

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209394Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

1 CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209394
Priority or Standard	Priority
Submit Date(s)	December 14, 2016
Received Date(s)	December 14, 2016
PDUFA Goal Date	August 14, 2016
Division/Office	DAVP/OAP
Reviewer Name(s)	Larissa Stabinski, MD, MPH, Aimee Hodowanec, MD
Review Completion Date	June 6, 2017
Established Name	glecaprevir and pibrentasvir
(Proposed) Trade Name	Mavyret®
Applicant	AbbVie
Formulation(s)	Fixed-dose combination treatment regimen (100 mg/40 mg tablets)
Dosing Regimen	Three tablets once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic HCV infection in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of chronic HCV infection in adults

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Table of Contents

1	CLINICAL REVIEW	1
	Glossary	10
1	Executive Summary	12
1.1.	Product Introduction	12
1.2.	Conclusions on the Substantial Evidence of Effectiveness	13
1.3.	Benefit-Risk Assessment	13
2	Therapeutic Context	20
2.1.	Analysis of Condition	20
2.2.	Analysis of Current Treatment Options	21
3	Regulatory Background	22
3.1.	U.S. Regulatory Actions and Marketing History	22
3.2.	Summary of Presubmission/Submission Regulatory Activity	22
3.3.	Foreign Regulatory Actions and Marketing History	23
4	Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	23
4.1.	Office of Scientific Investigations (OSI)	24
4.2.	Product Quality	24
4.3.	Clinical Microbiology	25
4.4.	Nonclinical Pharmacology/Toxicology	27
4.5.	Clinical Pharmacology	28
4.5.1.	Mechanism of Action	28
4.5.2.	Pharmacodynamics	28
4.5.3.	Pharmacokinetics	29
4.6.	Devices and Companion Diagnostic Issues	32
4.7.	Consumer Study Reviews	32
5	Sources of Clinical Data and Review Strategy	32
5.1.	Tables of Clinical Studies	32
	CDER Clinical Review Template 2015 Edition	2
	<i>Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)</i>	

5.2.	Review Strategy.....	34
6	Review of Relevant Individual Trials Used to Support Efficacy.....	36
6.1.	Phase 2 and 3 Pooled Efficacy Study DataSet.....	36
6.1.1.	Study Design.....	36
6.1.2.	Study Results.....	42
6.2.	MAGELLAN-1 (M15-410).....	69
6.2.1.	Study Design.....	69
6.2.2.	Study Results.....	70
6.3.	EXPEDITION-4 (M15-462).....	77
6.3.1.	Study Design.....	77
6.3.2.	Study Results.....	79
7	Integrated Review of Effectiveness.....	82
7.1.	Assessment of Efficacy Across Trials.....	82
7.1.1.	Primary Endpoints.....	82
7.1.2.	Subpopulations.....	84
7.1.3.	Dose and Dose-Response.....	84
7.1.4.	Onset, Duration, and Durability of Efficacy Effects.....	84
7.2.	Additional Efficacy Considerations.....	84
7.2.1.	Considerations on Benefit in the Postmarket Setting.....	84
7.3.	Integrated Assessment of Effectiveness.....	85
8	Review of Safety.....	86
8.1.	Safety Review Approach.....	86
8.2.	Review of the Safety Database.....	87
8.2.1.	Overall Exposure.....	87
8.2.2.	Relevant characteristics of the safety population:.....	88
8.2.3.	Adequacy of the safety database:.....	90
8.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	90
8.3.1.	Issues Regarding Data Integrity and Submission Quality.....	90
8.3.2.	Categorization of Adverse Events.....	90

8.3.3. Routine Clinical Tests	90
8.4. Safety Results	91
8.4.1. Deaths	93
8.4.2 Serious Adverse Events	99
8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects	105
8.4.3. Significant Adverse Events	107
8.4.4. Treatment Emergent Adverse Events and Adverse Reactions	110
8.4.5. Laboratory Findings	113
8.4.6. Vital Signs	117
8.4.7. Electrocardiograms (ECGs).....	121
8.4.8. QT	122
8.4.9. Immunogenicity	122
8.5. Analysis of Submission-Specific Safety Issues	124
8.5.1. Hepatobiliary Events	124
8.5.2. Rash and Skin Disorders.....	134
8.5.3. Neuropsychiatric Disorders	138
8.5.6 Gastrointestinal Disorders	140
8.6. Safety Analyses by Demographic Subgroups	142
8.7. Specific Safety Studies/Clinical Trials	144
8.8. Additional Safety Explorations	158
8.8.1. Human Carcinogenicity or Tumor Development	158
8.8.2. Human Reproduction and Pregnancy.....	159
8.8.3. Pediatrics and Assessment of Effects on Growth	160
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	161
8.9. Safety in the Postmarket Setting.....	161
8.9.1. Safety Concerns Identified Through Postmarket Experience	161
8.9.2. Expectations on Safety in the Postmarket Setting	162
8.10. Integrated Assessment of Safety.....	162
9 Advisory Committee Meeting and Other External Consultations.....	164

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

10	Labeling Recommendations	164
10.1.	Prescribing Information	164
10.2.	Patient Labeling	176
10.3.	Nonprescription Labeling	176
11	Risk Evaluation and Mitigation Strategies (REMS)	176
11.1.	Safety Issue(s) that Warrant Consideration of a REMS	176
11.2.	Conditions of Use to Address Safety Issue(s)	176
11.3.	Recommendations on REMS	176
12	Postmarketing Requirements and Commitments.....	176
13	Appendices	177
13.1.	Appendix A: References.....	177
13.2.	Appendix B: Financial Disclosure	179
13.3.	Appendix C: Reported Hypertension Adverse Reactions Phase 2/3 Dataset, excluding those with renal impairment (<i>considered causal by Investigator</i>)	181
13.4.	Appendix D: Subjects with Potential Cardiovascular Events or Selected Symptoms and Systolic Blood Pressure Changes of ≥ 20 mmHg, Phase 2/3 safety dataset, excluding subjects with severe renal impairment	193
13.5.	Appendix E: Subjects with Potential Cardiovascular Events or Selected Symptoms and Diastolic Blood Pressure Changes of ≥ 10 mmHg, Phase 2/3 safety dataset excluding subjects with severe renal impairment	206

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table of Tables

Table 1 Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection 21
 Table 2 List of Phase 2 Trials Included in Review..... 32
 Table 3 List of Phase 3 Trials Included in Review..... 33
 Table 4 List of Clinical Trials Conducted with GLE/PIB to Support Efficacy in Subjects with HCV
 Genotype 1, 2, 3, 4, 5 or 6 Infection by Genotype 34
 Table 5 Protocol Violations 42
 Table 6 Baseline Demographic Characteristics..... 45
 Table 7 Baseline HCV Disease Characteristics Overall and By Genotype 46
 Table 8 Pooled SVR12 and virologic failure results for Treatment-naïve and Treatment-
 experienced- PRS subjects (excluding NS5A and/or NS3/4A PI inhibitor experienced subjects
 from MAGELLAN-1) who received GLE/PIB to-be-marketed dose levels in Phase 2 and 3 trials.
(Highlighted rows show data for regimens initially proposed by the sponsor for the label). 48
 Table 9 Genotype 1 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration,
 excluding NS3/4A PI- and NS5A Inhibitor-DAA Experienced Subjects enrolled in MAGELLAN -1
(data supporting final FDA recommended durations shown in red) 50
 Table 10 Genotype 2 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study
 Duration, *(pooled data supporting final FDA recommended durations shown in red)* 54
 Table 11 Genotype 3 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study
 Duration, *(data supporting final FDA recommended durations shown in red)* 57
 Table 12 ENDURANCE-3 Statistical Comparisons of SVR12..... 59
 Table 13 SURVEYOR-2 Genotype 3 SVR12 by Treatment Arm 59
 Table 14 GT3 Virologic Failures..... 61
 Table 15 Genotype 4 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study
 Duration, excluding NS3/4A PI- and NS5A Inhibitor-DAA Experienced Subjects enrolled in
 MAGELLAN -1 *(data supporting final FDA recommended durations shown in red)*..... 63
 Table 16 Genotype 5 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study
 Duration, *(data supporting final FDA recommended durations shown in red)* 66
 Table 17 Genotype 6 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study
 Duration, *(data supporting final FDA recommended durations shown in red)* 67
 Table 18 MAGELLAN-1 Baseline Characteristics/Demographics 71
 Table 19 MAGELLAN-1 SVR12..... 72
 Table 20 SVR12 for NS5A and/or NS3/4A PI Experienced Subjects by Treatment Duration 73
 Table 21 MAGELLAN-1 Subgroup Analysis..... 75
 Table 22 EXPEDITION-4 Demographic and Baseline Disease Characteristics (ITT)(N=104) 80
 Table 23 Proportion of Subjects Achieving SVR12 in EXPEDITION-4..... 81
 Table 24 SVR 12 by Recommended Treatment Duration, Pooled Analysis Phase 2/3 Efficacy
 Dataset 83
 Table 25 Development Program: Population and Size 88

