serious adverse event (SAE), transient ischemic attack, considered by the Investigator as reasonably related to the study drug, the Applicant did not agree that the SAE was related to GLE/PIB administration. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.3% (7/2,265).

The safety in EXPEDITION-4, which evaluated GLE/PIB for 12 weeks duration in subjects with chronic Stage 4 and Stage 5 CKD, including those on hemodialysis, was similar to the overall population. The most common adverse reactions observed in greater than or equal to 5% of subjects were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In the CKD subjects treated with GLE/PIB who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). None of the subjects experienced a serious adverse reaction; however, 24% of the subjects experienced SAEs, which is a similar rate observed in other development programs evaluating HCV DAAs in CKD. The proportion of CKD subjects who permanently discontinued treatment due to adverse reactions was 2%.

Approval of GLE/PIB for treatment of adult patients with HCV GT 1 through 6 infection is fully supported by the available evidence of efficacy and safety. Additionally, GLE/PIB will address an unmet medical need for HCV GT1 subjects who have previously failed an NS5A inhibitor, and will expand treatment options for those with CKD and HCV GT2, 3, 5 or 6 infection. The Phase 2 and 3 efficacy data support the FDA indicated GLE/PIB treatment regimens in the following patient populations, some of which differ from the original Applicant proposal:

Treatment-naïve
GTs 1 ,2, 3, 4, 5 or 6 subjects without cirrhosis for 8 weeks
GTs 1, 2, 3, 4, 5 or 6 with compensated cirrhosis (Child-Pugh A) for 12 weeks

Treatment-experience-PRS *(defined as prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin and/or sofosbuvir, but no prior treatment experience with an NS5A inhibitor or NS3/4A protease inhibitor)*

GTs 1 ,2, 4, 5 or 6 without cirrhosis for 8 weeks
GTs 1 ,2, 4, 5 or 6 with compensated cirrhosis for 12 weeks
GT3 with or without cirrhosis for 16 weeks

Treatment-experienced with a regimen containing an HCV NS5A Inhibitor or NS3/4A Inhibitor (Not Both)
GT1 with or without compensated cirrhosis and any prior treatment regimen containing an NS5A inhibitor (no prior NS3/4A protease inhibitor) for 16 weeks
GT1 with or without compensated cirrhosis and any prior treatment regimen containing an NS3/4A protease inhibitor (no prior NS5A inhibitor) for 12 weeks

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 infected with HCV,	If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population. Patients can

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	including approximately 3.5 million people in the United States (U.S.). • The prevalence rate of HCV among patients undergoing hemodialysis has been reported as 7.8%, and it is estimated that over 60,000 HCV-infected patients will require HD by 2020. • There are at least six distinct 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. GT7 has been identified but is currently limited the Democratic Republic of Congo. • 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.	experience symptoms that are severe and debilitating. HCV infection is a significant and growing public health concern.
Current Treatment Options	• The current standard-of-care treatments for CHC are interferon-free, all-oral DAA regimens. Treatment options vary based on HCV GT, however all currently approved regimens, have a 12 week or longer indication (with the exception of ledipasvir/sofosbuvir for which 8 weeks can be considered in GT1 treatment-naïve patients without cirrhosis who have pretreatment HCV RNA <6 million IU/mL): • GT1: sofosbuvir/velpatasvir; ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir (in combination with sofosbuvir); and simeprevir (in combination with sofosbuvir) • GT2: sofosbuvir/velpatasvir; sofosbuvir + ribavirin • GT3: sofosbuvir/velpatasvir; daclatasvir + sofosbuvir; sofosbuvir + ribavirin • GT4: sofosbuvir/velpatasvir; ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/paritaprevir/ritonavir with RBV • GT5: sofosbuvir/velpatasvir; ledipasvir/sofosbuvir • GT6: sofosbuvir/velpatasvir; ledipasvir/sofosbuvir • Treatment with DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in > 93% of CHC patients with compensated liver disease	Patients with chronic HCV infection would greatly benefit from new therapeutic options that are well tolerated, of a shorter duration, ribavirin-free, and equally or more efficacious than current interferon-free DAA options in patients with or without severe renal impairment. A specific unmet medical need exists for patients who have previously failed a prior DAA regimen, particularly for those who are NS5A inhibitor experienced, because currently no approved regimens are available.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>and sofosbuvir/velpatasvir provides a treatment option for patients with decompensated cirrhosis. However, there remains a critical gap of treatment options for patients with severe renal impairment for GTs 2, 3, 5 and 6 and for patients with treatment experience with DAA therapy.</td><td></td></tr>
<tr><td>Benefit</td><td>

The efficacy 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.
The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the table below, SVR12 results overall, as recommended by FDA, ranged from 91-100% depending on the Phase 2 or 3 trial regimen, HCV GT, cirrhosis status, prior treatment history, and treatment duration. Efficacy did not vary according to renal or HCV/HIV-1 co-infection status.

<table>
<tr><th colspan="5">% SVR12 by Recommended Treatment Duration</th></tr>
<tr><th>GT</th><th>Treatment Experience</th><th>Cirrhotic Status</th><th>GLE/PIB x 8 w</th><th>GLE/PIB x 12 w</th><th>GLE/PIB x 16 w</th></tr>
<tr><td>1</td><td>TN</td><td>NC</td><td>99%</td><td></td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td>99%</td><td></td><td></td></tr>
<tr><td></td><td>TN</td><td>C</td><td></td><td>97%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>C</td><td></td><td>96%</td><td></td></tr>
<tr><td></td><td>TE- NS3/4A PI (NS5A inhibitor naïve)</td><td>NC/C</td><td></td><td>92%</td><td></td></tr>
<tr><td></td><td>TE- NS5A inhibitor (NS3/4A PI naïve)</td><td>NC/C</td><td></td><td></td><td>94%</td></tr>
<tr><td>2</td><td>TN</td><td>NC</td><td>99%</td><td></td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td>91%</td><td></td><td></td></tr>
<tr><td></td><td>TN</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td>3</td><td>TN</td><td>NC</td><td>95%</td><td></td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td></td><td></td><td>96%</td></tr>
<tr><td></td><td>TN</td><td>C</td><td></td><td>99%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>C</td><td></td><td></td><td>94%</td></tr>
<tr><td>4</td><td>TN</td><td>NC</td><td>92%</td><td></td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td>100%</td><td></td><td></td></tr>
<tr><td></td><td>TN</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td>5</td><td>TN</td><td>NC</td><td>100%</td><td>100%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td></td><td>100%</td><td></td></tr>
<tr><td></td><td>TN/TE-PRS</td><td>C</td><td></td><td>100%</td><td></td></tr>
</table>
</td><td>Nine clinical trials provide substantial evidence of effectiveness of GLE/PIB for treatment of CHC GT1-6.

GLE/PIB fills an important unmet need for a therapy in GT2, 3, 5 and 6 infected patients with severe renal impairment.

GLE/PIB helps address a gap in the availability of regimens for the retreatment of DAA experienced patients.</td></tr>
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<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><td>6</td><td>TN</td><td>NC</td><td>100%</td><td>100%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>NC</td><td>100%</td><td>100%</td><td></td></tr>
<tr><td></td><td>TN</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td></td><td>TE-PRS</td><td>C</td><td></td><td>100%</td><td></td></tr>
<tr><td colspan="6">NC=non-cirrhotic; C=cirrhotic; PRS= treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, PI=protease inhibitor</td></tr>
</table>
</td><td></td></tr>
<tr><td>Risk</td><td>• The safety database for GLE/PIB includes 2,265 subjects without severe renal impairment and 104 subjects with renal impairment (evaluated separately for safety).
• ENDURANCE-2 included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo.
• No major safety issues were encountered during this review.
• Headache, fatigue, nausea and diarrhea were the most commonly (>=5%) reported adverse drug reactions reported across trials, excluding subjects with severe renal impairment enrolled in EXPEDITION-4. Pruritus, fatigue, nausea, asthenia and headache were the most commonly experienced adverse drug reactions in the population of subjects with severe renal impairment.</td><td>GLE/PIB demonstrated an overall favorable safety profile.</td></tr>
<tr><td>Risk Management</td><td>• Although no safety signals were detected in this review, the GLE/PIB prescribing information will contain safety information regarding the risk of HBV reactivation required for all HCV DAA labels.</td><td>Safety concerns associated with GLE and PIB are adequately addressed in product labelling.</td></tr>
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2. Background

Chronic hepatitis C virus (HCV) infection is a serious and life-threatening condition. In 2015, it was estimated that globally 71 million people were living with chronic hepatitis C, and another 1.75 million new HCV infections occurred worldwide. Among other long-term and life-threatening complications of infection, left untreated, HCV infection can lead to cirrhosis and hepatocellular carcinoma in approximately 20-30% of infected individuals. Cirrhosis and hepatocellular carcinoma account for 96% of global deaths due to viral hepatitis; and mortality from viral hepatitis has increased by 20% since 2000 (HBV and HCV combined). Additionally, cofactors including HCV/HIV co-infection or use of alcohol can accelerate the rate of disease progression towards end-stage liver disease or cirrhosis (Global Hepatitis Report 2017, World Health Organization).

The global increase in HCV infections and mortality are similar to trends observed in the United States. Despite the availability of direct acting antivirals (DAAs) and increasingly higher rates of cure, approximately 3.5 million people are estimated to be living with chronic HCV in the US. Between 2010 and 2015, reported cases of acute HCV infection increased more than 2.9-fold, rising annually throughout these five years. This rise is being attributed to the epidemic of injection-drug use, and to a much smaller extent, improved case detection. Mortality among HCV-infected individuals, primarily adults aged 55-64 years, has also increased from 2006-2010. In 2013, HCV associated deaths were higher than the combined number of deaths with 60 other infectious diseases as underlying causes (Surveillance for Viral Hepatitis - United States, 2015, Centers for Disease Control and Prevention).

In the United States the majority (70-75%) of chronic HCV infections are with HCV genotype (GT) 1, and predominately with subtype 1a. Approximately 20% of HCV infections are with HCV GT2 or 3, approximately 5% are with HCV GT4 and less than 1% with HCV GT5 or GT6. Genotype 7 has been identified but is currently only present in the Democratic Republic of Congo.

The treatment of HCV infection has rapidly evolved since the 2011 approvals of the first DAAs, boceprevir and telaprevir, NS3/4A protease inhibitors. These initial approvals were followed by the approvals of simeprevir, an NS3/4A protease inhibitor, and sofosbuvir, an NS5B nucleotide analog polymerase inhibitor, in 2013. At that time, boceprevir, telaprevir, sofosbuvir and simeprevir all required the use of interferon (IFN) and ribavirin (RBV) for treatment of HCV GT1. However since 2013, several other interferon-free DAA regimens were approved for treatment of GTs 1-6, many of which offer SVR12 rates in excess of 90% for most GTs and exceed 95% for certain populations and GTs. Recommended regimens for CHC treatment for all GTs no longer require the use of IFN; however, RBV is still recommended for certain GTs or subpopulations. Approved interferon-free regimens for specific GTs include:

- Sofosbuvir/ledipasvir (GT 1, 4, 5, 6)

- Sofosbuvir+daclatasvir (GT 1, 3)
- Sofosbuvir+simeprevir (GT 1)
- Sofosbuvir+ribavirin (GT 2, 3)
- Dasabuvir, ombitasvir, paritaprevir/ritonavir (GT1)
- Ombitasvir, paritaprevir/ritonavir (GT4)
- Elbasvir/grazoprevir (GT1, 4)
- Sofosbuvir/velpatasvir (GT 1, 2, 3, 4, 5, 6)

This New Drug Application (NDA) submitted by AbbVie Inc. contains information to support the approval of Mavyret, an interferon and ribavirin-free, complete regimen for the treatment of chronic HCV GTs 1, 2, 3, 4, 5 and 6. Mavyret is comprised of glecaprevir (GLE), an HCV NS3/4A protease inhibitor, and pibrentasvir (PIB), an HCV NS5A inhibitor, coformulated as a fixed dose combination (FDC) 100mg/40mg tablet and administered as three tablets once daily. If approved, GLE would represent the 7th HCV NS3/4A protease inhibitor and PIB would represent the 6th NS5A inhibitor to date.

The regulatory history of GLE/PIB was notable for fast track designation grated on January 24, 2013. Additionally, Breakthrough designation was granted on April 21, 2016 for treatment of chronic HCV infection in GT1 DAA-experienced patients, as this represents a population with no currently available treatment options.

This NDA received a priority review under PDUFA V and was not presented at the Antimicrobial Advisory Committee because GLE/PIB received breakthrough designation and because the benefit/risk assessment did not appear controversial based on the review team's preliminary assessment of top line trial results.

To date, the GLE/PIB FDC tablet has not been marketed outside the United States; however, a marketing application is currently under consideration by both the European Medicines Agency and Health Canada.

FDA's policy for the approval of fixed combination prescription drugs for humans is described in 21 CFR 300.50. The Federal Food, Drug and Cosmetics Act states, in part, "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug". The regulations are interpreted to require a factorial analysis of proposed combination ingredients to demonstrate the combination is more effective than each component of the combination alone. However, for HCV drugs it is not feasible or ethical to evaluate the efficacy of a FDC in a clinical trial with a factorial design in which the entire combination would be compared to its individual components. This type of trial design requires HCV-infected individuals to be exposed to suboptimal regimens that would quickly result in virologic failure and drug resistance, not only to the drug or drugs under study, but in many cases to other drugs from

the same class. For those patients exposed to a single HCV drug in a factorial design trial, the suboptimal therapy may also jeopardize the success of future therapeutic options, or risk disease progression. Combination therapy with more than one DAA, each inhibiting different targets of the viral replication cycle, prevents selection of resistance and increases the probability of achieving virologic cure.

Therefore, in this scenario for HCV, where components of the combination cannot be administered individually for more than a few days due to rapid development of resistance, other evidence to demonstrate the contribution of each agent to the combination is required. The evidence to show the contribution of each agent comes from short duration monotherapy and dose ranging clinical trials of the individual agents, and combination, respectively. Following three days of monotherapy in HCV GT1 infected subjects (trial M13-595), maximum decreases in mean HCV plasma RNA viral load from baseline were similar for GLE doses of 100 mg to 700 mg once daily (-3.8 to -4.3 $\log_{10}$ IU/mL), and for PIB doses of 40 mg to 400 mg once daily (approximately -4 log10 IU/mL). Additionally, Phase 2 trials evaluating the efficacy of GLE/PIB in combination in HCV GT1 and GT3 infected subjects demonstrated small increases in the rate of virologic breakthrough and/or relapse for combinations using lower doses of GLE 200mg relative to 300mg, and for PIB 40 mg relative to 120 mg. Overall, both the short duration monotherapy dose evaluation and the Phase 2 combination dose-ranging trials demonstrate the contribution of each drug to the combination of GLE/PIB for treatment of HCV and satisfy 21 CFR 300.50.

This cross-discipline team leader review/Division Director summary will present the major findings from the NDA review of the Mavyret fixed dose combination (FDC) tablet. For a more comprehensive assessment, please refer to the specific discipline reviews for the Mavyret NDA.

3. Product Quality

General Product Quality Considerations

GLE/PIB tablets for oral administration are immediate release bilayer tablets each containing GLE 100 mg in one layer and PIB 40 mg in the other layer. They are pink-colored, film-coated, oblong biconvex shaped and debossed with “NXT” on one side. The tablets are packaged in child-resistant blister cards of 3 tablets each in weekly, monthly and 8-week cartons.

According to the product quality reviewers, the data provided in the NDA are adequate to ensure that the composition, manufacturing processes, control strategies and specifications for the GLE/PIB FDC tablets are appropriate. The control strategy (b) (4) was determined to be acceptable for both GLE and PIB. Based on the primary stability data a 24-month self-life is acceptable when stored under the recommended conditions of at or below 30°C (86°F). No product quality microbiology issues were identified. The dissolution method was determined to be appropriate for both GLE and

PIB. The proposed product quality related labeling is considered adequate by the review team, with minor revisions.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) for glecaprevir and pibrentasvir in accordance with 21 CFR Part 25.31(b). The claims for categorical exclusion from an EA for both actives were found to be acceptable, once supported by additional information for pibrentasvir.

Facilities Review/Inspection

There are 15 facilities involved in the manufacturing, testing and packaging of GLE/PIB. The facility inspections were found to be acceptable.

Please see the Office of Product Quality review for details.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile of GLE and PIB has been evaluated in a complete nonclinical package consisting of *in vitro* studies and studies in mice, rats, rabbits, monkeys and dogs. The nonclinical package included over 140 studies to assess the safety pharmacology, pharmacokinetics/ADME, general toxicity, carcinogenicity, reproductive and developmental toxicology, genetic toxicology, special toxicology, and impurities. The following summarizes review findings by Dr. Ilona Bebenek who concluded that the submitted nonclinical data were sufficient to support approval of GLE/PIB. Please refer to the Pharmacology/Toxicology review by Dr. Bebenek for additional details.

General nonclinical pharmacology/toxicology considerations

Glecaprevir

No clinically relevant adverse effects were identified on cardiovascular, neurological, or respiratory endpoints for GLE in the safety pharmacology studies. Repeat dose toxicology studies in rats (up to 120 mg/kg/day) and dogs (up to 200 mg/kg/day) administered GLE orally for up to 26 and 39 weeks, respectively. GLE was not associated with clinically relevant adverse effects in pivotal studies. However, non-adverse findings of limited clinical relevance were noted in clinical chemistry, hematology, heart, peripheral nerve, gall bladder and testes in dogs and in liver and kidneys in rats.

Pibrentasvir

No clinically relevant adverse effects were identified on cardiovascular, neurological, or respiratory endpoints for PIB in the safety pharmacology studies. Repeat dose toxicology studies in mice (up to 100 mg/kg/day) and dogs (up to 100 mg/kg/day) administered GLE orally for up to 26 and 39 weeks, respectively. PIB was not associated with clinical relevant

adverse effects in pivotal studies. However, non-adverse findings of limited clinical relevance were noted with a decrease in spleen weight in mice in the 13-week study, and clinical signs of unformed, watery mucoid feces in dogs dosed with 10 or 100 mg/kg/day in the 13-week dog study and decreased absolute reticulocytes in dogs receiving 100 mg/kg/day in the 39 week study. All were recoverable, except for the clinical signs of fecal changes in dogs. Of note, mild to moderate diarrhea was reported as a common adverse event in clinical trials.

Genetic toxicology and carcinogenicity

GLE and PIB were not mutagenic or clastogenic as tested in the Ames assay, the in vitro chromosomal aberration assay in CHO cells and in vivo rat micronucleus assays. Carcinogenicity studies with GLE and PIB are not being conducted, given the intended treatment duration (<6 months) and lack of a specific cause for concern.

Reproductive toxicology

Glecaprevir
GLE was administered orally to pregnant rats (up to 120 mg/kg/day) and rabbits (up to 60 mg/kg/day) during the period of organogenesis. No adverse embryo-fetal effects were observed in rats at doses up to 120 mg/kg/day (50 times the exposure in humans at the recommended human dose (RHD)). However, in rabbits the highest GLE exposure achieved was 7% (0.07 times) of the exposure in humans at RHD. Therefore, data in rabbits during organogenesis are not available for GLE at systemic exposures at or above the exposures in humans at the RHD. Additionally, the peri/postnatal developmental study in rats showed no adverse effects with GLE doses up to 100 mg/kg/day.

There were no clinically relevant adverse effects on male or female fertility in rats.

Pibrentasvir

Pibrentasvir was administered orally to pregnant mice and rabbits (up to 100 mg/kg/day) during the period of organogenesis. No adverse embryo-fetal effects were observed at any studied dose level in either species. The systemic exposures at the highest doses were 51 times (mice) and 1.5 times (rabbits) the exposures in humans at the RHD.

In the peri/postnatal developmental study in mice, PIB was administered orally (up to 100 mg/kg/day) and no adverse effects were observed at maternal exposures approximately 74 times the exposures in humans at the RHD.

There were no clinically relevant adverse effects on male or female fertility in mice.

Combination toxicology

Because there were no concerning safety signals or overlapping toxicity with GLE and PIB, a combination study was not conducted. (b) (4) a four-week safety study at low doses of GLE and PIB was conducted in Sprague-Dawley rats. There were no adverse findings in this rat safety study. The AUC exposures for GLE were equivalent to or 2-fold higher than exposures at the recommended clinical dose in cirrhotic and non-cirrhotic patients, respectively.

5. Clinical Pharmacology

Approval is recommended from the clinical pharmacology and pharmacometrics review teams (Drs. Amal Ayyoub, Islam Younis, Simbarashe Zvada, and Jeffry Florian). This section provides a high level summary of some key clinical pharmacology findings for GLE/PIB. Please refer to the clinical pharmacology review for additional details.

Food Effect

When co-administered with PIB under fed conditions, the Tmax of GLE occurs 3 to 5 hours after dosing. GLE is a substrate of P-gp and BCRP transporters. When co-administered with GLE under fed conditions, the Tmax of PIB occurs approximately 5 hours after dosing. PIB is a substrate of P-gp and BCRP transporters. Mean GLE and PIB exposures increased by 163% and 40%, respectively, with moderate fat meals, and by 114% and 105%, respectively, with high fat meals. In all Phase 3 trials, subjects were instructed to take GLE/PIB with food without regard to fat or calorie count. Based on the available data, it is recommended that GLE/PIB should be taken with food, without regard to calorie count.

Critical intrinsic factors potentially affecting elimination: hepatic impairment, renal impairment, age, gender, race and age

Hepatic impairment

A dedicated hepatic impairment study demonstrated that, relative to healthy subjects, GLE AUC is 11-fold higher in subjects with Child-Pugh C cirrhosis. GLE AUC was also numerically higher (AUC ratio= 2.0) in subjects with Child-Pugh B cirrhosis. PIB AUC did not change in subjects with Child-Pugh B cirrhosis and was 2-fold higher in subjects with Child-Pugh C cirrhosis. Based on these data, the regimen is contraindicated in subjects with Child-Pugh C cirrhosis; however, the increases in AUC in those with Child-Pugh B were not considered clinically significant. It is important to note that the clinical trials supporting this NDA enrolled only subjects with compensated Child-Pugh A cirrhosis and therefore, there are no clinical data available for GLE/PIB in subjects with Child-Pugh B decompensated cirrhosis. Moreover, post-marketing cases of hepatic decompensation and hepatic failure have been reported for some regimens containing other HCV protease inhibitors (paritaprevir and

simeprevir) in patients with decompensated cirrhosis. Therefore, based on the available data for GLE/PIB and for HCV protease inhibitors, Child-Pugh B decompensated cirrhosis is not recommended and Child-Pugh C cirrhosis is contraindicated.

Renal impairment

In a dedicated renal impairment study, the highest AUC change was an increase by 45% and 46% of GLE and PIB, respectively. GLE and PIB are minimally eliminated via the renal route (<0.7% of dose); thus, no dosage adjustments are proposed in patients with mild, moderate, or severe renal impairment (b) (4) with or without hemodialysis. Both drugs are not removed by dialysis due to high protein binding. It should be noted that the applicant conducted a single-arm, open label trial (M15-462) to evaluate the efficacy and safety of GLE/PIB 300/120 mg in 104 HCV-infected subjects (GT 1-6) with eGFR < 30 mL/min/1.73 m2 including those on dialysis. SVR12 was achieved by 98% of the subjects, with no virologic failures, and the safety profile was comparable to that of the overall population.

Demographic factors: age, gender, race, BMI and cirrhosis status

Demographic factors such as age, gender, race, body mass index (BMI) and compensated (Child-Pugh A) cirrhosis status were evaluated to determine if these factors have an effect on the PK of GLE and PIB. No clinically relevant effect was identified for age, race, gender, or BMI. In subjects with compensated Child-Pugh A cirrhosis (n=280), the AUC was 2.19 fold higher compared to non-cirrhotic subjects (n=1804). However, the review team fully evaluated the distribution of the AUC and determined that AUC demonstrates significant overlap between the cirrhotic and non-cirrhotic subjects; therefore, clinical recommendations pertinent to drug-drug interactions should not be different for cirrhotic subjects.

Extrinsic Factors: Drug Interactions

Generally, the clinical pharmacology team agreed with the Applicant regarding labeling for drug-drug interactions; however, discussions centered on the co-administration of GLE/PIB with P-gp inducers. Due to a significant decrease in GLE and PIB exposures, GLE/PIB AUC decreased by 88%/87% and 67%/51% when co-administered with rifampin and carbamazepine, respectively, the review team believed that the co-administration of P-gp inducers should be contraindicated. However, the Applicant disagreed stating their rationale that despite the decreases in exposure, the SVR12 rate (approximately 89%) in HCV genotype 3 subjects who also had lower exposures, similar to those expected with these drug-drug interactions, were still acceptable. Despite lower exposures, the SVR12 rates remained acceptable in this more difficult to treat subgroup; therefore, the Applicant believed the co-administration of GLE/PIB and P-gp inducers, (b) (4) carbamazepine, efavirenz, and St. John's wort should be 'not recommended,' rather than 'contraindicated,' in product labeling. Additionally, they pointed out that HCV treatment options are limited for those who are taking carbamazepine and argued that GLE/PIB could

provide a possible treatment option for this population. Based on the assessment of all of the data, the review team agreed with the 'not recommended' recommendation. Labeling will include warning language stating the risk of reduced therapeutic effect due to concomitant use of GLE/PIB with carbamazepine, efavirenz and St. John's wort.

During the preNDA meeting, the applicant reported that GLE exposure was 2-fold higher in subjects with compensated cirrhosis compared to those without cirrhosis. This finding prompted the clinical pharmacology review team to evaluate if the clinical recommendations pertinent to drug-drug interactions should be different for cirrhotic and non-cirrhotic patients in cases where GLE is a victim or a perpetrator of drug-drug interactions. However, due to the high variability in GLE exposure, it was determined that there is significant overlap between the distribution of AUC in cirrhotic and non-cirrhotic subjects. Therefore, recommendations for drug-drug interactions should not be different for cirrhotic and non-cirrhotic subjects.