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 26 Summary Demographic Characteristics, Phase 2/Phase 3 Safety Dataset, excluding M15-462 (severe renal impairment)	89
Table 27 Overall Safety Events by Duration	92
Table 28 Overall Safety Events by Cirrhosis Status.....	93
Table 29 Deaths in Phase 2 and 3 Safety Analysis Set	94
Table 30 Treatment-emergent SAEs by SOC and Cirrhosis Status in the Phase 2/3 Safety Dataset, excluding subjects with severe renal impairment.....	99
Table 31 Treatment-emergent SAEs by SOC and Dictionary Derived Term, where SOC >= 1% of the Cirrhotic sub-population.....	100
Table 32 Subjects with Discontinuations Due to Adverse Events in the Phase 2/3 Safety Data-Set, excluding subjects with severe renal impairment (shading indicates events considered causal).....	105
Table 33 Grade 3 and 4 Adverse Events Occurring in More than One Subject by Cirrhosis Status in the Phase 2/3 Safety Data-Set, excluding subjects with severe renal impairment.....	108
Table 34 Treatment-emergent AEs Reported ≥2*% of Subjects in Either Treatment Group Endurance-2 (M15-464), All Grades and All Causality.....	110
Table 35 Treatment-emergent ADRs Reported in ≥ 2%* of Subjects, All Grades	112
Table 36 Abnormalities in key chemistry parameters by highest toxicity grade, ENDURANCE -2 (M-15464), placebo controlled study	113
Table 37 Abnormalities in key chemistry parameters by highest toxicity grade, Phase 2/3 Safety Dataset	114
Table 38 Abnormalities in key hematology parameters by highest toxicity grade, ENDURANCE -2 (M-15464), placebo controlled.....	116
Table 39 Abnormalities in key chemistry parameters by highest toxicity grade, Phase 2/3 Safety Dataset, excluding subjects with severe renal disease	117
Table 40 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ABT-493 400 MG + ABT-530 120 MG and ABT-493 600 MG + ABT-530 240 MG and the Largest Lower Bound for Moxifloxacin 400 mg (FDA Analysis).....	122
Table 41 Liver Laboratories Subject 206205.....	126
Table 42 Cases of Hepatocellular Carcinoma	133
Table 43 HLGT Epidermal and Dermal Conditions, Angioedema and Urticaria for Phase 2/3 Safety Dataset	135
Table 44 Angioedema and Urticarial Events, Phase 2/3 Safety Dataset	136
Table 45 Treatment Emergent Neuropsychiatric Disorders, Phase 2/3 Safety Dataset	138
Table 46 Treatment Emergent Gastrointestinal Disorders.....	141
Table 47 Overview of Adverse Events by Age Phase 2/3 Safety Dataset.....	142
Table 48 Overview of Adverse Events by Sex Phase 2/3 Safety Dataset.....	142
Table 49 Overview of Adverse Events by Race Phase 2/3 Safety Dataset	143
Table 50 EXPEDITION-4 Safety Summary	145
Table 51 SAEs occurring in at least 1 Subject, Trial EXPEDITION-4	146

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Table 52 Treatment-Emergent AEs in ≥5% of subjects, all severity and irrespective of causality, EXPEDITION-4.....	151
Table 53 Treatment-Emergent Grade 3 and 4 AEs in ≥2 subjects irrespective of causality, EXPEDITION-4.....	151
Table 54 Related AEs in ≥ 2 subjects, all severity, EXPEDITION-4	152
Table 55 Treatment-emergent abnormalities* in key chemistry parameters by highest toxicity grade, EXPEDITION-4	153
Table 56 Treatment emergent abnormalities* in key hematology parameters by highest toxicity grade, EXPEDITION-4	154
Table 57 Subjects with Neoplasms Benign, Malignant, and Unspecified Phase 2/3 Dataset, excluding those with renal failure	158

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Table of Figures

Figure 1 M15-610 MAGELLAN-1 Trial Design 69
Figure 2 GLE Inhibition of Human Proteases in Biochemical Assays 123
Figure 3 Liver Laboratories Results Ratio to ULN Subject 206205 127

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Glossary

AE	adverse event
APRI	aspartate aminotransferase: platelet ratio index
AUC	area under the concentration-time curve
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHC	Chronic Hepatitis C
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
CTP	Child-Turcotte- Pugh score
CYP	cytochrome P450
DAA	direct acting antiviral
DMC	data monitoring committee
DDI	drug-drug interaction
DILI	drug-induced liver injury
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ECI	event of clinical interest
FDA	Food and Drug Administration
FDC	fixed-dose combination
FU	follow up
GLE	glecaprevir
GT	genotype
HCV	hepatitis C virus
ICH	International Conference on Harmonization
IND	Investigational New Drug
IFN	interferon alfa
ITG	immediate treatment group
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease score
NC	noncirrhotic
NDA	new drug application
NME	new molecular entity

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

OSI	Office of Scientific Investigation
OTVF	on treatment virologic failure
PD	pharmacodynamics
PI	protease inhibitor
PIB	pibrentasvir
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
P/R	regimens containing interferon, pegylated interferon, and ribavirin
PRS	regimens with interferon, pegylated interferon, ribavirin, and/or sofosbuvir
PREA	Pediatric Research Equity Act
PT	Preferred Term (aka Dictionary Derived Term)
RBV	ribavirin
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOF	sofosbuvir
SVR	sustained virologic response
TE	treatment experienced
TEAE	treatment emergent adverse event
TN	treatment naïve
TW	treatment week
US	United States

1 Executive Summary

1.1. Product Introduction

Glecaprevir (GLE) and pibrentasvir (PIB) is a fixed-dosed combination (FDC) tablet that contains two new molecular entities (NMEs). GLE is a hepatitis C virus (HCV) NS3/4A protease inhibitor (PI) and PIB is an HCV NS5A inhibitor, neither of which is available as a single drug. The proposed indication is for treatment of chronic HCV genotype (GT) 1 through 6 infection in adults, including those with severe renal disease, HIV-co-infection and a subpopulation of those with GT1 infection with previous HCV directly acting antiviral therapy. The recommended dosage is three (100 mg/40 mg) tablets taken orally with food once daily. The originally proposed treatment duration is dependent upon prior treatment experience and GT.

The original proposed dosage regimens and durations for HCV mono-infected and HCV/HIV-1 co-infected patients including those with severe renal disease were as follows:

Treatment-Naïve:

- **GT1-6 without cirrhosis:** 8 weeks
- **GT1-6 with compensated (Childs Turcotte Pugh A) cirrhosis:** 12 weeks

Treatment-Experienced:



NOTE: BOC = boceprevir; GLE = glecaprevir; GT = genotype; NS5A = nonstructural protein 5A; PIB = pibrentasvir; P/R = regimens containing interferon, pegylated interferon, and/or ribavirin; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; TE = treatment-experienced; TVR = telaprevir

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Application contains substantial evidence of effectiveness required by law 21 CFR 314.126(a)(b) to support approval of GLE/PIB for treatment of chronic HCV GT 1 to 6 infection in adults with and without compensated Child-Turcotte-Pugh (CTP) A cirrhosis, including in those with severe renal impairment and HCV/HIV-1 co-infection. In addition, the Application contains substantial evidence of effectiveness to support an indication for patients with HCV GT1 infection and prior treatment experience with NS5A inhibitors or NS3/4A protease inhibitors (but not both).

Phase 2 and Phase 3 trials evaluated GLE/PIB in various subpopulations, including GT 1- 6 infected subjects, cirrhotics and non-cirrhotics, HCV/HIV-1 coinfecting subjects, those with severe renal impairment, and treatment naïve (TN) and treatment experienced (TE) subjects. The overall sustained virologic response (SVR12) rates, considered a virologic cure, across trials for the durations recommended by the FDA review team were 91-100%. The number of GT 1- 4 infected subjects studied and the effectiveness of GLE/PIB for these genotypes was adequate for the recommended durations of 8 weeks for patients without cirrhosis and 12 weeks for those with compensated (CTP A) cirrhosis. The number of genotype 5 and 6 subjects and efficacy in this subpopulation was sufficient to support an indication for 12 weeks for patients without and with compensated CTP A cirrhosis. In addition, the NDA contained sufficient data to support an indication for patients with GT1 infection and treatment experience with NS5A inhibitors or NS3/4A protease inhibitors.

However, the data were too limited to support approval of GLE/PIB for 8 weeks duration for treatment-naïve subjects without cirrhosis with HCV GT 5 (n=2) or GT 6 (n=9) infection. However, there were adequate data to support approval of a 12 week duration for treatment naïve HCV GT 5 (n=22) and GT 6 (n=28) patients without cirrhosis; the overall SVR12 rate was 100% for both genotypes. In order to shorten the duration from 12 weeks to 8 weeks in labeling, the Applicant must provide data on an adequate number of treatment-naïve HCV GT 5 or 6 subjects without cirrhosis who are successfully treated with GLE/PIB for 8 weeks duration.

The NDA also does not contain substantial evidence of effectiveness [REDACTED] (b) (4)

[REDACTED] given the lack of data submitted for other genotypes. Additionally, the NDA does not contain substantial evidence of effectiveness to support an indication for HCV GT1 patients with both NS5A inhibitor and NS3/4A protease inhibitor treatment experience.

1.3. Benefit-Risk Assessment

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

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 directly acting antiviral therapy (DAAs), patients with advanced chronic kidney disease (CKD), including those receiving hemodialysis and patients with HIV-co-infection.

HCV infection is a serious disease, affecting an estimated 3 million people in the U.S. and over 100 million people worldwide. Although often asymptomatic in early stages, if untreated, chronic HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. The current standard of care treatments for HCV GT 1-6 infection consist of oral direct-acting antivirals (DAAs) that result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in up to 93-99% of patients. However, a major treatment gap remains for CKD receiving dialysis in patients infected with GTs 2, 3, 5 and 6 as no IFN-sparing regimens are currently available for this patient population. Additionally, treatment options are needed for patients who have failed DAA-only treatment, such as NS5A inhibitor-containing regimens or NS3/4A inhibitor-containing regimens.