Thorough QT Trial

The effect of doses up to glecaprevir 600 mg (2 times the recommended dosage) with doses up to pibrentasvir 240 mg (2 times the recommended dosage) on QTc interval was evaluated in an active-controlled (moxifloxacin 400 mg) thorough QT study. The thorough QT study was reviewed by FDA's Interdisciplinary Review Team for QT Studies. At 20-fold of GLE and 5-fold of PIB therapeutic concentrations, the GLE/PIB combination was found not to prolong the QTc interval to any clinically relevant extent.

Pharmacogenomic data

The *in vitro* and clinical drug interaction data indicate that GLE is transported by SLCO1B1. Theoretically, subjects with reduced function alleles may have lower levels of GLE exposure in the liver if the SLCO1B1 genotype was expressed. The NDA included data from 12 pooled clinical trials, showing no association between SLCO1B1 genotype (intermediate and normal function) and GLE exposure. PIB exposure is not affected. The function of OATP1B1/3 plays a significant role in the disposition of GLE, but not PIB.

Formulation

The pivotal clinical trials were performed with the to-be-marketed fixed-dose film coated bilayer tablet formulation; therefore, bridging information between formulations is not required.

6. Clinical Microbiology

Please refer to the virology review by Dr. Patrick Harrington for a detailed assessment of the non-clinical and clinical virology data. The following provides a brief summary of antiviral

activity and clinical resistance data to support the discussion of the clinical virology data provided in Section 7, Clinical/Statistical Efficacy.

Antiviral activity

In HCV replicon assays, GLE had median EC_{50} values of 0.08-4.6 nM against laboratory and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4d, 5a, and 6a. PIB had median EC_{50} values of 0.5-4.3 pM against laboratory and clinical isolates from subtypes 1a, 1b, 2a, 2b, 3a, 4a, 4b, 4d, 5a, 6a, 6e and 6p.

Clinical resistance data

Treatment-naïve and Treatment-Experienced PRS

A treatment-emergent resistance analysis was conducted in subjects who were treatment naïve or treatment experienced PRS, but naïve to NS5A inhibitors or NS3/4A protease inhibitors. Twenty-two subjects (2 GT-1, 2 GT-2, 18 GT-3) who experienced virologic failure after receiving GLE/PIB for 8, 12 or 16 weeks were included in this analysis. No subjects with HCV genotype 4, 5 or 6 experienced virologic failure.

Both genotype 1 subjects who experienced virologic failure had genotype 1a and developed treatment emergent substitutions in NS5A known to be associated with resistance. Both genotype 2 subjects who experienced virologic failure had subtype 2a, and no treatment-emergent substitutions were observed in NS3 or NS5A.

Among the 18 genotype 3 subjects who experienced virologic failure, treatment-emergent NS3 substitutions Y56H/N, Q80K/R, A156G, or Q168L/R were observed in 11 subjects. Five subjects had A166S or Q168R present at baseline and post-treatment. Treatment-emergent NS5A substitutions M28G, A30G/K, L31F, P58T, or Y93H were observed in 16 subjects, of which 13 subjects had A30K (n=9) or Y93H (n=5) at baseline and post-treatment.

Baseline HCV polymorphisms in genotypes 1, 2, 4, 5 and 6 had no impact on treatment outcome. Among treatment-naïve genotype 3 infected subjects without cirrhosis who received 8 weeks of GLE/PIB, all 16 subjects with Y93H in NS5A at baseline achieved SVR12. The NS5A A30K polymorphism was detected in 10% (18/181) of treatment-naïve, genotype 3 non-cirrhotic subjects, of whom 78% (14/18) achieved SVR12. There were too few subjects with cirrhosis or prior-treatment experience to characterize the impact of A30K for these subgroups.

Subjects with treatment-experience to NS3/4A protease inhibitors or NS5A inhibitors (MAGELLAN-1)

Treatment-emergent resistance analyses were conducted for 11 HCV genotype 1 subjects (10 genotype 1a, 1 genotype 1b) who were prior NS3/4A protease inhibitor or NS5A inhibitor treatment experienced, and who experienced virologic failure after treatment with GLE/PIB with or without ribavirin, in MAGELLAN-1. Treatment-emergent NS3 substitutions V36A/M, Y56H, R155K/T, A156G/T/V, or D168A/T were observed in 73% (8/11) of subjects. Nine of 10

subjects (90%, not including one subject missing NS5A data at failure) had treatment-emergent NS5A substitutions M28A/G (or L28M for genotype 1b), P29Q/R, Q30K/R, H58D or Y93H/N. All 11 subjects also had NS5A inhibitor resistance-associated substitutions (RAS) detected at baseline, and 7/11 had NS3 protease inhibitor RAS detected at baseline.

Among NS5A inhibitor-experienced/protease inhibitor-naïve subjects who received GLE/PIB for 16 weeks, baseline NS5A RAS, were detected in 73% (11/15) of subjects with available data, of whom 91% (10/11) achieved SVR12. The non-SVR12 subject experienced on-treatment virologic failure and had a genotype 1a infection with baseline NS5A Q30R and L31M substitutions.

The next generation sequencing data (NGS) provided by the Applicant was reviewed by Dr. Eric Donaldson. The goal of the independent assessment of NGS data was to confirm the results reported by the Applicant, to determine which known RASs were present in the virus of subjects who failed treatment, and to determine if additional substitutions occurring in two or more subjects could be associated with treatment failure. Based on the NGS analysis by Dr. Donaldson, the results were in agreement with those of the Applicant, with a few minor exceptions; and, no additional substitutions could be determined to be associated with resistance for the subjects analyzed.

7. Clinical/Statistical- Efficacy

This section focuses on the efficacy analyses conducted by the review team for the key trials supporting this NDA. This section will generally focus on the overall efficacy results by genotype, prior treatment history, and cirrhosis status; where pertinent, a discussion of the clinical virology will also be included. For a detailed discussion of the individual trials, results and statistical analyses please see the statistical review by Drs. LaRee Tracy and Therri Usher. For the details regarding the impacts of the clinical virology findings, including baseline polymorphisms and treatment emergent resistance associated substitutions, please refer to the virology review by Dr. Patrick Harrington. In addition, please refer to the clinical review by Drs. Lara Stabinski and Aimee Hodowanec for a more detailed discussion of the efficacy findings.

Overall, the FDA reviewers' independent analyses confirmed the Applicant's primary and secondary efficacy findings for the pivotal trials. However, the review team's assessment differed from the Applicant's assessment, because we did not agree with inclusion of an indication for treatment of subjects who previously have been treated with a regimen containing both an NS5A inhibitor **and** an NS3/4A protease inhibitor (PI). Additionally, given that all but 4 subjects enrolled in MAGELLAN-1 (NS5A and/or NS3/4A PI experienced population) were infected with HCV genotype 1, the review team believed the data limited the indication in this population to HCV genotype 1.

Another major efficacy review issue was whether the data supported an 8-week treatment duration for treatment-naïve patients without cirrhosis across all HCV genotypes 1-6, in particular, whether the data were adequate to support the 8 week duration for HCV

genotypes 3, 5 and 6. The following section will provide further discussion of these issues and the data and rationale supporting the review team's decisions.

Supportive evidence for this NDA comes from nine Phase 2 and 3 trials, with summary details provided in Table 1 and Table 2 below. Among these trials, four were considered Phase 3 in design; two were comparative: ENDURANCE-2 which included a placebo-control delayed treatment, and ENDURANCE-3 which included a sofosbuvir/daclatasvir active-control. The other two Phase 3 trials were ENDURANCE-1, a large trial comparing 8 and 12 week durations of GLE/PIB, and EXPEDITION-4, a trial evaluating 12 weeks of GLE/PIB in subjects with chronic kidney disease stages 4 or 5, including those on hemodialysis. The remaining five trials were designed as Phase 2 trials, three of which were dose-finding trials. These trials were included in this application and were considered part of the pivotal analyses due to their inclusion of subjects with less common genotypes (GT) such as GT4, GT5 and GT6, and they included subjects in various important subgroups such as treatment-experienced GT3 subjects and subjects with cirrhosis. MAGELLAN-1, a Phase 2 trial, is the only trial that enrolled subjects who were NS5A inhibitor and/or NS3/4A PI experienced.

Table 1: Summary of Phase 3 Clinical Trials

Trial ID (NAME)	Design	Population	HCV Treatment History	Treatment	Endpoint/Analysis
M13-590 (ENDURANCE-1)	R (1:1), OL, PG, MC	GT1, NC, w/w/o HIV	TN or TE-PRS	GLE/PIB 12w (n=352) GLE/PIB 8w (n=351)	1 : SVR12 (vs. HC of 91%) ITT-PS 8W vs. 12W SVR12 (5% NI) in ITT-PS & ITT-PS-PP (fixed sequence testing)
M15-464 (ENDURANCE-2)	R (2:1), DB, PC (delayed trt), MC	GT2, NC	TN or TE-PRS	GLE/PIB 12w (n=202) PC 12w followed by GLE/PIB OL 12w (n=100)	1 : SVR12 (vs. ref rate of 95%, 6% NI margin) ITT (excl. prior PRS failures) 2 : SVR12 versus 95% ref rate (superiority)
M13-594 (ENDURANCE-3)	R (2:1), R, MC, AC, OL, NI (6% Margin), PG, open enrollment to third group	GT3, NC	TN	GLE/PIB 12w (n=233) SOF/DCV 12w (n=115) GLE/PIB 8 w (n=157) NR	1 : SVR12 (12W vs. AC, 6% NI margin) ITT Key 2 : SVR12 (12W and 8W vs. 92% HC) SVR12 (8W vs. 12W, 6% NI)
M15-462 (EXPEDITION-4)	Single-arm, NR, OL, MC	GT1-6 w/ CKD stages 4, 5 or dialysis, NC or C	TN or TE-PRS	GLE/PIB 12w (n=104)	1 : SVR12 in ITT-PS 2 : On-tx VF, post-tx relapse, both in ITT-PS

R: randomized, MC: multi-center, MP: multi-part, NR: non-randomized, NI: non-inferiority, PC: placebo-control, OL: open-label, DB: double-blind, PG: parallel-group, AC: active controlled, TN: treatment-naïve, TE-PRS: treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, GLE: glecaprevir, PIB: pibrentasvir, SOF: sofosbuvir, DCV: daclatasvir, NC: non-cirrhotic, C: cirrhotic, HC: historical control, 2^o: secondary endpoint, 1^o: primary endpoint, VF: virologic failure, CKD: chronic kidney disease, ITT-PS: intent-to-treat subset of HCV monoinfected DAA-naïve subjects, ESRD=End-Stage Renal Disease
Source: table created by Drs. Usher and Tracy

Table 2: Summary of Phase 2 Clinical Trials

Trial ID (NAME)	Design	Population	HCV Treatment History	Treatment (proposed GLE/PIB regimen only)	Endpoint/Analysis
M14-867 (SURVEYOR-1)	NR, OL, MC, MP	Part 1 GT1, NC Part 2 GT1, 4-6, NC or C	TN or TE-PRS	*Part 2* Arm K (GT1 C): GLE/PIB 8W (n=34) Arm I: (GT4-6 NC): GLE/PIB 12W (n=34)	1 : SVR12 in ITT-PS 2 : SVR4, on-tx VF, post-tx relapse, both in ITT-PS
M14-868 (SURVEYOR-2)	R, OL, MC, MP	Part 1 GT2, NC or C Part 2 GT2-GT3, NC or C Part 3 GT3, NC or C Part 4 GT2, GT4-GT6, NC	TN or TE-PRS	*Part 1* Arm A (GT2 NC): GLE/PIB 12W (n=25) Arm D (GT3 NC): GLE/PIB 12W (n=30) *Part 2* Arm J (GT2 NC): GLE/PIB 8W (n=55) Arm L (GT3 NC): GLE/PIB 8w (TN) or 12w (TE) (n=53) Arm O (GT3 C): GLE/PIB 12w (n=28) *Part 3* Arm Q (GT3 TN C, TE NC): GLE/PIB 12w (n=62) Arm R (GT3 TE C, TE NC): GLE/PIB 16w (n=70) *Part 4* Arm S (GT2, 4-6 NC): GLE/PIB 8w (n=203)	1 : SVR12 in ITT-PS 2 : SVR4, on-tx VF, post-tx relapse, both in ITT-PS
M14-172 (EXPEDITION-1)	Single-arm, NR, MC	GT1, GT2, GT4-GT6, C	TN or TE-PRS	GLE/PIB 12w (n=146)	1 : SVR12 (no formal hypothesis)
M15-410 (MAGELLAN-1)	R, OL, MC, MP	GT1, GT4-6 (Part 2), NC or C	NS5A- and/or NS3/4A PI-experienced	*Part 1* Arm C (GT1 NC): GLE/PIB 12w (n=22) *Part 2* Arm D: GLE/PIB 12w (n=44) Arm E: GLE/PIB 16w (n=47)	1 : SVR12 in ITT-PS 2 : SVR4, on-tx VF, post-tx relapse, both in ITT-PS
M13-583 (ENDURANCE-4)	Single-arm, NR, OL, MC	GT4-6, NC	TN or TE-PRS	GLE/PIB 12w (n=121)	1 : SVR12 in ITT-PS 2 : On-tx VF, post-tx relapse, both in ITT-PS