GLE/PIB demonstrated SVR12 rates ranging from 91-100% for treatment durations recommended by the FDA review team. SVR rates varied depending on the regimen, 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 as little as 8 weeks for HCV GT 1-4 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. Additionally, there were too few treatment-naïve, non-cirrhotic subjects with GT 5 or 6 infection evaluated for an 8-week duration, although there were sufficient data to recommend a 12 week duration for both cirrhotic and non-cirrhotic subjects with GT 5 or 6 infection.

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 ADRs and occurred at greater than or equal to 5% in ENDURANCE-2, the 12 week placebo controlled study of subjects without severe renal impairment. All ADRs, except fatigue and asthenia, occurred at higher rates in the GLE/PIB arm of the placebo

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

controlled trial. They 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 only one serious adverse event, transient ischemic attack, considered by the Investigator as reasonably related to the study drug. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.3% (7/2,265). In subjects with severe renal impairment, ADRs observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with GLE/PIB were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with GLE/PIB who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). No subjects experienced a serious adverse reaction. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 2%.

The safety in EXPEDITION-4, which evaluated GLE/PIB for 12 weeks duration in subjects with chronic Stage 4 and Stage 5 renal disease, 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 subjects treated with GLE/PIB who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). The proportion of 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. 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, or 4 subjects without cirrhosis for 8 weeks

GTs 1, 2, 3, or 4 with compensated Cirrhosis (Child-Pugh A) for 12 weeks

GT5 or 6 with or without Compensated cirrhosis 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 or 4 without cirrhosis for 8 weeks

GT1, 2 or 4 with compensated cirrhosis for 12 weeks

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

GT3 with or without cirrhosis for 16 weeks
GT5 or 6 with or without compensated cirrhosis 12 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 100 million people are infected with HCV, including approximately 3 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 ($\leq 1\%$) in the U.S. but may predominate in other parts of the world. • HCV infection is typically asymptomatic in its early stages. However, if left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the U.S.	If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population. Patients can experience symptoms that are severe and debilitating. HCV infection is a significant and growing public health concern.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Current Treatment Options</u>	• 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 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.	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons																																																																																																																				
Benefit	- 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 coinfection status.	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.																																																																																																																				
	<table border="1"> <thead> <tr> <th colspan="6"> % 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> </thead> <tbody> <tr> <td rowspan="6">1</td> <td>TN</td> <td>NC</td> <td>99%</td> <td></td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>NC</td> <td>99%</td> <td></td> <td></td> </tr> <tr> <td>TN</td> <td>C</td> <td></td> <td>97%</td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>C</td> <td></td> <td>96%</td> <td></td> </tr> <tr> <td>TE- NS3/4A PI (NS5A inhibitor naïve)</td> <td>NC/C</td> <td></td> <td>92%</td> <td></td> </tr> <tr> <td>TE- NS5A inhibitor (NS3/4A PI naïve)</td> <td>NC/C</td> <td></td> <td></td> <td>94%</td> </tr> <tr> <td rowspan="4">2</td> <td>TN</td> <td>NC</td> <td>99%</td> <td></td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>NC</td> <td>91%</td> <td></td> <td></td> </tr> <tr> <td>TN</td> <td>C</td> <td></td> <td>100%</td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>C</td> <td></td> <td>100%</td> <td></td> </tr> <tr> <td rowspan="4">3</td> <td>TN</td> <td>NC</td> <td>95%</td> <td></td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>NC</td> <td></td> <td></td> <td>96%</td> </tr> <tr> <td>TN</td> <td>C</td> <td></td> <td>99%</td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>C</td> <td></td> <td></td> <td>94%</td> </tr> <tr> <td rowspan="4">4</td> <td>TN</td> <td>NC</td> <td>92%</td> <td></td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>NC</td> <td>100%</td> <td></td> <td></td> </tr> <tr> <td>TN</td> <td>C</td> <td></td> <td>100%</td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>C</td> <td></td> <td>100%</td> <td></td> </tr> <tr> <td rowspan="2">5</td> <td>TN</td> <td>NC</td> <td></td> <td>100%</td> <td></td> </tr> <tr> <td>TE-PRS</td> <td>NC</td> <td></td> <td>100%</td> <td></td> </tr> </tbody> </table>	% SVR12 by Recommended Treatment Duration						GT	Treatment Experience	Cirrhotic Status	GLE/PIB x 8 w	GLE/PIB x 12 w	GLE/PIB x 16 w	1	TN	NC	99%			TE-PRS	NC	99%			TN	C		97%		TE-PRS	C		96%		TE- NS3/4A PI (NS5A inhibitor naïve)	NC/C		92%		TE- NS5A inhibitor (NS3/4A PI naïve)	NC/C			94%	2	TN	NC	99%			TE-PRS	NC	91%			TN	C		100%		TE-PRS	C		100%		3	TN	NC	95%			TE-PRS	NC			96%	TN	C		99%		TE-PRS	C			94%	4	TN	NC	92%			TE-PRS	NC	100%			TN	C		100%		TE-PRS	C		100%		5	TN	NC		100%		TE-PRS	NC		100%	
	% SVR12 by Recommended Treatment Duration																																																																																																																					
	GT	Treatment Experience	Cirrhotic Status	GLE/PIB x 8 w	GLE/PIB x 12 w	GLE/PIB x 16 w																																																																																																																
	1	TN	NC	99%																																																																																																																		
		TE-PRS	NC	99%																																																																																																																		
		TN	C		97%																																																																																																																	
		TE-PRS	C		96%																																																																																																																	
		TE- NS3/4A PI (NS5A inhibitor naïve)	NC/C		92%																																																																																																																	
		TE- NS5A inhibitor (NS3/4A PI naïve)	NC/C			94%																																																																																																																
2	TN	NC	99%																																																																																																																			
	TE-PRS	NC	91%																																																																																																																			
	TN	C		100%																																																																																																																		
	TE-PRS	C		100%																																																																																																																		
3	TN	NC	95%																																																																																																																			
	TE-PRS	NC			96%																																																																																																																	
	TN	C		99%																																																																																																																		
	TE-PRS	C			94%																																																																																																																	
4	TN	NC	92%																																																																																																																			
	TE-PRS	NC	100%																																																																																																																			
	TN	C		100%																																																																																																																		
	TE-PRS	C		100%																																																																																																																		
5	TN	NC		100%																																																																																																																		
	TE-PRS	NC		100%																																																																																																																		

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Dimension	Evidence and Uncertainties						Conclusions and Reasons
	6	TN/TE-PRS	C		100%		
		TN	NC		100%		
		TE-PRS	NC		100%		
		TN	C		100%		
		TE-PRS	C		100%		
	NC=non-cirrhotic; C=cirrhotic; PRS= treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, PI=protease inhibitor						
<u>Risk</u>	- 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.						GLE/PIB demonstrated an overall favorable safety profile.
<u>Risk Management</u>	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.						Safety concerns associated with GLE and PIB are adequately addressed in product labelling.

2 Therapeutic Context

Analysis of Condition

Chronic infection with hepatitis C virus (HCV) is a global health problem affecting an estimated 130-150 million people worldwide, including approximately 3 to 5 million people in the United States (US). At least seven different HCV GTs have been identified, numbered 1 to 7, with further breakdown into subtypes for several of the known GTs (e.g., GT 1 subtypes 1a and 1b).[1] In the US, GT 1 is the most common (70-75%; mostly subtype 1a), followed by GT 2 (11%), GT 3 (9%), and GT 4 (6%). GTs 5 and 6 occur uncommonly ($\leq 1\%$) in the US but may predominate in other parts of the world.[1-3]

HCV is a leading cause of chronic liver disease and is currently the most common reason for liver transplantation in the US. The natural history of chronic HCV (CHC) typically involves an asymptomatic period in the early stages with progression to cirrhosis, hepatocellular carcinoma (HCC), liver failure, or death, if left untreated. Once cirrhosis is established, complications such as jaundice, ascites, variceal hemorrhage, and encephalopathy may develop which defines decompensated cirrhosis, or end-stage liver disease. In patients with decompensated cirrhosis, the 5-year survival rate is approximately 50%.[4, 5]

The ultimate goal of HCV treatment is to reduce the occurrence of end-stage liver disease and its related complications by achieving a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the completion of treatment (SVR12). SVR12 is generally considered a virologic cure. Achieving sustained HCV viral eradication through successful HCV treatment is associated with improvements in clinical outcomes such as decreased development of HCC, hepatic events, fibrosis, and all-cause mortality.[6-8]

Over the past five years, numerous direct acting antiviral (DAA) agents have been approved for the treatment of chronic HCV infection, initially in combination with pegylated interferon and ribavirin (PR). Treatment with these early regimens resulted in substantially higher SVR rates than PR alone, but the toxicity of PR, particularly the interferon component, made these regimens suboptimal. More recently approved all-oral DAA regimens have demonstrated high SVR12 rates without use of interferon, and in many cases, without ribavirin (RBV).

However, the approved regimens are not equally effective across all HCV genotypes and subpopulations. Limitations of some current regimens include the requirement of ribavirin (RBV) for certain populations, significant drug to drug interactions, limited options for subjects with renal insufficiency, reduced efficacy in patients with baseline amino acid polymorphisms

associated with reduced susceptibility to the HCV nonstructural viral protein 5A (NS5A) inhibitors or nonstructural viral protein 3/4A (NS3/4A) protease inhibitors (PIs), and limited options for patients who have failed DAA- IFN-free treatment regimens. Historically, efficacy in GT3-infected patients, particularly those who are treatment-experienced (TE) and/or cirrhotic, has been less than optimal and substantially less than what is observed for other genotypes.

In the current NDA, the Applicant seeks approval of GLE/PIB for the treatment of HCV GT 1-6 in subjects with or without compensated cirrhosis including those with severe renal insufficiency and prior treatment with DAA or INF-based regimens.

2.2. Analysis of Current Treatment Options

Treatment with interferon (IFN)-sparing DAA regimens is the current standard-of-care for all HCV GTs. Table 1 provides a brief synopsis of single agents and fixed-dose combination products that are approved for use without IFN. For additional details regarding the specific populations that are indicated (e.g. patients with cirrhosis or undergoing liver transplant), please refer to the complete prescribing information for the product of interest.

Table 1 Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection

Product (s) Name	Product Class	HCV GT	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Sofosbuvir and Velpatasvir (Epclusa®)	NS5B inhibitor, NS5A inhibitor	1-6	2016	One tablet orally once daily for 12 weeks	SVR 94-99%	HBV reactivation; Serious symptomatic bradycardia when coadministered with amiodarone
Elbasvir and grazoprevir (Zepatier®)	NS5A inhibitor, NS3/4A protease inhibitor (PI)	1, 4	2016	1 tablet orally once daily with or without RBV for 12 or 16 weeks	SVR 94-97%	HBV reactivation; Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients. Approved for use in subjects with CKD including patients with hemodialysis (GT1,4).
Ombitasvir, paritaprevir and ritonavir (Technivie®)	NS5A inhibitor, NS3/4A PI, PK enhancer	4	2015	2 tablets orally once daily with RBV for 12 weeks	SVR 100%	HBV reactivation; Hepatic decompensation and hepatic failure in cirrhotics; ALT elevation in all patients
Daclatasvir (Daklinza®)	NS5A inhibitor	1, 3	2015	1 tablet orally with sofosbuvir and with or without RBV for 12 weeks	SVR 82-97%	HBV reactivation; No serious drug-specific toxicity identified
Ledipasvir and sofosbuvir (Harvoni®)	NS5A inhibitor/ NS5B inhibitor (nucleotide)	1, 4, 5, 6	2014	1 tablet orally once daily with or without RBV for 8, 12, or 24 weeks	SVR 93-99%	HBV reactivation ;Serious symptomatic bradycardia when coadministered with amiodarone

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Product (s) Name	Product Class	HCV GT	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Dasabuvir, ombitasvir, paritaprevir and ritonavir (Viekira Pak®)	NS5B inhibitor (non-nucleoside), NS5A inhibitor, NS3/4A PI	1	2014	2 FDC tablets once daily + 1 dasabuvir tablet twice daily (+/- RBV) for 12 or 24 weeks	SVR 95-99%	HBV reactivation; Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients
Sofosbuvir (Sovaldi®)	NS5B inhibitor (nucleotide)	2, 3	2013	One tablet orally once daily with RBV for 12 or 24 weeks	SVR 82-95%	HBV reactivation ; Serious symptomatic bradycardia when coadministered with amiodarone
Simeprevir (Olysio®)	NS3/4 PI	1	2013	1 capsule orally once daily (with sofosbuvir) for 12 or 24 weeks	SVR 93-97%	HBV reactivation; Hepatic decompensation and hepatic failure; photosensitivity; rash

Source: Product labeling.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

GLE/PIB contains two NMEs and neither component is currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

AbbVie Inc. submitted an initial IND application for GLE (IND 116169) and for PIB (IND 116170) for treatment of chronic HCV infection on October 15, 2012. Development of the combination of GLE and PIB occurred under IND 127416. This section describes key events or activities that occurred under IND 127416 during the GLE and PIB clinical development program prior to submission of the NDA.

Fast Track Designation

On January 24, 2013, FDA granted AbbVie's request for Fast Track designation for the development program of GLE (IND 116169) and PIB (IND116170) in combination with other Direct Acting Antiviral Agents (DAAs), for the treatment of chronic hepatitis C virus infection.

Breakthrough Therapy Designation

On April 21, 2016, FDA granted AbbVie's request for Breakthrough Therapy designation for treatment of chronic HCV infection in the GT1 DAA-experienced patient population due to the unmet medical need in this patient population. As such, this application was given a Priority Review.

End-of-Phase 2 Meeting

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

FDA and the Applicant agreed upon the adequacy of the clinical pharmacology data to transition to Phase 3; Phase 3 virology approach, dose and duration selection, overall design of Phase 3 studies. FDA indicated the adequacy of proposed size and design of safety database to support the New Drug Application. FDA reinforced the desire to have several populations, including HIV coinfecting subjects included in the clinical trial population. Preliminary comments provided to the Applicant were sufficient, and the Applicant cancelled the meeting.

Pre-NDA Meeting

On November 3, 2016 FDA and Applicant met to gain alignment on the adequacy of the clinical data to support an NDA for the combination regimen of glecaprevir (ABT-493, GLE) and pibrentasvir (ABT-530, PIB). FDA and the Applicant had preliminary discussions on proposed dosing recommendations, including treatment durations for the studied populations; the FDA indicated that treatment durations for the different genotypes and subpopulations remained a review issue.

During the pre-NDA meeting, FDA recommended the Applicant form an external expert hepatic panel to evaluate a subset of 10 subjects who had total bilirubin (tbili) $\geq 2xULN$ and direct/tbili ratio >0.4 (7 subjects); had ALT $> 3xULN$ and tbili $\geq 2xULN$ (2 subjects); had ALT increase $> 5xULN$ (3 subjects); met the hepatic decompensation/hepatic failure pre-defined criteria (1 subject), and provide the assessment to the Division very early in the review cycle, and later in the review cycle to provide an assessment of all subjects with a tbili $\geq 2xULN$. The Applicant agreed to these recommendations.

3.3. Foreign Regulatory Actions and Marketing History

GLE/PIB is not currently marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

No additional significant issues were identified.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

4.1. Office of Scientific Investigations (OSI)

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. Multinational trials were necessary because the prevalence of HCV GTs varies between geographic regions, and including trial sites around the world enables greater accrual of subjects with HCV GTs that are uncommon in the US. It is desirable to include foreign sites in the OSI inspections to verify the quality of conduct of the trials.

Six of the clinical sites, including two foreign sites, had no regulatory findings. The remaining two sites had Voluntary Action Indicated classifications, one of which is final and the other is pending. 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 sponsor under this NDA.

4.2. Product Quality

The commercial GLE/PIB drug product is an immediate release fixed-dose combination bilayer tablet containing 100 mg of glecaprevir in one layer and 40 mg of pibrentasvir in the other layer for once daily oral administration. The proposed dosing regimen consists of a total daily dose of glecaprevir/pibrentasvir 300 mg/120 mg (or three 100 mg/40 mg tablets daily).

The tablets are pink, oblong-shaped, film-coated, and debossed with "NXT" on one side. The tablets include the following inactive ingredients: copovidone (type K 28), vitamin E (tocopherol) polyethylene glycol succinate, colloidal silicon dioxide, propylene glycol monacrylate (type II), croscarmellose sodium, sodium stearyl fumarate, hypromellose 2910, lactose monohydrate, titanium dioxide, polyethylene glycol 3350 and iron oxide red. The tablets do not contain gluten. The approximate dimensions of each tablet are: length 18.8 mm, width 10.0 mm, and thickness 6.8 mm.

The GLE/PIB tablets will be dispensed in a 4-week (monthly) or 8-week carton. Each weekly carton contains seven daily dose wallets. Each child resistant daily dose wallet contains three 100 mg/40 mg glecaprevir/pibrentasvir tablets. The products should be stored at or below 30°C (86°F).

The film-coated GLE/PIB 100 mg/40 mg co-formulated tablet (Phase 3 formulation) is the proposed commercial formulation and was used in all Phase 3 studies and in select Phase 1 studies. In addition to the Phase 3 formulation, GLE and PIB were administered as individually formulated first-in-human (FIH), Phase 2a (Ph2a), and Phase 2b (Ph2b) tablets in various Phase

CDER Clinical Review Template 2015 Edition
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

1 and 2 studies. Several other experimental formulations of individually- or co-formulated GLE and PIB were evaluated in bioavailability studies only.

Please refer to the Office of Product Quality (OPQ) Reviews by Dr. Danuta Gromek-Woods, Dr. Balajee Shanmugam, Dr. Raymond Frankewich, Dr. Kasturi Srinivasachar, Dr. Ying Wang and Dr. Upinder Atwal for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for GLE/PIB. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.3. **Clinical Microbiology**

This section provides a brief summary of key glecaprevir and pibrentasvir nonclinical virology characteristics to support clinical trials evaluating this combination regimen. Specific discussions of clinical virology assessments conducted during the pivotal trials, development of resistance, impact of baseline NS5A resistance associated polymorphisms, and consequences of virologic failure, are provided in Sections 6 and 7 (clinical efficacy).