R: randomized, MC: multi-center, MP: multi-part, NR: non-randomized, NI: non-inferiority, PC: placebo-control, OL: open-label, DB: double-blind, PG: parallel-group, AC: active controlled, TN: treatment-naïve, TE-PRS: treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, GLE: glecaprevir, PIB: pibrentasvir, SOF: sofosbuvir, DCV: daclatasvir, NC: non-cirrhotic, C: cirrhotic, HC: historical control, 2^o: secondary endpoint, 1^o: primary endpoint, VF: virologic failure, CKD: chronic kidney disease, ITT-PS: intent-to-treat subset of HCV monoinfected DAA-naïve subjects, ESRD=End-Stage Renal Disease
Table created by Drs. Usher and Tracy

The primary endpoint for all the clinical trials was sustained virologic response or SVR (defined as the proportion of subjects achieving a HCV RNA below the lower limit of quantification) measured 12 weeks following the end of treatment, referred to as SVR12. SVR12 represents the Agency's preferred primary endpoint for HCV clinical trials. The specific planned endpoints and analysis are provided in Tables 1 and 2 above. For the Phase 3 trials, the SVR12 rates were, in general, compared to a pre-specified historical rate determined according to the standard-of-care for the HCV genotype and/or subpopulation being evaluated and/or compared with a non-inferiority margin to another duration or comparator arm for ENDURANCE-1, -2 and -3. There are limitations to historically controlled trials, but for HCV trials they are informative because the endpoint is an objective laboratory assessment (SVR) and it is known that untreated patients do not spontaneously achieve SVR. For the specific details regarding these analyses, please see both the statistical and clinical reviews. Where pertinent, discussions of any statistical considerations are provided below in the *Integrated Assessment of Efficacy by Genotype* subsection. Regardless, the SVR12 rates were high across all genotypes and subpopulations, ranging from 91-100% across the treatment durations as recommended by the FDA review team (Table 3).

Table 3: Summary of SVR12 data from Pooled Phase 2 and 3 Efficacy Data by the Recommended Treatment Duration

			% SVR12 (n/N) 95% CI*		
GT	**Treatment History**	**Cirrhosis Status**	**GLE/PIB 8W**	**GLE/PIB 12W**	**GLE/PIB 16W**
1	**TN**	**NC**	**98.8 (245/248) 96.5, 99.6**		
	TE-PRS	**NC**	**99.3 (137/138) 96.0, 100.0**		
	TN	**C**		**97.4(75/77) 91, 99.3**	
	TE-PRS	**C**		**95.8 (23/24) 79.8, 99.3**	
	TE- NS3/4A PI (NS5A inhibitor naïve)	**NC/C**		**92.0 (23/25) 75.0, 97.8**	
	TE- NS5A inhibitor (NS3/4A PI naïve)	**NC/C**			**94.1 (16/17) 73.0, 99.0**
2	**TN**	**NC**	**98.8 (172/174) 95.9, 99.7**		
	TE-PRS	**NC**	**91.3 (21/23) 73.2, 97.6**		
	TN	**C**		**100(28/28) 87.9, 100**	
	TE-PRS	**C**		**100 (7/7) 64.6, 100**	
3	**TN**	**NC**	**95.2(177/186) 91.1, 97.4**		
	TE-PRS	**NC**			**95.5 (21/22) 78.2, 99.2**
	TN	**C**		**98.5(64/65)**	

			% SVR12 (n/N) 95% CI*		
GT	**Treatment History**	**Cirrhosis Status**	**GLE/PIB 8W**	**GLE/PIB 12W**	**GLE/PIB 16W**
				91.8, 99.7	
	TE-PRS	C			94.1 (48/51) 84.1, 98.0
4	TN	NC	92.3(36/39) 79.7, 97.3		
	TE-PRS	NC	100 (7/7) 64.6, 100		
	TN	C		100 (16/16) 80.6, 100	
	TE-PRS	C		100 (4/4)	
5	TN	NC	100 (2/2)	100(22/22) 85.1, 100	
	TE	NC		100 (6/6) 61.0, 100	
	TN/TE[†]	C		100(2/2)	
6	TN	NC	100 (8/8)[‡]	100(28/28) 87.9, 100	
	TE	NC	100 (2/2)	100 (3/3)	
	TN	C		100 (6/6) 61, 100	
	TE	C		100 (1/1)	

[†]Data was extrapolated in this subpopulation as there were no treatment experienced cirrhotics in the application.
[‡]One subject did not have virologic data in the window at time of submission, however, subsequently was found to have achieved SVR12, and is counted as a success in this table.
NC=non-cirrhotic; C=cirrhotic; PRS= treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, PI=protease inhibitor; NS=not studied
* Confidence intervals were calculated using the Wilson score method, no CI calculated for group sizes less than 5
Source: Modified Table from Dr. Larissa Stabinski

Integrated Assessment of Key Efficacy by Genotype

This section will describe the data supporting the efficacy decisions for each genotype, and provide the data supporting the important subgroups by prior treatment history (treatment-naïve or treatment-experienced PRS) and compensated cirrhosis status. Where appropriate, discussions of the labeling are integrated into the discussion of the efficacy findings and review issues. Throughout this review, treatment-experienced PRS is defined as prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

The data from MAGELLAN-1 and EXPEDITION-4 will be discussed separately as they both represent specific subpopulations of prior NS5A inhibitor and/or NS3/4A PI experience and renal impairment, respectively.

Subgroup analyses were completed and detailed in the statistical review. There were no significant trends observed across various subgroups including sex, age, baseline HCV RNA, IL28 genotype, or geographic region; however, due to high SVR12 rates and small numbers in GT4-6, overall subgroup analyses for these GTs were not informative. Please see the statistical review for details regarding subgroup analyses. Baseline cirrhosis status and prior treatment history are important subgroups for HCV clinical trials and are detailed below.

Genotype 1

In total, 889 genotype 1 subjects with and without cirrhosis, treatment-naïve and treatment-experienced with interferon, pegylated interferon, ribavirin and/or sofosbuvir (PRS) were treated with 8 or 12 weeks of GLE/PIB in the Phase 2 and 3 clinical trials. Of these 889 subjects, 101 (11.4%) subjects had compensated cirrhosis and 561 (63.1%) subjects were treatment naïve. Only 2 subjects experienced virologic failure; one treatment-naïve subject who received 8 weeks duration had on-treatment virologic failure and one subject with cirrhosis experienced relapse after 12 weeks of treatment.

The data supporting the 8 week treatment duration for treatment-naïve and treatment-experienced-PRS patients comes primarily from ENDURANCE-1, a randomized, open-label trial comparing the efficacy of 8 and 12 weeks of treatment in HCV GT1 subjects without cirrhosis and with or without HIV-1 co-infection (n=33 co-infected). The SVR12 results for the 8 week and 12 week GLE/PIB treatment durations were 99.1% (348/351) [95%CI (97.5, 99.7)] and 99.7% (351/352)[95% CI (98.4, 100)], respectively. In the 8 week arm, one subject experienced on-treatment failure, two subjects were missing the SVR12 assessment and one subject prematurely discontinued treatment on study Day 2. In the 12 week arm, one subject was missing the SVR12 assessment.

The data supporting the efficacy of GLE/PIB for 12 weeks in HCV GT1 subjects with cirrhosis who are treatment-naïve or treatment-experienced PRS comes primarily from EXPEDITION-1, a Phase 2, open-label, single arm trial. The SVR12 rate was 99% (89/90), with one subject experiencing virologic relapse.

The single on-treatment virologic failure amongst the total cohort of treatment-naïve, non-cirrhotic subjects indicates that a longer treatment duration would not have influenced treatment outcome in this single subject. Therefore, GLE/PIB for 8 weeks is well supported for noncirrhotic, HCV GT1 infected patients. Among cirrhotic HCV GT1 infected subjects treated with GLE/PIB for 12 weeks, 1/90 (1%) experienced virologic failure (relapse). Both virologic failure subjects had ≥2 treatment-emergent/enriched NS5A resistance-associated substitutions (RASs) detected at the time of virologic failure, and one subject had a

treatment-emergent NS3 A156V substitution. Please see the virology review for more details.

Based on the data from the Phase 2 and 3 trials, the HCV GT1 treatment indication is well supported for treatment-naïve or treatment experienced patients with GLE/PIB for 8 weeks in those without cirrhosis and 12 weeks in those with cirrhosis.

Genotype 2

In total, 466 subjects with HCV genotype 2 who were treatment naïve or treatment-experienced PRS were treated with 8 or 12 weeks of GLE/PIB in the Phase 2 and 3 trials. Of these, 35 (8%) subjects had compensated cirrhosis and 369 (79%) were treatment-naïve. In total, two subjects, both treatment-experienced PRS and without cirrhosis, received GLE/PIB for 8 weeks duration and experienced virologic relapse; one of these subjects had a history of a gastric bypass and had low GLE exposures. Four additional subjects did not achieve SVR12 due to non-virologic reasons, including early discontinuation (n=3) and missing the SVR12 assessment (n=1).

The data supporting the 8 week treatment duration for treatment-naïve and treatment-experienced-PRS HCV GT2 patients is from SURVEYOR-2, a Phase 2, single-arm, open-label trial. The SVR12 rate was 98% (193/197), with two subjects experiencing virologic relapse (as described above) and two subjects having non-virologic reasons for failure. The data supporting the 12 week treatment duration in treatment-naïve and treatment-experienced PRS HCV GT2 patients with cirrhosis comes from EXPEDITION-1, a Phase 2, single-arm, open-label trial. In total, 31 HCV GT2 subjects with cirrhosis were treated for 12 weeks and all achieved SVR12 (SVR12 100%; 31/31).

Both virologic failure subjects had a subtype 2a infection with an NS5A M31 sequence, which is the consensus sequence for this subtype. Neither subject had treatment-emergent or treatment-enriched substitutions at known resistance-associated positions at the time of failure.

The data from the Phase 2 and 3 trials supports a treatment indication for HCV GT2 treatment-naïve or treatment experienced patients with GLE/PIB for 8 weeks in those without cirrhosis and 12 weeks in those with cirrhosis.

Genotype 3

Hepatitis C genotype 3 has been established as the most difficult HCV genotype to treat. One of the major review issues was whether there were adequate data to support the 8 week treatment duration of GLE/PIB in treatment-naïve, non-cirrhotic HCV GT3 subjects, rather than the 12-week duration. The Applicant had proposed a more conservative 16 week duration for HCV GT3 subjects with prior-treatment experience with PRS regardless of cirrhosis status, which was supported by adequate data and is also discussed in this section.

ENDURANCE-3 and SURVEYOR-2 provided the basis of the efficacy data to support the HCV GT3 labeling indications.

Treatment-naïve, non-cirrhotic genotype 3

ENDURANCE-3 was a partially-randomized, open-label, active-controlled trial in treatment-naïve subjects without cirrhosis. This trial included three treatment arms, GLE/PIB for 12 weeks (arm A), sofosbuvir/daclatasvir (SOF/DCV) for 12 weeks (arm B) and GLE/PIB for 8 weeks (arm C). Randomization was conducted in a 2:1 ratio for arm A: arm B. Once enrollment to arms A and B were completed, subjects were assigned to arm C in a non-randomized manner. Arm C (8-week duration) was added to the trial following input from the Division based on emerging Phase 2 data, and after the trial was initiated. The SVR12 data are summarized in Table 4 below.

Table 4. ENDURANCE-3: SVR12 and Outcomes in Treatment-Naive, HCV GT3 Subjects Without Cirrhosis

	GLE/PIB 8 Weeks (N=157)	**GLE/PIB 12 Weeks* (N=233)**	**DCV+SOF 12 Weeks (N=115)**
SVR12	94.9% (149/157)	95.3% (222/233)*	96.5% (111/115)
Outcome for Subjects Without SVR12			
On-treatment VF	1% (1/157)	<1% (1/233)	0/115
Relapse	3% (5/150)	1% (3/222)	1% (1/114)
Other[2]	1% (2/157)	3% (7/233)	3% (3/115)

VF=virologic failure
[1]GLE/PIB 8 weeks was a non-randomized treatment arm.
[2] Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
* Data for GLE/PIB 12-week treatment is displayed to reflect the original randomized study design. The treatment difference (95% confidence interval) was -1.2% (-5.6, 3.1) between the randomized arms of GLE/PIB 12 weeks and DCV + SOF 12 weeks.

Source: Modified from proposed product labeling

There were several review issues surrounding ENDURANCE-3, including its partially randomized design, as described above, and the statistical efficacy analyses. Generally, the statistical review team agreed with the primary comparison of the GLE/PIB 12 week regimen to DCV/SOF, and their results were similar to the Applicant's results, finding the SVR12 rates to be 95.3% and 96.5%, respectively with a treatment difference of -1.2% [95%CI (-5.4, 4.2)]. The lower bound of -5.4 fell within the pre-specified 6% margin and therefore the 12-week regimen was considered non-inferior to the comparator.