Hepatitis C virus is a small, positive-strand RNA virus belonging to the Flaviviridae family. At least seven HCV genotypes (GT) have been identified, numbered GT 1 to 7, with further breakdown into subtypes for several of the known GTs (e.g. GT1 subtypes 1a and 1b). DAAs act by inhibiting viral proteins involved in RNA replication. Despite having similar targets, various DAAs of the same class (e.g. NS3/4 PIs, NS5A inhibitors), may have differential degrees of activity across the various HCV GTs.

Mechanism of Action

GLE is an inhibitor of the HCV NS3/4A protease, which mediates cleavage of the HCV encoded polyprotein and is essential for viral replication.

PIB is an inhibitor of HCV NS5A protein, which is a viral phosphoprotein essential for HCV replication.

Antiviral Activity in Biochemical Assays and Cell Culture

Glecaprevir

In biochemical assays, GLE inhibited the activity of recombinant NS3/4A protease enzymes from HCV genotype/subtypes 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a, with IC50 values of 3.5-11.3 nM. In cell culture assays, GLE inhibited the replication of HCV replicons carrying NS3 protease genes from HCV subtypes 1a, 1b, 2a, 2b, 3a, 4a and 6a, with EC50 values of 0.85-4.6 nM, and a therapeutic index of approximately 85,000. GLE also had consistent, sub- to low nanomolar activity against a panel of transient HCV replicons derived from clinical isolates.

CDER Clinical Review Template 2015 Edition

25

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

In cell culture resistance selection studies, GLE exposure of HCV replicons from HCV subtypes 1a, 1b, 3a, 4a or 6a resulted in the emergence of amino acid substitutions in NS3. The most common substitutions observed occurred at NS3 amino acid position A156, which is a known NS3/4A PI resistance-associated position. The selection of amino acid substitutions at this position, in addition to others (e.g. Y56 and D/Q168) indicates that GLE has at least partially overlapping resistance mechanisms with other HCV NS3/4A PIs.

Analyses of HCV replicons demonstrated that GLE maintained activity against replicons harboring individual amino acid substitutions at certain NS3 positions commonly associated with resistance to other NS3/4A PIs, including positions V36, Y56, Q80 and R155. However, GLE activity was reduced by amino acid substitutions at NS3 positions A156 and D168 (or Q168 for GT3), in some cases by as much as >1,000-fold, consistent with the emergence of substitutions at these positions in GLE-selected replicons. Certain combinations of amino acid substitutions, including these key positions, further reduced GLE anti-HCV activity.

Pibrentasvir

PIB inhibited the replication of HCV replicons carrying NS5A genes from genotype/subtypes 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a, with EC₅₀ values of 1.4-5 pM, and a therapeutic index >10,000,000. PIB was also shown to have consistent, sub- to low pM activity against a panel of transient HCV replicons derived from clinical isolates. In cell culture combination studies, PIB had non-antagonistic antiviral activity with other anti-HCV agents including GLE (NS3/4A PI), SOF (uridine nucleotide analogue NS5B polymerase inhibitor), and RBV.

In cell culture resistance selection studies, PIB exposure of HCV GT1a or GT1b replicons resulted in the emergence of amino acid substitutions in NS5A of GT1a replicons, but no PIB-resistant GT1b replicons were selected. PIB-resistant GT1a replicons primarily carried an NS5A Y93H substitution, while a few clones had emergent NS5A Q30D, Q30-deletion, Y93N, or H58D + Y93H substitutions. All of these substitutions occurred at known NS5A inhibitor resistance-associated positions, confirming that PIB is an NS5A inhibitor, and also indicating that PIB has at least partially overlapping resistance mechanisms with other NS5A inhibitors. Similar PIB resistance selection and characterization studies were conducted for replicons harboring NS5A genes from non-GT1 isolates, which again showed resistance selection at known resistance-associated positions, although, in general, few drug-resistant clones were obtained.

Analyses of HCV replicons engineered to carry specific NS5A amino acid substitutions demonstrated that PIB maintained activity against replicons harboring various single amino acid substitutions associated with resistance to NS5A inhibitors. Among all of the site-directed mutant replicons evaluated across all HCV GTs, the only single NS5A amino acid substitutions that reduced PIB activity ≥ 10 -fold were M28G and Q30D in GT1a, and P29-deletion and P32-deletion in GT1b. Nevertheless, with the exception of the P32-deletion PIB remained active at

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

picomolar levels against these replicons. The presence of two or more NS5A inhibitor resistance-associated substitutions had a greater impact on PIB activity, indicating that combinations of substitutions can act synergistically to confer resistance to PIB.

Please refer to Dr. Patrick Harrington's Clinical Virology review for additional details.

4.4. **Nonclinical Pharmacology/Toxicology**

This section provides a brief review of key outcomes of the pharmacology/toxicology program. Please see the primary nonclinical review by Ilona Bebenek for complete details.

Glecaprevir

The oral bioavailability of GLE was 90% in the rat, 44% in the dog and 25% in the monkey. In vitro protein binding was >99% in all species and >97.5% in human. In radiolabeled testing, GLE was widely distributed with the highest concentrations being found in the liver in the rat. GLE does not readily cross the blood:brain barrier, blood:eye barrier, blood:testis barrier or bind to melanin. In a clinical single dose study of GLE 800 mg once daily for 10 days in healthy volunteers (M13-356), the metabolite profile of the pooled plasma determined that GLE was the major component; there were no significant circulating clinical metabolites (e.g., >10% of total drug-related exposure) requiring non-clinical safety assessment. Elimination primarily occurred through the biliary route in rats and humans. GLE was transferred to rat pups during lactation.

GLE was not associated with clinically relevant adverse effects on cardiovascular, neurological, or respiratory endpoints evaluated in safety pharmacology studies. No clinically relevant adverse effects were observed in pivotal repeat-dose general toxicology studies; clinically relevant non-adverse effects included elevated ALT and GGT levels in dog. GLE was not considered genotoxic based on negative results in the in vitro bacterial mutation assay, in vitro mammalian chromosome aberration assay, and in vivo rat micronucleus assay. Because GLE was not genotoxic and will be administered to humans for, at longest, a 16 week duration, carcinogenicity studies were not required. There were no clinically relevant adverse effects on male or female fertility, embryofetal development, or pre/post-natal development in rats.

Pibrentasvir

The oral bioavailability of GLE was 7.9% in the rat, 30% in the dog and 14% in the monkey. In vitro protein binding was >99% in all species and in humans. In radiolabeled testing, PIB was widely distributed with the highest concentrations being found in the liver, kidney, fat, and large intestine in the rat. PIB does not readily cross the blood:brain barrier, blood:eye barrier, blood:testis barrier or bind to melanin. In a clinical single dose study of PIB 600 mg once daily

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

for 10 days in healthy volunteers, the metabolite profile of the pooled plasma determined that PIB was the major component, accounting for 98.% of total drug related materials; there were no significant circulating clinical metabolites requiring non-clinical safety assessment. Elimination primarily occurred through the biliary route in rats, dogs and humans. PIB was transferred to rat pups during lactation.

PIB was not associated with clinically relevant adverse effects on cardiovascular, neurological, or respiratory endpoints evaluated in safety pharmacology studies. No clinically relevant adverse effects were observed in pivotal repeat-dose general toxicology studies. PIB was not considered genotoxic based on negative results in the in vitro bacterial mutation assay, in vitro mammalian chromosome aberration assay, and in vivo rat micronucleus assay. Because PIB was not genotoxic and will be administered to humans for, at longest, a 16 week duration, carcinogenicity studies were not required. There were no clinically relevant adverse effects on male or female fertility in mice, embryofetal development in mice or rabbits, or pre/post-natal development in mice.

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.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

GLE is a nonstructural (NS) protein 3/NS protein 4A (NS3/4A) protease inhibitor of hepatitis C virus (HCV). PIB is an NS protein 5A (NS5A) inhibitor.

4.5.2. Pharmacodynamics

The final selection of the GLE and PIB doses was informed by the results of the monotherapy study M13-595. The results demonstrated that a GLE dose ≥ 100 mg QD or a PIB dose ≥ 40 mg QD achieved an approximately 4 log₁₀ viral load decline with 3 days of therapy among GT1-infected subjects. GLE exposures at a 300 mg dose and PIB exposures at 120 mg were expected to provide near maximal antiviral effect, and higher doses would not result in further meaningful reductions in HCV RNA.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

The proposed dosing regimen of 300 mg GLE/120 mg PIB QD is acceptable in the general population because high SVR12 (> 90%) rates were observed across HCV genotype 1-6 in both treatment naïve and treatment-experienced patients in the phase 2 and 3 trials. Exposure-response efficacy analyses based on the Phase 2 and 3 trials results could not identify a role of both GLE and PIB exposures on outcome, so assessments were instead based on Phase 2 dose-ranging results. Limited data from lower doses of GLE and PIB support that a decrease in response may be anticipated in more difficult to treat genotypes, such as genotype 3, with a 50% decrease in exposures. Exposure-response safety analyses based on the same data support the safety of 300 mg GLE/120 mg PIB in HCV-infected patients.

4.5.3. Pharmacokinetics

Adsorption

When co-administered with PIB under fed conditions, the T_{max} 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 T_{max} 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.

Distribution

GLE is approximately 97.5% bound to human plasma proteins, independent of concentration from 0.1 to 30 µM (800 to 25,200 ng/mL). Mean human blood-to-plasma ratio of GLE is 0.57. The steady state apparent volume of distribution is 170 L.