The Applicant's approach to evaluating the efficacy of the GLE/PIB 8-week regimen compared the 8-week regimen to the investigational GLE/PIB 12-week regimen, instead of the DCV/SOF regimen. The FDA statistical review team disagreed with this approach because the GLE/PIB 12-week regimen had yet to be proven effective at trial onset and the 8-week treatment arm was not randomized. Therefore, the FDA statistical review team's assessment of the 8-week efficacy was based on a comparison to a historical SVR12 threshold of 92% (determined by applying a 6% margin to the expected SVR12 of 98% for the active control), as a superiority assessment. Based on the Wilson method to calculate CI, the statistical reviewer focused on the lower bound around the SVR12 which was 90.3% for the 8 week treatment duration. This was slightly lower than the historical threshold of 92% and did not meet superiority to this historical control. Additionally, the statistical review team's analysis of the difference in the SVR12 rates (8W-DCV/SOF) was -1.6% with a 97.5%CI (adjusted for multiple testing) of -7.7% to 5.1%. In total, these data suggest that the 8 week treatment duration provides a clinically acceptable range of SVR12 from 90-97%, which is, at most, 8% worse than the DCV/SOF comparator. However, the non-randomized 8 week arm did not demonstrate superiority over the 92% historical threshold.

From a clinical perspective, the SVR rates in ENDURANCE-3 were comparable at 95%, and there were only two additional subjects who experienced virologic relapse in the 8-week duration compared to the 12 week duration. And although the 8 week duration did not demonstrate superiority to the historic control, any chosen historic thresholds are arbitrary and overall there was acceptable precision around the point estimates with similar SVR rates for the 8 and 12 week durations. Both the 8 week and 12 week arm had one subject each who experienced on-treatment virologic failure.

Additional Phase 2 data from SURVEYOR-2 (Arm L) are available from 29 HCV GT3 subjects who were treatment-naïve and noncirrhotic and received 8 weeks of GLE/PIB. The SVR12 rate was 97% (28/29) [95%CI; (82.8, 99.4)] with no virologic failures; the one subject who did not achieve SVR12 was categorized as 'other' (discontinued early due to adverse event, lost-to-follow up or subject withdrawal).

When evaluating all the available GT3 treatment-naïve, non-cirrhotic data pooled and censored for those with non-virologic reasons for failure, the SVR rates were 97% (177/183) and 99% (258/261) for those who received GLE/PIB for 8 and 12 weeks, respectively. The virologic relapse rate was 1.9% higher (2.7% vs. 0.8%) with the 8 week versus 12 week duration, again, a two subject difference between the 8 and 12 week durations.

Additional analyses conducted by statistical and virology reviewers did not identify a specific subgroup that clearly benefited from a 12 week compared to an 8 week treatment duration. The virology assessment determined the baseline NS5A A30K polymorphism may play a role in virologic relapse for GT3a subjects. Relapse rates for GT3a subjects with the A30K polymorphism were 17.6% (3/17) and 0% (0/13) for subjects who received the 8-week and 12-week durations, respectively. But these data were insufficient to fully assess the impact of this polymorphism.

During the review the Applicant reported SVR12 results from an additional 21 HCV GT3 infected subjects with HIV-1 co-infection who received GLE/PIB for 8 weeks in an ongoing trial (EXPEDITION-2), and all 21 subjects achieved SVR12. The Applicant also reported that 5 HCV GT3 infected subjects who failed treatment with GLE/PIB in Phase 2 trials were successfully re-treated with SOF-based regimens outside of GLE/PIB clinical trials.

After numerous internal discussions, the review team concluded that the totality of the data supports GLE/PIB for 8 weeks for treatment-naïve, noncirrhotic HCV GT3 infected patients, based on the high SVR rate (with acceptable precision around the point estimate) and the low relapse rate observed in the clinical trials, with a reasonable sample size (total of n=186 from Phase 2 and 3 data for GLE/PIB 8 weeks).

Treatment-naïve or treatment-experienced PRS GT3 subjects with or without compensated cirrhosis

SURVEYOR-2 Part 3, was a Phase 2, open-label trial that randomized treatment-experienced PRS subjects with HCV GT3 without cirrhosis to 12 or 16 weeks of GLE/PIB treatment. In addition, the trial evaluated the efficacy of GLE/PIB in GT3 infected subjects with compensated cirrhosis in two dedicated treatment arms using 12 week (treatment-naïve) and 16 week (treatment-experienced PRS) durations. Among PRS treatment-experienced subjects treated with GLE/PIB for 16 weeks, 49% (34/69) had prior treatment experience with a sofosbuvir-containing regimen.

Results of HCV GT3 Treatment-Naïve Subjects With Cirrhosis – 12 weeks

- The SVR12 rate in SURVEYOR-2 Part 3 was 98% (39/40) for HCV GT3 treatment-naïve subjects with compensated cirrhosis who received GLE/PIB for 12 weeks duration. No subjects experienced virologic failure and one subject had non-virologic failure.
- In the pooled Phase 2 and 3 efficacy data there were, in total, 64 subjects (censored for non-virologic failure) who were treatment-naïve HCV GT3 infected and received 12 weeks duration; among these 64 subjects, none experienced virologic failure.

Results of HCV GT3 Treatment-Experienced PRS Without Cirrhosis – 12 or 16 weeks

- SURVEYOR-2 Part 3 arm Q evaluated HCV GT3 subjects who were treatment-experienced PRS without cirrhosis and treated with GLE/PIB for 12 weeks. The SVR rate was 91% (20/22) [95%CI; (72.2, 97.5)]; two subjects (9%) experienced virologic relapse.
- SURVEYOR-2 Part 3 arm R evaluated HCV GT3 subjects who were treatment-experienced PRS without cirrhosis and treated for 16 weeks duration. The SVR rate was 96% (21/22) [95%CI; (78.2, 99.2)]; one subject (5%) had virologic relapse.
- Lastly, SURVEYOR-2 Part 3 arm Q also evaluated HCV GT3 subjects who were treatment-experienced PRS with compensated cirrhosis and treated for 16 weeks duration. The SVR rate was 94% (45/48) [95% CI; (83.3, 97.9)] with one subject (2%)

experiencing on-treatment virologic failure, one subject (2%) experiencing relapse, and one subject (2%) having non-virologic failure (other).

Overall, for treatment-experienced PRS GT3 subjects, with or without cirrhosis, SVR rates were high, ranging from 91-96%, for GLE/PIB for 12 to 16 weeks duration; however, the relapse rate was 2-5% for the 16 duration treatment compared to 9% for the 12 week duration. Therefore, the review team agreed with the Applicant that a conservative 16-week duration be recommended for treatment-experienced PRS HCV GT3 infected patients, regardless of cirrhosis status, to reduce the risk of relapse.

Based on the analysis of the available resistance data, there was no clear association between the detection of NS3 resistance-associated polymorphisms and treatment outcome for subjects treated with GLE/PIB. However, it was found that baseline and treatment-emergent resistance data indicate that certain NS5A resistance-associated polymorphisms, particularly A30K, may influence GLE/PIB efficacy for GT3 (also discussed above for treatment-naïve, noncirrhotic GT3). The A30K or Y93H polymorphisms appeared to be more commonly present at baseline among treatment-experienced, HCV GT3 infected subjects who subsequently experienced virologic failure with GLE/PIB for 12 or 16 weeks, although the data were insufficient to make definitive conclusions about the impact of these polymorphisms. Most GT3 infected subjects who experienced virologic failure with a GLE/PIB regimen had treatment-emergent RASs in NS3 and NS5A. A variety of different NS3 amino acid substitutions emerged but for NS5A, Y93H was the predominant treatment-emergent resistance pathway, occurring in 15/18 (83%) subjects. However, there was no obvious trend indicating that treatment duration (8-16 weeks) affected the likelihood of detecting NS3 and NS5A RASs at the time of virologic failure. Therefore, it is likely that any HCV GT3 subject who has virologic failure after any duration > 8 weeks of GLE/PIB will develop treatment-emergent NS3 and NS5A RASs.

HCV GT3 is considered a difficult to treat genotype and has been associated with a higher risk of steatosis leading to accelerated fibrosis and a higher risk of hepatocellular carcinoma (HCC) (Tapper 2013). The available data from the clinical trials, as discussed in detail above, supports the proposed 8, 12 and 16 week durations in the subpopulations of HCV GT3 of treatment-naïve, noncirrhotic, treatment-naïve cirrhotic, and treatment-experienced PRS regardless of cirrhosis status, respectively.

Genotype 4

Overall in the Phase 2 and 3 trials, 178 HCV GT4 subjects were treated with GLE/PIB for 8 or 12 weeks duration. Of these, 20 (11%) were subjects with compensated cirrhosis and 122 (69%) were treatment-naïve; the remaining subjects were treatment-experienced PRS. No subjects experienced virologic failure; however, four subjects had non-virologic reasons categorized as 'other' (missing SVR12 assessment and early discontinuation).

The data supporting labeling for HCV GT4 treatment-naïve and treatment-experienced PRS subjects without cirrhosis comes from SURVEYOR-2 Part 4. The SVR rate was 93% (43/46); there were no virologic failures and the remaining 3 subjects (7%) were considered non-virologic failures.

The data supporting labeling for HCV GT4 treatment-naïve and treatment-experienced PRS subjects with compensated cirrhosis comes from EXPEDITION-1. Sixteen subjects were treated with GLE/PIB for 12 weeks duration and all 16 subjects achieved SVR12.

Genotype 5 and 6

Genotypes 5 and 6 are rare in the United States representing less than 1% of the overall HCV infected population. Therefore to support labeling, FDA has generally relied on the overall data supporting an HCV treatment regimen including data from other genotypes, in particular HCV GT1 and 3, along with a limited amount of data in the uncommon genotypes 5 and 6. A key review issue, which was identified and discussed at the preNDA meeting, was whether there were adequate data to recommend GLE/PIB for the shorter 8 week duration in treatment-naïve and treatment experienced PRS subjects without cirrhosis.

At the time of filing, data were available on 32 HCV GT5 subjects who received GLE/PIB for 8 or 12 weeks in clinical trials; no subjects experienced virologic failure, however, only 2 subjects received the 8 week treatment duration. In addition, these 2 subjects did not appear to be representative of the broader population, in that they both had relatively low baseline HCV RNA and therefore could be considered "easier to treat." In addition, there remained some concern that an NS3 D168E polymorphism could affect the antiviral activity of GLE and potentially impact the efficacy results in HCV GT5 subjects, particularly for a shorter duration of treatment. However, 13 of 31 subjects (42%) of the HCV GT5 subjects had an NS3 D168E polymorphism detected; but all 13 subjects achieved SVR12 after 12 weeks of GLE/PIB.

Similarly for GT6, only 10 subjects received GLE/PIB for 8 weeks (one subject originally was reported as non-virologic failure but subsequently returned to the site and had achieved SVR12), while the other 38 subjects (7 with cirrhosis, 31 without cirrhosis) received GLE/PIB for 12 weeks. While there is no baseline polymorphism issue for NS3 with GT6, GT6 is highly diverse with at least 28 various subtypes, with the potential for NS5A associated resistance associated polymorphism across different GT6 subtypes.

At the time of completion of the primary reviews, the review team had decided that based on the available information, the data for HCV GT5 and GT6 were insufficient to recommend the shorter 8 week duration. Additionally, the Applicant has recently initiated and ongoing trial, M16-126, that is assessing the efficacy of the 8 week duration in additional noncirrhotic subjects with HCV GTs 5 and 6; however, at the time of submission, no further data were available from this trial. This decision was discussed with the Applicant at the Midcycle communication. At the Midcycle, the Division agreed to allow the Applicant to provide an

update on other emerging supportive data for HCV GT5 and GT6 from the ongoing trials, and the Division requested available SVR24 data to confirm the durability of response, and any available nonclinical data to address the potential impact of a GT5 NS3 D168E substitution on the activity of GLE.

Subsequent to the finalization of the primary reviews, the Applicant provided emerging efficacy data to the NDA (SD 46). Within this data, the Applicant confirmed that the one GT6 subject (2811) who failed GLE/PIB for 8 weeks for non-virologic reasons (lost to follow-up) in SURVEYOR-2, did achieve SVR12 and SVR24. In addition, four other GT6 infected subjects from the ENDURANCE-4 and EXPEDITION-2 trials all achieved SVR12 and SVR24 with GLE/PIB durations of 8 weeks or less (Table 5). Thus, the pooled SVR12 rate is 100% (14/14) for GT6 infected patients who received GLE/PIB dosed for 8 weeks or less.