PIB is greater than 99.9% bound to human plasma proteins, independent of concentration from 0.1 to 30 µM (110 to 33400 ng/mL). Mean human blood-to-plasma concentration ratio of PIB is 0.62. The steady state apparent volume of distribution is 3630 L.

Metabolism

GLE exhibited limited metabolism in vitro, predominantly by CYP3A4/5, and to a much less extent by CYP2D6, CYP2C9, and CYP2C8. Metabolism plays a minimal role in the elimination of PIB.

Elimination

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Both GLE and PIB are predominantly excreted through the biliary-fecal route with 92.1 % and 96.6 % of the administered dose recovered in the feces, respectively. The terminal elimination half-life of GLE and PIB is 6 hours and 13 hours, respectively.

Intrinsic Factors

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. Currently there are no clinical data available for GLE/PIB in subjects with Child-Pugh B or C decompensated cirrhosis. Efficacy and safety of GLE/PIB in HCV infected subjects with Child-Pugh B decompensated cirrhosis should be established in clinical efficacy and safety trials in order to extend dosing recommendations to subjects with Child-Pugh B cirrhosis.

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 or patients with end-stage renal disease 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: 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

P-gp inducers: The co-administration of GLE/PIB with P-gp inducers results in 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. Moreover, following co-

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

administration with efavirenz, GLE and PIB exposures were more than 50% lower when compared to GLE/PIB exposures observed in healthy subjects. Therefore, the co-administration of GLE/PIB and P-gp inducers, including rifampin, carbamazepine, efavirenz, and St. John's wort, should be contraindicated.

HIV Protease Inhibitors: The co-administration of GLE/PIB with HIV protease inhibitors results in a significant increase in GLE and PIB exposures. Atazanavir (ATV)/ritonavir (RTV), lopinavir (LPV)/RTV, and darunavir (DRV)/RTV increased GLE AUC by 6.35-, 4.97-, and 4.38- fold respectively. ALT elevations were observed upon co-administration of GLE/PIB and ATV/RTV in healthy subjects. Based on these data, the co-administration of GLE/PIB and ATV/RTV should be contraindicated. There were no safety signals observed in the healthy volunteer studies of GLE/PIB with LPV/RTV or DRV/RTV, but due to GLE exposure increases the coadministration of GLE/PIB with these medications is not recommended. There is an ongoing trial M14-730 (EXPEDITION-2) in ^{(b) (4)} HCV/HIV-1 coinfecting subjects. Formal submission of M14-730 will be requested as a post-marketing requirement.

Cyclosporine: The administration of a single 100 mg cyclosporine dose increases GLE AUC by 37% and the administration of a single 400 mg cyclosporine dose increases GLE exposure by 5-fold. The exposure may be higher with multiple dosing; however, this was not evaluated in this DDI study. The co-administration of GLE/PIB with cyclosporine is not recommended due to GLE exposure increase.

Ethinyl Estradiol containing medications: The co-administration of GLE/PIB with two oral contraceptive medications containing ethinyl estradiol resulted in ALT elevations in healthy subjects. There were no changes in the exposure of GLE, PIB, or the components of oral contraceptive. The co-administration of GLE/PIB with medications containing ethinyl estradiol is not recommended.

Digoxin: The co-administration of GLE/PIB with digoxin increases digoxin AUC by 50%. Digoxin dose should be reduced by 50% when co-administered with GLE/PIB.

Dabigatran: The co-administration of GLE/PIB with dabigatran increases dabigatran AUC by 2.38-fold. Dabigatran dose should be reduced to 75 mg BID when co-administered with GLE/PIB in subjects with creatinine clearance between 30 and 50 mL/min. The co-administration of GLE/PIB with dabigatran should be avoided in subjects with creatinine clearance < 30 mL/min.

HMG-CoA Reductase Inhibitors: The co-administration of GLE/PIB with statins increases atorvastatin, simvastatin, simvastatin hydroxyl acid, lovastatin, lovastatin hydroxy acid, pravastatin, and rosuvastatin by 8.27-, 2.32-, 4.48-, 1.70-, 4.10-, 2.30-, and 2.15-fold, respectively. The co-administration of GLE/PIB with simvastatin, lovastatin, and atorvastatin is not recommended. When co-administered with GLE/PIB, pravastatin dose should be reduced

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

by 50% and rosuvastatin dose should not exceed 10 mg.

Please see the Clinical Pharmacology review by Dr. Amal Ayyoub for further details.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Tables of Clinical Studies

Table 2 and Table 3 contain a summary of all Phase 2 and Phase 3 trials, respectively, in the Applicant's clinical safety database for GLE and PIB that were submitted with this NDA. These data were used for safety analysis as described in Section 8 and a portion of these data were used for efficacy analysis as described below and in Section 6.

Table 2 List of Phase 2 Trials Included in Review

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	1 : SVR12 in ITT-PS 2 : SVR4, on-tx VF, post-tx relapse, both in ITT-PS

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

				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)	
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 : secondary endpoint, 1 : 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

Table 3 List of Phase 3 Trials Included in Review

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,	TN or TE-PRS	GLE/PIB 12w (n=104)	1 : SVR12 in ITT-PS 2 : On-tx VF, post-tx relapse, both

5 or dialysis,
 NC or C

in ITT-PS

R: randomized, MC: multi-center, 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 : secondary endpoint, 1 : primary endpoint, VF: virologic failure, CKD: chronic kidney disease, ITT-PS: intent-to-treat subset of HCV monoinfected DAA-naïve subjects, ITT-PS-PP: ITT-PS subset excluding subjects who prematurely discontinued prior to Week 8, subjects who experienced virologic failure prior to Week 8 (subjects with on treatment virologic failure before Day 52), subjects without virologic failure who had no HCV RNA value in the SVR12 visit window or later, and subjects who are SVR12 non-responders due to reinfection. **Table created by Drs. Usher and Tracy**

Table 4 summarizes the clinical trials discussed in this review according to genotype treatment history and cirrhosis status to support efficacy, and labeling in Dosage and Administration.

Table 4 List of Clinical Trials Conducted with GLE/PIB to Support Efficacy in Subjects with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection by Genotype

Genotype (GT)	Clinical Trial	Summary of Trial Design
TN and PRS-TE Subjects without Cirrhosis		
GT1	ENDURANCE-1	GLE/PIB for 8 (n=351) or 12 weeks (n=352)
GT2	SURVEYOR-2	GLE/PIB for 8 weeks (n=197)
GT3	ENDURANCE-3	GLE/PIB for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2	GLE/PIB for 16 (PRS-TE only) weeks (n=22)
GT4, 5, 6	ENDURANCE-4	GLE/PIB for 12 weeks (n=26, GT5; n=19, GT6)
	SURVEYOR-1	GLE/PIB for 12 weeks (n=1, GT5; n=11, GT6)
	SURVEYOR-2	GLE/PIB for 8 weeks (n=46, GT4)
TN and PRS-TE Subjects with Compensated Cirrhosis		
GT1, 2, 4, 5, 6	EXPEDITION-1	GLE/PIB for 12 weeks (n=146)
GT3	SURVEYOR-2	GLE/PIB for 12 weeks (TN only) (n=40) or 16 weeks (PRS-TE only) (n=47)
Subjects with CKD Stage 4 and 5 without Cirrhosis or with Compensated Cirrhosis		
GT1-6	EXPEDITION-4	GLE/PIB for 12 weeks (n=104)
NS5A Inhibitor or PI-Experienced Subjects without Cirrhosis or with Compensated Cirrhosis		
GT1	MAGELLAN-1	GLE/PIB for 12 (n=25) or 16 weeks (n=17)

TN=treatment naïve

PRS-TE= 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 protease inhibitor or NS5A inhibitor.

PI=protease inhibitor CKD=chronic kidney disease

Table created by Drs. Tracy and Usher.

5.2. Review Strategy

Dr. Lara Stabinski is the primary clinical reviewer for eight clinical trials presented in Section 8.7 [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

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

MAGELLAN-1 (M15-410)] evaluating subjects with compensated liver disease without severe renal impairment. Dr. Aimee Hodowanec is the primary clinical reviewer for the clinical trial evaluating subjects with severe disease renal disease [EXPEDITION-4 (M15-462)].

The clinical efficacy review is based on the nine pivotal Phase 2 and Phase 3 trials described in Section 5.1. The clinical reviewers along with the statistical and virology reviewers collaborated extensively during the review process, and a number of analyses included in this review were performed by the statistical reviewers, Drs. Laree Tracy and Therri Usher, and the virology reviewer, Dr. Patrick Harrington. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

This clinical review provides a complementary assessment of efficacy focused on clinically relevant genotype-specific efficacy and issues of trial design. Section 6 provides a review of the pooled Phase 2/3 data from across the registrational datasets. MAGELLAN-1, the single study including NS5A- and/or NS3/4A PI-experienced subjects, and EXPEDITION-4, including subjects with severe renal impairment, are also reviewed separately in this section. Please refer to statistics and virology reviews for further details on the nature of individual trial design, statistics and virology outcomes.

Only the primary efficacy endpoint, SVR12, will be discussed in detail in this review, accompanied by a discussion regarding virologic status of subjects who did not achieve SVR12 and a discussion regarding efficacy outcomes by HCV genotype and other relevant factors. Detailed analyses of other endpoints such as SVR4, percentage of subjects with HCV RNA < LLOQ while on treatment, and change from baseline in HCV RNA (log₁₀ IU/mL) through end of treatment (EOT), will not be discussed here but are presented in statistics and virology reviews. Because the trials are ongoing, SVR24 data are not available for a significant proportion of Phase 3 subjects, and therefore are not discussed this review.