The Applicant also provided data from the recently initiated trial M16-126, that is evaluating a larger cohort of HCV GT5 and GT6 subjects for 8 weeks (noncirrhotic) and 12 weeks (cirrhotic). As of 6/13/17, there were 20 non-cirrhotic subjects (5 GT5, 15 GT6) assigned to 8 weeks of GLE/PIB treatment. Four subjects (1 GT5, 3 GT6) have reached the SVR4 analysis timepoint, and all achieved SVR4 (Table 5). The other 16 subjects have HCV RNA data available through Treatment Weeks 4 or 8, with HCV RNA <LLOQ (n=1, GT6 subject at Week 4) or not detected (n=15) through the last available timepoint; no subjects have experienced virologic failure.

Table 5: Emerging Efficacy Data for HCV GT5 or GT6 Subjects Who Received GLE/PIB for ≤8 Weeks.

Subject	GT Subtype	Study	SVR4	SVR12	SVR24	Study Description/Comments
2811	6a/b	SURVEYOR-2-Part-4 (M14-868)	Yes	Yes*	Yes	*Previously counted as lost-to-follow-up
200402	6a	ENDURANCE-4 (M13-583)	Yes	Yes	Yes	Received 19 days of tx
110207	6u	EXPEDITION-2 (M14-730)	Yes	Yes	Yes	Study in HIV-1 co-infected subjects
302202	6e	EXPEDITION-2 (M14-730)	Yes	Yes	Yes	Study in HIV-1 co-infected subjects
302203	6n	EXPEDITION-2 (M14-730)	Yes	Yes	Yes	Study in HIV-1 co-infected subjects
30002	6a	M16-126	Yes	Ongoing		Study in GT5 or GT6-infected subjects
30001	6a	M16-126	Yes	Ongoing		Study in GT5 or GT6-infected subjects
30004	6a	M16-126	Yes	Ongoing		Study in GT5 or GT6-infected subjects
50002	5a	M16-126	Yes	Ongoing		Study in GT5 or GT6-infected subjects

Source: NDA 209394 SD 46

In regards to the durability of response, the Applicant reported that all subjects infected with GT5 or GT6 without cirrhosis who were treated with GLE/PIB for 8 or 12 weeks and whose SVR12 data were available and included in the NDA submission had also achieved SVR24; 11/11 and 56/56 subjects for GT5 and GT6, respectively.

The Applicant also provided new cell culture data regarding the impact of the NS3 D168E substitution on the antiviral activity of GLE in GT5 subjects. Introduction of D168E into a GT5a replicon conferred a relatively modest 4.2-fold reduction in GLE activity, despite this,

activity remained in the sub-nanomolar level (mean GLE EC_{50} value 0.409 nM), which is comparable to the activity against wild-type HCV replicons of other genotypes. Of note, wild-type HCV GT3 similarly has an NS3 D168Q change relative to GT1, and GLE/PIB for 8-weeks is well supported for treatment-naïve, non-cirrhotic GT3-infected patients (a genotype that has typically been more difficult to treat than other genotypes), with an SVR12 rate of 95% (149/157) and relapse rate of 3% (5/150).

Therefore, based on the available data across the development program, as well as the supportive high efficacy rates observed in noncirrhotic HCV GT1-4 subjects, and in particular for GT3 subjects who were treated with GLE/PIB for 8 weeks, the review team finds that for the treatment regimen for patients with HCV GT5 and 6 without cirrhosis, including for those who are treatment-experienced PRS, there is sufficient evidence to support the shorter 8 week duration. Similar to other applications where data have been limited for these rare genotypes, reliance on data from other genotypes is necessary to extend the 8 week indication to HCV GT5 and GT6 patients, particularly for GT5 patients and treatment-experienced PRS GT5 or GT6 patients. In order to be fully transparent, and to demonstrate the supportive data for patients with these genotypes, the review team believes it is important to provide both the 8 and 12 week duration SVR12 results by genotype in Section 14 of the product labeling.

The situation of limited data is similar for subjects with HCV GT5 or GT6 and cirrhosis. In total there are 2 HCV GT5 subjects and 7 HCV GT6 subjects, all with compensated cirrhosis and treated with GLE/PIB for 12 weeks; all 9 subjects achieved SVR12. Again, these data are supported by the high SVR rates of GTs1, 2 and 4 (99-100%; n=137) subjects with compensated cirrhosis who were treated with GLE/PIB for 12 weeks and where the overall virologic relapse rate was <1% (1/137).

Trial M16-126 is currently ongoing. This trial will provide additional data evaluating the 8 week treatment duration in HCV GT5 and GT6 subjects without cirrhosis. The Applicant has agreed to submit a final SVR12 study report along with [redacted] (b) (4) drug resistance datasets from M16-126 as a PMC.

MAGELLAN-1: Treatment-Experienced with NS5A Inhibitors and/or NS3/4A Protease Inhibitors

Currently, there are no approved treatment options for patients who have previously failed a DAA treatment regimen containing an NS5A inhibitor. AASLD Guidelines recommend deferral of treatment in a HCV GT1 patient who is NS5A inhibitor experienced, if the patient does not have cirrhosis or an urgent need for treatment. There are limited published data that support the Guideline recommendations of various re-treatment strategies, which all use a sofosbuvir based regimen, including 1 to 3 more DAAs + RBV for a longer duration of treatment, generally 24 weeks. SVR rates with such strategies have reported varied success from 60-100%, which have also depended on the identification of some baseline NS5A RASs. On April 21, 2016, FDA granted the request for Breakthrough Therapy designation for GLE/PIB for the treatment of HCV GT1 DAA-experienced patients due to the unmet medical

need in this patient population; in particular for those previously treated with a regimen containing an NS5A inhibitor.

MAGELLAN-1 was a Phase 2b randomized, multipart, open-label trial in 141 GT1 or GT4 subjects who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A PI. Part 1 (n=50) was a randomized trial exploring 12 weeks of glecaprevir 200 mg and pibrentasvir 80 mg, glecaprevir 300 mg and pibrentasvir 120 mg, with and without ribavirin (only data from glecaprevir 300 mg plus pibrentasvir 120 mg without ribavirin are included in the analyses). Part 2 (n=91) randomized GT1 or GT4 subjects without cirrhosis or with compensated cirrhosis to 12- or 16-weeks of treatment with GLE/PIB.

This trial predominantly enrolled HCV GT1 subjects; only 4 GT4 subjects were enrolled. Therefore, the following analyses only include the GT1 subjects. Of the 42 genotype 1-infected subjects treated in Parts 1 and 2, who were either NS5A inhibitor-experienced only (and treated for 16 weeks), or NS3/4A PI-experienced only (and treated for 12 weeks), the median age was 58 years (range: 34 to 70); 40% of the subjects were NS5A-treatment experienced only and 60% were PI experienced only; 24% had cirrhosis; 19% were ≥65 years, 69% were male; 26% were Black; 43% had a body mass index ≥ 30 kg/m^2; 67% had baseline HCV RNA levels of at least 1,000,000 IU per mL; 79% had subtype 1a infection, 17% had subtype 1b infection and 5% had non-1a/1b infection.

The key review issue for this trial was whether there were adequate data to support an indication in each of the key subpopulations evaluated in this trial: those that were NS5A inhibitor experienced and NS3/4A PI-naïve, those that were NS3/4A PI experienced and NS5A naïve, and those that were both NS5A inhibitor *and* NS3/4A PI experienced. The SVR results for these populations are provided in Table 6 below.

Table 6: MAGELLAN-1 SVR12 data for NS5A Inhibitor and/or NS3/4A PI Experienced Subjects for 12 or 16 Weeks Duration

Treatment Experience	*GLE/PIB 12 weeks n=65 (%)*	*GLE/PIB 16 weeks n=44 (%)*
NS5A-experienced & NS3/4A PI-naïve	***18/20 (90.0)*** (95% CI: 69.9, 97.2) OTVF: 1/20 (5.0) Relapse: 1/20 (5.0)	***16/17 (94.1)*** (95% CI: 73.0, 99.0) OTVF: 1/17 (5.9)
NS3/4A PI-experienced & NS5A-naïve	***23/25 (92.0)*** (95% CI: 75.0, 97.8) 2 missing SVR12	**12/12 (100)** (95% CI: 75.8, 100)
NS5A & NS3/4A PI-experienced	***16/20 (80.0)*** (95% CI: 58.4, 91.9) OTVF: 1/20 (5.0)	***12/15 (80.0)*** (95% CI: 54.8, 93.0) OTVF: 3/15 (20.0)

	Relapse: 3/20 (15.0)

OTVF= on treatment virologic failure
Source: Modified from Table 21 in Statistical Review by Drs. Usher and Tracy.

The SVR12 rate was 92% (23/25) for HCV GT1 subjects who were NS3/4A PI experienced and NS5A inhibitor naïve and received GLE/PIB for 12 weeks; there were no virologic failures, however, 2 subjects had missing data at the SVR12 assessment. Based on the data in this PI experienced only subpopulation, there was no clinical benefit of a longer duration of GLE/PIB treatment or a benefit with the addition of RBV. Therefore, the review team agreed that these data, along with other data in the application for patients with HCV GT1 (and other genotypes) supported the indication of GLE/PIB for 12 weeks in patients who were NS3/4A PI experienced and NS5A inhibitor naive.

However, the more difficult review issue was whether the data supported an indication in patients with prior NS5A experience, with or without prior NS3/4A PI experience. Among HCV GT1 infected NS5A inhibitor experienced and NS3/4A PI naïve subjects, the SVR12 rates were 90% (18/20) and 94% (16/17) for those who received GLE/PIB for 12 or 16 weeks, respectively. Efficacy was lower for those with *both* prior NS5A inhibitor *and* NS3/4A PI experience, with SVR12 rates of 80% (16/20) and 80% (12/15) with the 12 and 16 week durations, respectively.

All 11 subjects who experienced virologic failure had prior treatment experience with an NS5A inhibitor containing regimen. Results on the impact of cirrhosis status on treatment outcome were inconclusive due to limited data, particularly when accounting for GLE/PIB treatment regimen and prior DAA class experience. Prior NS5A inhibitor experience was associated with the presence of baseline NS5A RASs that either existed as natural baseline amino acid polymorphisms, or emerged from prior NS5A inhibitor experience. Virologic failure with GLE/PIB treatment was associated with the presence of baseline NS5A RASs, particularly at position Q30, or at multiple NS5A positions. Baseline NS3 D168 RASs were also associated with virologic failure for subjects who had been treated previously with both an NS5A inhibitor *and* an NS3/4A PI. Most virologic failure subjects had treatment emergent or evolving RASs in NS3 or NS5A, or in both targets, indicating the possibility for development of further treatment-emergent resistance with GLE/PIB failure.

As stated above, a key review issue for MAGELLAN-1 was whether the data were adequate to support an indication for treatment of HCV GT1 subjects with prior NS5A inhibitor experience. Based on data presented above, the review team concluded that the data did support a treatment recommendation for GLE/PIB for 16 weeks for HCV GT1 patients who are NS5A inhibitor-experienced and NS3/4A PI naïve. While the overall numbers were small, the outcome was reasonable with a 94% SVR rate in a population that currently has no approved treatment options and was given Breakthrough Therapy Designation. However, due to the lower SVR12 rates and higher virologic relapse, the review team concluded that

the data did not support a treatment recommendation for HCV GT1 infected patients with prior treatment experience to both NS5A inhibitors *and* NS3/4A PIs.

EXPEDITION-4: Treatment-Naïve and Treatment-Experienced PRS Subjects with Severe Stage 4 or 5 Renal Disease

EXPEDITION-4 was a single-arm, open-label trial of GLE/PIB for 12 weeks in subjects who were treatment-naïve or treatment-experienced PRS, with or without compensated cirrhosis, and who had severe renal impairment (CKD Stages 4 and 5). There were 104 subjects enrolled, 82% were on hemodialysis, and 53% (n=54), 15% (n=16), 11% (n=10), 19% (n=20), 1% (n=1) and 1% (n=1) were infected with HCV genotypes 1, 2, 3, 4, 5 and 6; respectively. Overall, 19% (n=20) of subjects had compensated cirrhosis and 81% (n=84) of subjects were non-cirrhotic; 58% (n=60) and 42% (n=44) of subjects were treatment-naïve and PRS treatment-experienced, respectively.

The overall SVR12 rate was 98% (102/104); no subjects experienced virologic failure, however, two GT1 subjects failed for non-virologic reasons. The presence of renal impairment did not affect the efficacy of GLE/PIB; no dose-adjustments were required during the trial. GLE/PIB for 12 weeks was highly efficacious in subjects with severe renal impairment, regardless of HCV genotype, cirrhosis status or prior treatment with PRS. The high efficacy rate of the 12 week duration in subjects with severe renal impairment supports that GLE/PIB performed similarly to the 12 week duration in those without renal impairment. It is important to note that the interpretation of the data from some of these subgroups is limited due to small numbers, in particular for genotypes 5 and 6 (n=1 for each) and for those with prior sofosbuvir experience (n=2); however, sofosbuvir, pegylated interferon and ribavirin are not expected to have cross resistance to GLE/PIB as they are all in different classes of drugs. It is scientifically reasonable to rely on data from other genotypes and non-renally impaired patients to support inclusion of renally impaired patients with HCV GTs 1-6 for the recommended treatment durations. Taking the following into consideration: 1) moderate to severe renal impairment does not affect efficacy of GLE/PIB, 2) the regimen is minimally renally excreted, and 3) considering the response rates across genotypes for patients without renal impairment, the review team supported the 8 week treatment recommendation to include those with severe renal impairment.

Overall Efficacy Conclusion

The data from the nine Phase 2 and Phase 3 clinical trials demonstrate that GLE/PIB provides a high rate of efficacy with SVR rates ranging from 91-100% across all HCV genotypes 1-6, amongst patients with and without compensated cirrhosis, and with and without severe renal disease, including hemodialysis. Currently, GLE/PIB will be the only anti-HCV regimen that provides a treatment option for those with severe renal disease who are infected with HCV GT 2, 3, 5 or 6. Additionally, GLE/PIB will fill another important unmet need to allow for treatment of HCV genotype 1 patients who have previously been treated with an NS5A inhibitor-based treatment regimen.

8. Safety

This section provides a focused summary of the safety findings from the Phase 2 and 3 trials for which subjects were administered GLE/PIB 300mg/120mg daily for 8, 12, or 16 weeks.

Eight of the nine pivotal Phase 2 and 3 trials were included in the pooled safety population for the majority of safety analyses: ENDURANCE-1 (M13-590), EDURANCE-2 (M15-464), ENDURANCE-3 (M15-594), ENDURANCE-4 (M13-583), SURVEYOR-1 (M14-867), SURVEYOR-2 (M14-868), EXPEDITION-1(M14-172) and MAGELLAN-1 (M15-410). The Phase 2/3 pooled safety population included data from 2,265 subjects with or without cirrhosis who received at least one dose of GLE/PIB at the proposed labelling dosage ((b) (4) co-formulated GLE 300 mg QD and PIB 120 mg QD without RBV) for 8, 12 or 16 weeks. The pooled safety population excluded subjects with severe renal impairment enrolled in EXPEDITION-4 (M15-462), as subjects with severe renal impairment have different baseline health status and this trial was reviewed separately.

Dr. Lara Stabinski conducted the overall clinical safety analyses for this application and Dr. Aimee Hodowanec conducted the safety analyses for EXPEDITION-4. For a complete description of the data, analyses and findings please refer to the joint clinical review by Drs. Stabinski and Hodowanec.

Adequacy of the safety database, Applicant's safety assessments and submission quality

The safety database for GLE/PIB is adequate to assess safety for the proposed indication, dosage regimen, duration of treatment and patient populations. The safety database was consistent with the safety considerations as outlined in the Draft Guidance for Industry: *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment*. Overall 3,311 subjects received at least one dose of GLE/PIB in the development program with 2,369 subjects who received at least one dose of co-administered or co-formulated GLE 300 mg QD and PIB 120 mg QD without RBV for 8, 12 or 16 weeks.

The Applicant performed a comprehensive assessment of safety, including but not limited to a detailed analysis of hepatotoxicity. The submission quality was adequate to perform a thorough safety review and no substantive issues with data integrity were identified. This application was also part of the JumpStart program within the Office of Computational Science which provided additional independent review of data fitness and overall safety findings.

Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, common adverse events and results of laboratory tests

Overall, the safety profile of GLE/PIB is acceptable. Headache, fatigue and nausea were the most common adverse reactions occurring in subjects across the phase 2 and 3 clinical trials. The majority of adverse events and adverse reactions were mild or moderate and did not

result in discontinuation of treatment. Extending the duration from 8 weeks to 12 or 16 weeks did not appear to negatively impact the safety profile in a substantive manner.

Deaths

A total of seven deaths occurred in the overall Phase 2/3 safety population. Adverse events that led to death included cerebral hemorrhage (2 subjects; including 1 subject in the severe renal impairment trial), hepatic cancer metastatic, pneumonia, accidental overdose, adenocarcinoma, and unknown cause (preferred term was death).

We concur with the assessments of the deaths, as not causally related to GLE/PIB, by Drs. Stabinski and Hodowanec and based on my review of the narratives and available data.

Serious Adverse Events (SAEs)

Treatment Emergent SAEs were infrequent overall, occurring in approximately 2% of subjects overall, 1% of the placebo comparator and 2% of the active comparator DCV/SOF. SAEs occurred in 1.6% of non-cirrhotic subjects and, as expected, occurred more frequently in subjects with cirrhosis, at approximately 6%.

Only one SAE of transient ischemic attack (TIA) was considered possibly related to GLE/PIB by the Investigator and not related by the Applicant. This SAE occurred in a 49 year old male with a long term history of tobacco use (>30 years), obesity and cardiac conduction abnormality who experienced two episodes of TIAs on Day 11 and Day 36 of study (GLE/PIB was withdrawn on Day12). There was no evidence of a sustained change in blood pressure in this subject (baseline 127/80, Week 2 133/93). Based on my assessment of the cumulative safety data, it seems unlikely that GLE/PIB was associated, other than by temporal association of the first event of TIA. This subject had a significant history of tobacco use which is a known risk factor. Additionally, study drugs were discontinued 23 days prior to the second event of TIA.

Hepatocellular carcinoma was reported by three subjects as a treatment-emergent SAE. Additionally, the only other SAE reported in more than one subject was transient ischemic attack. Related terms of angina pectoris and angina unstable were reported by one subject each, both with prior history of chest pain or other risk factors. While the clinical reviewer expressed some concerns regarding blood pressure fluctuations in the subjects with transient ischemic attack and those with cardiac related SAEs, there was no definitive pattern of treatment-emergent blood pressure elevation or decrease that could account for these events. Further additional analyses were performed to fully evaluate any trends for GLE/PIB associated hypo- or hypertension events, both serious and non-serious, in subjects with and without pre-existing blood pressure abnormalities, and no association could be made. Drug-drug interactions were also evaluated by the clinical pharmacology team without any evidence of a significant finding between GLE/PIB and common anti-hypertensives. Additionally, an evaluation of outlier events of hyper or hypotension was conducted across

recent DAA approvals with similar databases (similar populations, durations and on-treatment assessments). The proportions of subjects with outlier events of hyper or hypotension were similar across the various DAA programs. This suggests that the observed outlier events associated with GLE/PIB may be due to variability in blood pressure assessments (day-to-day variability, noise in cuff assessments), or a baseline finding in this population.

Approximately one quarter of subjects in EXPEDITION-4 experienced SAEs. However, none of these SAEs were considered by the Applicant to be treatment related. Pulmonary edema, hypertensive crisis, gastrointestinal hemorrhage and cardiac failure congestive were all SAEs reported in two or three subjects with severe renal impairment in EXPEDITION-4. These SAEs are not unexpected for this population with multiple comorbidities.

There was a lack of concerning trends across the SAEs and the vast majority of subjects who experienced an SAE had an alternate explanation for the SAE, experienced resolution of the SAE with continued treatment, or experienced negative dechallenge.

Discontinuations

Overall, discontinuations from GLE/PIB due to adverse events were infrequent. In the Phase 2/3 safety population, 7 subjects (0.3%) discontinued due to AEs. Of these seven subjects, three subjects (0.1%) discontinued due to an AE considered related to GLE/PIB. Additionally, four subjects (4%) discontinued due to AEs from EXPEDITION-4. One subject discontinued due to diarrhea and one subject discontinued due to pruritus, with both events being considered possibly related to GLE/PIB; the other two subjects had cardiovascular SAEs that were not considered related.

Common Adverse Events and Laboratory Abnormalities

The most common adverse reactions, all grades, observed in greater than or equal to 5% of subjects receiving 8, 12, or 16 weeks of treatment with GLE/PIB in the Phase 2/3 safety population were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving GLE/PIB who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1).

ENDURANCE-1 (M15-464) was the placebo controlled deferred treatment trial that was conducted to allow for a safety comparison of GLE/PIB to placebo.
Table 7 summarizes the treatment-emergent adverse events (AEs), irrespective of causality or severity, for GLE/PIB for 12 weeks compared to placebo for 12 weeks. The most common AEs (>5%) were headache, fatigue, diarrhea, asthenia, nausea and pruritus. Headache, fatigue and asthenia were reported in similar proportions for GLE/PIB and placebo; however, diarrhea and nausea were reported in higher proportions in the GLE/PIB arm for diarrhea (9.9% vs 3.0%) and nausea (7.4% vs. 3.0%), respectively.

Table 7: ENDURANCE-2 -Treatment-Emergent AEs Reported ≥2% of GLE/PIB Subjects, All Grades and All Causality

Dictionary Derived Term	GLE/PIB 12 WEEKS N=202	PLACEBO FOR 12 WEEKS N=100
Headache	24 (11.9%)	12 (12.0%)
Fatigue	23 (11.4%)	10 (10.0%)
Diarrhea	20 (9.9%)	3 (3.0%)
Asthenia	19 (9.4%)	8 (8.0%)
Nausea	15 (7.4%)	3 (3.0%)
Pruritus	12 (5.9%)	6 (6.0%)
Abdominal distension	8 (4.0%)	1 (1.0%)
Upper respiratory tract infection	8 (4.0%)	3 (3.0%)
Myalgia	7 (3.5%)	4 (4.0%)
Constipation	7 (3.5%)	3 (3.0%)
Insomnia	7 (3.5%)	4 (4.0%)
Abdominal pain	6 (3.0%)	0 (0.0%)
Dizziness	6 (3.0%)	5 (5.0%)
Influenza	5 (2.5%)	3 (3.0%)
Arthralgia	5 (2.5%)	2 (2.0%)
Pain in extremity	5 (2.5%)	0 (0.0%)
Back pain	5 (2.5%)	4 (4.0%)
Depression	4 (2.0%)	0 (0.0%)
Decreased appetite	4 (2.0%)	1 (1.0%)
Cough	4 (2.0%)	3 (3.0%)
Anxiety	4 (2.0%)	1 (1.0%)
Oropharyngeal pain	4 (2.0%)	5 (5.0%)

Source: Modified from Clinical Review Table 34

Across the Phase 2/3 trials, the common AEs were similar to the AEs considered related to investigational drug by the Investigator, defined as adverse drug reactions (ADRs). Again, headache, fatigue, nausea and diarrhea were the most common ADRs experienced by the safety population. Table 8 summarizes these findings across the safety database, and for those with and without compensated cirrhosis, and was the basis for the common adverse reaction labeling as highlighted by the dashed red box.

Table 8: Treatment-Emergent ADRs Reported in ≥ 2% of Subjects, All Grades

	ENDURANCE-2 M15-464, GT2 (Placebo controlled)		ENDURANCE-3 M15-594,GT3 (Active controlled)			Pooled Trials (n=2,265)	
Dictionary Derived Term	GLE/PIB 12 weeks (n=202)	Placebo 12 weeks (n=100)	GLE/PIB 12 weeks (n=233)	GLE/PIB 8 weeks (n=157)	SOF + DCV 12 weeks (n=115)	GLE/PIB All Durations Cirrhotic (n=288)	GLE/PIB All Durations not Cirrhotic (n=1,977)
Headache	18 (8.9%)	6 (6.0%)	39 (16.7%)	25 (15.9%)	17 (14.8%)	39 (13.5%)	259 (13.1%)
Fatigue	17 (8.4%)	8 (8.0%)	33 (14.2%)	17 (10.8%)	14 (12.2%)	43 (14.9%)	216 (10.9%)
Nausea	13 (6.4%)	2 (2.0%)	27 (11.6%)	14 (8.9%)	14 (12.2%)	24 (8.3%)	148 (7.5%)
Diarrhea	10 (5.0%)	2 (2.0%)	8 (3.4%)	11 (7.0%)	3 (2.6%)	16 (5.6%)	70 (3.5%)
Abdominal distension	7 (3.5%)	1 (1.0%)	5 (2.1%)	0 (0.0%)	0 (0.0%)	2 (0.7%)	21 (1.1%)
Insomnia	6 (3.0%)	1 (1.0%)	5 (2.1%)	0 (0.0%)	4 (3.5%)	6 (2.1%)	48 (2.4%)
Pruritus	5 (2.5%)	2 (2.0%)	4 (1.7%)	1 (0.6%)	1 (0.9%)	16 (5.6%)	59 (3.0%)
Depression	3 (1.5%)	0 (0.0%)	1 (0.4%)	1 (0.6%)	0 (0.0%)	4 (1.4%)	12 (0.6%)
Flatulence	3 (1.5%)	0 (0.0%)	2 (0.9%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	21 (1.1%)
Decreased appetite	3 (1.5%)	1 (1.0%)	5 (2.1%)	3 (1.9%)	3 (2.6%)	7 (2.4%)	30 (1.5%)
Constipation	3 (1.5%)	1 (1.0%)	4 (1.7%)	0 (0.0%)	1 (0.9%)	5 (1.7%)	25 (1.3%)
Dyspepsia	2 (1.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	7 (2.4%)	25 (1.3%)
Abdominal pain	1 (0.5%)	0 (0.0%)	2 (0.9%)	2 (1.3%)	1 (0.9%)	6 (2.1%)	24 (1.2%)

Source: Modified Table 35 from Clinical Review

Overall, laboratory analyses did not reveal any significant safety concerns that were not already well characterized prior to the NDA submission. Grade 3 and 4 laboratory abnormalities were uncommon across the safety population. There were no clinically significant trends for abnormalities in liver biochemistries or in hematology laboratories, and therefore, no laboratory findings are highlighted in Section 6 of labeling. Overall in the Phase 2/3 safety population, 7% (154/2265) and 2% (51/2265) of subjects had an on-treatment Grade 1 or Grade 2 elevation of bilirubin, respectively. In the placebo controlled trial, EXPEDITION-1, there was an approximate 4% higher incidence of grade 1 and 2 elevations in bilirubin in subjects who received GLE/PIB as compared to placebo, attributable to GLE/PIB inhibition of OATP1B1, OATP1B3 and weak inhibition of UGT1A1 which impacts bilirubin transport and metabolism. However, in the clinical trials subjects the impact of these laboratory findings were minimal; subjects were continued on therapy despite these small, and often transient, increases in bilirubin, no subjects experienced jaundice and total bilirubin levels decreased after completion of therapy. Therefore, labeling with the ENDURANCE-2 trial (placebo comparison) in Section 6 includes a statement regarding the potential for impacts on the bilirubin transport and metabolism. Routine safety monitoring for laboratory abnormalities will continue post-marketing.