The clinical safety review was primarily based on the nine aforementioned trials; data from ENDURANCE-1, EDURANCE-2, ENDURANCE-3, ENDURANCE-4, SURVEYOR-1, SURVEYOR-2, EXPEDITION-1 and MAGELLAN-1 were pooled to include only the trial arms that contained the dose and durations to support labeling and the comparator arms from ENDURANCE-2 (placebo) and ENDURANCE-3 (daclatasvir/sofosbuvir) to form the integrated Phase 2/3 safety dataset (n=2,265). Safety data from EXPEDITION-4 was analyzed separately, and is discussed in Section 8.7.

Drs. Stabinski and Hodowanec used JReview, JMP, and MAED software to conduct the safety

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

analyses presented in this review; any analyses performed by the Applicant or other members of the FDA review team will be labeled as such. This NDA was also a part of the JumpStart Program, which confirmed the data fitness and overall safety findings of the independent review.

6 Review of Relevant Individual Trials Used to Support Efficacy

Compliance with Good Clinical Practices

Each of the trials presented below was conducted under a US IND application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The trial protocols, amendments and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSI inspected selected clinical sites, which were all found acceptable. A detailed discussion of the OSI audit is available in the Clinical Inspection Summary by Dr. Antoine El-Hage.

Data Quality and Integrity: Sponsor's Assurance

The review team considered the Applicant's methods for assuring data quality and integrity to be adequate. These methods included investigator and study center staff training on the trial protocols and study-specific procedures, study site monitoring in accordance with ICH GCP guidelines, compliance audits of investigative sites, use of electronic case report forms (eCRFs), and use of data validation specifications along with manual data review. The Applicant reviewed eCRF data to verify protocol and GCP adherence, and to verify the data against source documentation. The Applicant confirmed that missing data, selected protocol deviations and other data inconsistencies were addressed prior to database finalization. Clinical laboratory data were transferred electronically to the Applicant using defined transfer specifications.

Phase 2 and 3 Pooled Efficacy Study DataSet

6.1.1. Study Design

Overview and Objective

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

The combination treatment regimen of once-daily (QD) glecaprevir (GLE, ABT-493) and pibrentasvir (PIB, ABT-530) at the dose of GLE 300 mg and PIB 120 mg (as coformulated tablets) was developed for use in treatment-naïve (TN) and treatment-experienced (TE) hepatitis C virus (HCV) genotype (GT) 1- to GT6-infected subjects with compensated liver disease (with or without cirrhosis), including subjects with chronic kidney disease (CKD) Stage 4 or 5 and subjects coinfecting with human immunodeficiency virus-1 (HIV-1).

Trials included in the Phase 2 and 3 Pooled Efficacy Study Dataset include 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), MAGELLAN-1 (M15-410) and EXPEDITION-4 (M15-462). MAGELLAN-1 (M15-410) and EXPEDITION-4 (M15-462) are also discussed separately in Section 6.2 and in Section 6.3, respectively.

Analysis of Trial Designs

The individual Phase 2 and 3 trials employed different and complementary study designs:

- **Comparison to historical control:** Studies ENDURANCE-1, ENDURANCE-2, and SURVEYOR-2 Part 4 evaluated primary efficacy compared to a historical SVR12 rate for the current standard-of-care direct-acting antiviral agent (DAA) regimen at the time of study start. A –6% margin was used for noninferiority to the historical rate in all of these comparisons. Of note, the statistical team did not agree with a noninferiority comparison compared to a historical rate, rather than an active comparator. Instead, the appropriate comparison is considered to be superiority of the lower bound of the 95% confidence interval to the historical threshold. Both analyses are discussed below, where appropriate.
- **Duration controlled:** ENDURANCE-1, ENDURANCE-3, SURVEYOR-2 (Part 3) and MAGELLAN-1 (Part 2) each implemented a duration-controlled study design evaluating either 8 weeks versus 12 weeks with a –5% margin (ENDURANCE-1), 8 weeks versus 12 weeks with a –6% margin (ENDURANCE-3), or 12 weeks versus 16 weeks without hypothesis testing (SURVEYOR-2 Part 3 and MAGELLAN-1 Part 2) of GLE/PIB.
- **Placebo-controlled:** ENDURANCE-2 was randomized, double-blind, and placebo-controlled, and enabled characterization of the GLE/PIB safety profile.
- **Active-controlled:** ENDURANCE-3 was randomized and compared 12 weeks of GLE/PIB versus 12 weeks of sofosbuvir (SOF) and daclatasvir (DCV) with a –6% noninferiority margin.
- **Open-label, single arm:** Additional studies employed single-arm, open-label, assigned

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

duration study designs among important subpopulations, including: (1) subjects with compensated (Child-Pugh Class A) cirrhosis (EXPEDITION-1 and SURVEYOR-2 Part 3), (2) subjects with CKD Stage 4 or 5 (EXPEDITION-4), and (3) HCV GT2-, GT4-, GT5-, and GT6-infected subjects without cirrhosis (ENDURANCE-4, 12-weeks of GLE/PIB in HCV GT4, GT5 or GT6; SURVEYOR-2 Part 4: 8 weeks of GLE/PIB in HCV GT2, GT4, GT5, or GT6).

A single, active comparator or historical control was not used across the registrational studies, because, at the time of study conduct, there was no single regimen that was approved across all HCV genotypes. During the conduct of ENDURANCE-2, treatment assignment remained blinded to the investigator, subject, study site personnel, and the Applicant. All other Phase 2 and 3 studies were open-label.

Randomization

Randomization was utilized in Studies ENDURANCE-2, ENDURANCE-3, ENDURANCE-1, SURVEYOR-2, and MAGELLAN-1. ENDURANCE-4, EXPEDITION-1, and EXPEDITION-4 were single-arm studies; therefore, no randomization was performed. SURVEYOR-1 also was not randomized.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria to define study populations were harmonized across the majority of registrational studies, and are described below.

Key Inclusion Criteria

Male or female, at least 18 years of age at time of screening

- Subject had positive anti-HCV antibody and plasma HCV RNA viral load $\geq 1,000$ IU/mL at screening
- Chronic HCV infection defined as 1 of the following:
 - Positive for anti-HCV antibody or HCV RNA at least 6 months before screening; or
 - A liver biopsy consistent with chronic HCV infection; or
 - Abnormal alanine aminotransferase levels for at least 6 months before screening
- BMI is ≥ 18 kg/m² at the time of screening
- Voluntarily signed and dated an informed consent form, approved by an institutional Review Board/Independent Ethics Committee prior to the initiation of any screening or study specific procedures
- Able to understand and adhere to the study visit schedule and all other protocol requirements

Key Exclusion Criteria

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

38

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

- History of severe, life-threatening or other significant sensitivity to excipients of the study drug
- Positive test result at screening for hepatitis B surface antigen (all studies) or anti-HIV-1 antibody (except ENDURANCE-1; M13-590)
- Females who are pregnant or intending to become pregnant, or breastfeeding, and males with a female partner who was pregnant or is intending to become pregnant during the course of the study
- HCV genotyping performed during screening indicating coinfection with more than 1 HCV genotype
- Any cause of liver disease other than chronic HCV infection
- Consideration by the investigator, for any reason, that the subject was an unsuitable candidate to receive GLE, PIB, or GLE/PIB
- Child-Pugh B or C or history of liver decompensation.

Screening laboratory inclusion criteria were similar across all 9 studies, except for small differences in the Phase 2 supportive studies (for the study/parts in cirrhotic subjects or in CKD Stage 4 or 5 subjects, as appropriate). The following laboratory parameters must have been fulfilled at screening in the majority of these studies:

- Alanine aminotransferase and aspartate aminotransferase $\leq 10 \times$ the upper limit of normal (ULN);
- Direct bilirubin $\leq$ ULN (for subjects without cirrhosis) or a total bilirubin $\leq 3 \times$ ULN (for subjects with cirrhosis);
- Platelets $\geq 60,000/\mu\text{L}$ ($\geq 40,000/\mu\text{L}$ in EXPEDITION-4; M15-462) and $\geq 90,000/\mu\text{L}$ in subjects with and without cirrhosis, respectively;
- Hemoglobin A1c indicating no uncontrolled diabetes (e.g., ≤ 8 or $\leq 8.5\%$); Hemoglobin $\geq$ the lower limit of normal;
- Albumin ≥ 2.8 g/dL or $\geq$ lower limit of normal in subjects with or without cirrhosis, respectively;
- International normalized ratio ≤ 2.3 or ≤ 1.5 in subjects with or without cirrhosis, respectively, unless subject had known hemophilia or was stable on an anticoagulant regimen affecting international normalized ratio.

There were no upper limits for baseline body mass index (BMI) or age in the registrational studies. Subjects were included regardless of any positive toxicology screen result or history of bleeding disorders. The main differences between studies were related to HCV genotype, the presence or absence of severe renal impairment, and the presence or absence of compensated cirrhosis (Child-Pugh A).