As GLE/PIB is comprised of well-characterized small molecules with no biologic components, there are no concerns regarding immunogenicity.

Submission-specific safety issues

Drs. Stabinski and Hodowanec conducted detailed reviews to address safety concerns related to use of direct acting antivirals, in general, such as hepatotoxicity and other safety issues potentially related to GLE/PIB or the class of NS5A inhibitors or NS3/4A protease inhibitors, including rash, neuropsychiatric events and gastrointestinal events.

Hepatic Safety

A comprehensive safety evaluation was conducted by Dr. Lara Stabinski, AbbVie Inc., and an independent expert hepatic panel (EHP) comprised of five physicians with expertise in hepatic disorders and experience with assessment of hepatic safety with the administration of direct-acting antiviral therapy for HCV. DAVP requested an EHP review because a small proportion of subjects in Phase 2 trial had elevations of bilirubin, and because of known hepatic safety events observed with earlier generation protease inhibitors. In addition, other applicant's for DAAs have conducted an EHP review using an independent panel. .

The EHP was asked to assess all subjects with post-baseline total bilirubin elevations ≥2 times the upper limit of normal (ULN). The Applicant also asked the panel to review all cases that met their definition of on-treatment hepatic decompensation.

In total 33 cases (1.4%) were identified across the 2,369 subject safety database that met one of four categories for review (mixed hyperbilirubinemia n=4, Grade 2 or higher ALT and hyperbilirubinemia n=5, hepatic decompensation n=1, bilirubin elevation ≥2 ULN and not meeting other criteria n=23). The EHP concluded that none of the cases reviewed were consistent with a "definite," "highly likely" or "probable" event of drug-induced liver injury (DILI), based on the Drug Induced Liver Injury Network [DILIN] likelihood causality scoring. One case was considered to be a "possible" event of DILI but with a most likely alternative etiology recorded by the EHP as "most likely related to passage of gallstones." This subject had normal liver chemistries throughout the trial, but on Day 87 at the end of treatment visit he had a significant increase in ALT (7.5xULN), AST (5.8xULN), bilirubin (2xULN) and alkaline phosphatase (1.5xULN). Nineteen days later, after the liver chemistries had resolved, an ultrasound was performed and the subject had gallstones without ductal dilation at that time.

The overall occurrence of hepatic AEs was low across the Phase 2/3 safety population, with a total of three subjects reporting events of hepatic steatosis, hepatic pain and jaundice. All events were considered grade 1. The event of jaundice occurred at Week 12 in a subject with baseline cirrhosis and the investigator considered the event to be reasonably related to study medication. Additionally, five subjects met Hy's Law laboratory criteria; four subjects were reviewed by the EHP as discussed above. The remaining subject experienced a single event

of elevated AST to 8xULN, with associated increases of ALT (2xULN), bilirubin (2xULN) and ALP (1.6xULN) on Day 91, shortly after completing therapy. This subject also had reported AEs of alcohol abuse, weight decrease and anemia.

In sum, no hepatic signal for GLE/PIB was detected in the extensive analyses conducted across the Phase 2/3 safety population. Routine safety monitoring will continue post-marketing.

The Clinical Review also describes the results of focused safety analyses for hepatocellular carcinoma, rash and skin disorders, neuropsychiatric events and gastrointestinal events. No significant or novel safety signals related to GLE/PIB were identified in these safety explorations.

We concur with the overall conclusions of the clinical review. The overall safety profile and the overall high SVR rates clearly demonstrate that the benefit of treatment with GLE/PIB outweighs the risks and implications of the observed safety events.

9. Advisory Committee Meeting

This NDA was not presented at the Antimicrobial Drug Advisory Committee because GLE/PIB received breakthrough designation and the benefit/risk assessment did not appear controversial based on the review team's preliminary assessment of the top line trial results.

10. Pediatrics

AbbVie, requested deferral of pediatric studies for the proposed indication in pediatric patients ≥ 3 to < 18 years because the DAA regimen will be ready for approval for use in adults before pediatric studies are complete. A partial waiver was also requested and granted

for pediatric patients < 3 years of age because clinical trials in this age group are impossible or highly impractical.

11. Other Relevant Regulatory Issues

Financial Disclosures

Financial disclosures were provided for the nine covered Phase 2 and 3 clinical trials. The total number of covered investigators was 2,494. Overall, the number of investigators with a financial interest was low, approximately 2%. Due to the multicenter nature of these trials, the potential bias by any one investigator is minimized. Moreover, the efficacy endpoints are determined using objective measurements of HCV-RNA PCR by central laboratories and, hence, should not be vulnerable to bias on the part of the investigator. There were no financial disclosures of significant concern, individually or collectively. See the Clinical Review for additional details.

Other Good Clinical Practice (GCP) issues

The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines.

Office of Scientific Investigation (OSI) Inspections

Inspection sites were selected from four of the nine Phase 2 and 3 clinical trials submitted for review for this NDA: EXPEDITION-1 and -4, and ENDURANCE-1 and -3. A total of eight sites were selected, because both GLE and PIB are NMEs, and a substantial amount of clinical trial experience with these drugs has been at foreign sites. Six of the clinical sites, including two foreign sites, had no regulatory findings. The remaining two sites had Voluntary Action Indicated classifications. The overall conclusion of the OSI inspectional findings from the eight clinical trial sites support the validity and acceptability of the data as reported by the Applicant under this NDA. Please refer to the OSI Consult Review for further details.

12. Labeling

Prescribing Information

- INDICATIONS AND USAGE section:
  - The data and rationale supporting the broad indication for treatment of HCV GT 1-6 in patients who are treatment-naïve or PRS experienced for 8, 12 or 16 weeks is discussed in detail in Section 7. The indication is limited to HCV genotype 1 patients with prior NS5A treatment experience or NS3/4A protease inhibitor, not both based on the data from MAGELLAN-1.
- DOSAGE AND ADMINISTRATION section:
  - This section was updated to reflect the indicated patient populations.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
    - All DAAs have a BOX WARNING for HBV reactivation and will be included in this label
    - A CONTRAINDICATION for patients with severe hepatic impairment (Child-Pugh C) is included due to high exposures of GLE/PIB in this population.
    - A CONTRAINDICATION for coadministration with atazanavir or rifampin is recommended and accepted by the Applicant
- ADVERSE REACTIONS section:
    - In addition to the overall data provided, this section was expanded to provide safety information from the placebo controlled trial ENDURANCE-2 and the DCV/SOF comparator trial ENDURANCE-3. This section also includes safety data from EXPEDITION-4 that evaluated the safety and efficacy of GLE/PIB in adults with severe renal impairment.
- CLINICAL STUDIES section:
    - The Agency worked closely with the Applicant to ensure that the clinical trials of primary importance were displayed in as clear, concise, transparent and clinically meaningful a manner as possible given the complexity of the data. Table 13 in the label provides a summary of the eight clinical trials supporting efficacy and the indicated treatment durations by HCV genotype, cirrhosis status and prior treatment history. (Note: nine Phase 2 and 3 trials were used to support the safety and efficacy of this application; however, the placebo controlled trial ENDURANCE-2 is displayed only in Section 6 for safety and not in Section 14, or Table 13, because the 12 week treatment duration for GT2 is not indicated in treatment naïve or treatment experienced PRS subjects without cirrhosis).
    - Data from all three treatment arms of ENDURANCE-3 in Treatment-naïve HCV GT3 subjects without cirrhosis are displayed, despite the indication in this population being for 8 weeks duration. The review team believed it was important to provide the results from the randomized 12 week arm, as the comparison of the 12 week arm to the DCV/SOF arm was the primary statistical endpoint of the trial. Display of both the 8 and 12 week data allows for a better understanding and transparency regarding the outcomes of this controlled trial.
    - ENDURANCE-1 randomized HCV GT1 subjects 1:1 to 8 or 12 weeks duration of GLE/PIB. Table 14 in labeling only provides the 8 week data; however, the text above the table provides the rationale that due to numerically similar efficacy, MAVYRET is recommended for 8 weeks for treatment-naïve and PRS treatment-experienced genotype 1 subjects without cirrhosis, rather than 12 weeks.
    - Data in HCV GT 5 and 6 subjects without cirrhosis are displayed for both the 8 and 12 week duration. The consensus of the review team was to display both durations, because the data for both the 8 and 12 week durations for these

rare genotypes are important for informing dosing recommendation decisions, and therefore, transparency in labeling regarding these data is important.

Other Labeling

- The Division of Medication Error Prevention and Analysis concurred with the proprietary name, MAVYRET
- Patient Information is still under negotiation with the Applicant
- Carton and container labeling are deemed acceptable

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the safety profile of GLE/PIB FDC, the Division does not recommend a Risk Evaluation and Management Strategy (REMS).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

One PMR is proposed and four PMCs are recommended as shown below. A request for an efficacy supplement for data from M16-126 in patients with HCV GT5 or 6 will be included in the approval letter. The Applicant has agreed to provide an efficacy supplement based on M16-126 and to provide topline results in September 2018.

PREA PMR: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of glecaprevir and pibrentasvir in pediatric subjects 3 through less than 18 years of age with chronic hepatitis C infection

PMR Schedule Milestones:
Protocol Submission: January 2017
Study/Trial Completion: July 2022
Final Clinical Study Report Submission: January 2023

PMC Description: Submit the final SVR12 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.

PMC Schedule Milestones:
Protocol Submission: 11/17/2016
Study/Trial Completion (SVR12 database lock): 08/01/2018
Final SVR12 Report Submission: 03/31/2019

PMC Description: Submit the final SVR12 report and datasets for the ongoing Trial M14-730 (EXPEDITION-2) to provide additional efficacy and safety data in HIV/HCV co-infected subjects receiving glecaprevir and pibrentasvir.

PMC Schedule Milestones:
Final Protocol (Amendment 3) Submission: 07/22/2016
Study/Trial Completion (SVR12 database lock): 04/03/2017
Final SVR12 Report Submission: 10/31/2017

PMC Description: Conduct a study evaluating the efficacy of glecaprevir/pibrentasvir in HCV genotype 1 infected subjects with prior treatment experience with an NS5A inhibitor plus sofosbuvir regimen.

PMC Schedule Milestones:
Final Protocol Submission: 05/30/2017
Study/Trial Completion: 12/31/2018
Final SVR12 Report Submission: 06/30/2019

PMC Description: Conduct a study to characterize the phenotypic effect of the following individual NS3/4A or NS5A substitutions on the cell culture anti-HCV activity of glecaprevir or pibrentasvir, respectively: genotype 1a NS3_I18V, NS3_N77S, NS3_V116A, NS3_I354V and NS4A_V23A, genotype 3a NS3_I366V, and genotype 1a NS5A_A61T.

PMC Schedule Milestones: Final Report Submission: 03/31/2018

14. Recommended Comments to the Applicant

There are no additional comments to be conveyed to the Applicant at this time.

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/s/

WENDY W CARTER
08/02/2017

JEFFREY S MURRAY
08/02/2017

EDWARD M COX
08/03/2017

Cross Discipline Team Leader Memorandum

Date	July 17, 2017
From	Wendy Carter, DO
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	209394 000
Applicant	AbbVie Inc.
Date of Submission	December 14, 2016
PDUFA Goal Date	August 14, 2017
Proprietary Name / Non-Proprietary Name	Mavyret/glecaprevir and pibrentasvir (GLE/PIB)
Dosage form(s) / Strength(s)	Fixed dose combination tablets 100mg/40mg
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with chronic hepatitis C
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with chronic hepatitis C

The CDTL Summary Review is complete, and has been added to the combined CDTL and Division Director Summary Review. Currently, inspection findings from two foreign facilities are still under evaluation. My recommendation for this application is approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDY W CARTER
07/17/2017

JEFFREY S MURRAY
07/17/2017