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Genotype and Treatment Experience

As shown in Section 5.1, HCV GT1- – GT6-infected subjects who were either TN or TE, including subjects with prior failure to interferon (IFN) or pegIFN ± RBV, SOF and RBV (± pegIFN) were enrolled in ENDURANCE-1, ENDURANCE-2, SURVEYOR-2 Parts 3 and 4, ENDURANCE-4, ENDURANCE-2 and EXPEDITION-1. Genotype 3-infected subjects who were TN were enrolled in ENDURANCE-3. Subjects with experience to nonstructural viral protein 3/4A (NS3/4A) protease inhibitors (PI) and/or a nonstructural viral protein 5A (NS5A) inhibitors were enrolled in MAGELLAN-1. Genotype 1 HCV/HIV-1 coinfecting subjects were included in ENDURANCE-1. Subjects with a screening creatinine clearance ≥ 50 mL/min were allowed into the majority of the registrational studies, while subjects with CKD Stage 4 or 5 were evaluated in a dedicated study (EXPEDITION-4).

Cirrhosis Status

Subjects with cirrhosis were allowed in a number of the registrational studies (EXPEDITION-1, Study SURVEYOR-2 Part 3, MAGELLAN-1 Part 2, and EXPEDITION-4). The following definition for documenting the presence or absence of cirrhosis was employed.

An absence of cirrhosis was defined by documented evidence of:

- A liver biopsy within 24 months prior to or during screening, demonstrating the absence of cirrhosis, e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of ≤ 3 , Ishak fibrosis score of ≤ 4 ; or
- A FibroScan® score of < 12.5 kPa within 6 months of screening or during the screening period; or
- Subjects with an indeterminate FibroScan® score ($12.5 \leq \text{score} < 14.6$) were to have a qualifying liver biopsy
- A screening FibroTest score of ≤ 0.48 and aspartate aminotransferase to platelet ratio index (APRI) < 1 .
- Subjects with an indeterminate FibroTest ($0.48 < \text{result} < 0.75$), or conflicting FibroTest and APRI results (e.g., FibroTest ≤ 0.48 , but APRI ≥ 1) were to have a qualifying FibroScan® or qualifying liver biopsy

The presence of cirrhosis was defined by documented evidence of:

- Histologic diagnosis of cirrhosis on a liver biopsy e.g., a METAVIR, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec fibrosis score of > 3 or Ishak fibrosis score of > 4 ; or FibroScan® score ≥ 14.6 kPa;
 - Subjects with an indeterminate FibroScan® score ($12.5 \leq \text{score} < 14.6$) were to have a qualifying liver biopsy; or
- A screening FibroTest score of ≥ 0.75 and APRI > 2 ;
 - Subjects with an indeterminate FibroTest ($0.48 < \text{result} < 0.75$) or discordant FibroTest and APRI results (e.g., FibroTest ≥ 0.75 , but APRI ≤ 2) were to have a qualifying

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

FibroScan® or liver biopsy

Study Endpoints

The primary efficacy endpoint across all trials was SVR12, defined as HCV RNA < lower limit of quantitation (LLOQ) 12 weeks after discontinuation of the study drug.

Secondary efficacy endpoints included the number and percentage of subjects with on-treatment virologic failure and with relapse before or during the SVR12 window (Relapse12). HCV RNA levels in plasma were measured using the Roche COBAS® AmpliPrep/COBAS® Taqman® HCV Test, v2.0, with a LLOQ of 15 IU/mL and a lower limit of detection of 15 IU/mL. Virologic relapse was defined as confirmed HCV RNA $\geq$ LLOQ between end of treatment and 12 weeks after the last dose of study drug among subjects who completed treatment as planned with HCV RNA < LLOQ at the end of treatment.

Virologic failure was defined as confirmed increase of > 1 log₁₀ IU/mL above nadir during treatment, confirmed HCV RNA $\geq$ 100 after HCV RNA < LLOQ during treatment, or HCV RNA $\geq$ LLOQ at the end of treatment with at least 6 weeks of treatment.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

The primary efficacy analysis was performed on the intent-to-treat (ITT) population, which included all subjects who received at least one dose of study medication. Please refer above to Section 5.1, the trial design descriptions in this section and to Drs. Tracy and Usher’s statistics review for complete details.

6.1.2. Study Results

Patient Disposition

A total of 2,376 subjects were randomized or enrolled, of which 2,369 subjects received at least 1 dose of study drug and were included in the Phase 2 and 3 Analysis Set. One hundred and four of these subjects had severe renal impairment were enrolled in EXPEDITION-4. Overall, the percentage of subjects who prematurely discontinued study drug for any reason was low (37 [1.6%] of subjects). The most common primary reason for premature discontinuation of study drug was due to adverse events (11 [0.5%] subjects) followed by virologic failure (8 [0.3%] subjects), and ≤0.2% of subjects discontinued for reasons of withdrawn consent, loss to follow-up or other reasons.

Protocol Violations/Deviations

A summary of Protocol violations across all trials in the Phase 2/3 Efficacy dataset except for EXPEDITION-4 and MAGELLAN-1 are shown in the below table. Protocol violations for EXPEDITION-4 and MAGELLAN-1 are discussed in Sections 6.2 and 6.3 below.

Table 5 Protocol Violations

Trial	Number of Subjects with Significant Protocol Violations	Types of Protocol Violations (Subjects)
ENDURANCE-1	27	Inclusion/Exclusion Criteria (10 Subjects) • Not practicing acceptable methods of birth control (1) • Did not meet protocol-specific criteria for documenting fibrosis (5) at screening • HIV co-infected subject not on qualifying regimen 8 weeks prior to screening. (1) • Missing HCV/HIV laboratories at randomization (1 subject) • Enrolled prior to laboratory data availability Received an excluded concomitant medication(17) • 12/17 Received Herbal remedies • 5/17 received prohibited statins during a portion of the study

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

ENDURANCE-2	29	Inclusion/Exclusion Criteria (11 Subjects) • Subject did not have pregnancy test at 3 visits (1) • Male with partner practicing one form of birth control (1) • Randomized on a herbal drug/tea (4 Subjects) • Started/may have started prohibited concomitant medication (2) • Missing laboratories/diagnostic testing (5 subjects) Prohibited Herbal Supplement (7 Subjects) Subject administered placebo instead of study drug for four weeks(achieved SVR12)
ENDURANCE-3	17	Inclusion/Exclusion Criteria (11 Subjects) • Using Herbal supplements on randomization (2) • Missing laboratories at randomization (4) • Missing pregnancy test (1) • Subjects with pregnant partners (3) • Herbal supplements on(to close to) randomization (2) Wrong or incorrect dose of study medication (2 Subjects – both achieved SVR12) Prohibited Medication (1) Erroneously reported as concomitant medication (3)
ENDURANCE-4	4	Inclusion/Exclusion Criteria (1 Subjects) • Not practicing acceptable methods of birth control (1) Prohibited Herbal Supplement (2) Prohibited Medication (1)
EXPEDITION-1	2	Prohibited Herbal Supplement (2)
SURVEYOR-1	13	Inclusion/Exclusion Criteria (9 Subjects) • Not practicing acceptable methods of birth control (1) • Missing laboratory results (1) • Missing documentation of prior treatment (2) • Did not meet protocol-specific criteria for documenting fibrosis at screening (3) • Enrolled with prohibited screening laboratories (AST/ALT) (2) Prohibited Medications (4 Subjects) Incorrect (lower) dose of study medication (2subjects)
SURVEYOR-2	10	Inclusion/Exclusion Criteria (9 Subjects) • Missing objective evidence of HCC exclusion(1) • Did not meet protocol-specific criteria for documenting fibrosis at screening (4) • Enrolled with prohibited screening past medical history of prostate cancer within 5 years • ECG results above the protocol defined threshold for QTc using Fridericia's correction formula Received the wrong dose of study drug (Arm P, not included in the Pase2/3 dataset)

Source: Individual Study Reports

Reviewer Comment: All violations were appropriately addressed and remediated. The protocol violations had no bearing on the interpretability of the trial results; no AEs applicable to the Phase 2/3 dataset were reported by the Applicant, as a result of errors.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table of Demographic Characteristics

The tables below present the baseline demographic and disease characteristics. Subjects from MAGELLAN-1 and EXPEDITION-4 are a part of the overall, GLE/PIB Phase 2/3 dataset. Demographic data from these trials are also shown separately in Sections 6.2 and 6.3.

Table 6 Baseline Demographic Characteristics

Demographic Parameters	GLE/PIB Phase 2/3 Dataset All durations (N=2369)
Sex	
Male	1318 (55.6%)
Female	1051 (44.4%)
Age	
Mean years (SD)	52.5 (11.8)
Median (years)	54
Min, max (years)	19, 88
Age Group	
< 65 years	2041 (86.2%)
≥ 65 years	328 (13.8%)
Race	
White	1898 (80.1%)
Black or African American	149 (6.3%)
Asian	272 (11.5%)
Other ¹	47 (2.0%)
Not disclosed	3 (0.1%)
Ethnicity: Hispanic/Latino	
Yes	211 (8.9%)
No	1522 (64.2%)
Not disclosed	636 (26.8%)
Region	
United States	750 (31.7%)
Non-US	
Canada	178 (7.5%)
Australia	176 (7.4%)
New Zealand	110 (4.6%)
Europe	891 (37.6%)
HIV Status	
HIV-Infected	33 (1.4%)
Renal Impairment	
Severe Renal Impairment (CKD 4,5)	104 (4.4%)

Source: Produced by Dr. Usher; ADSL

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 7 Baseline HCV Disease Characteristics Overall and By Genotype

	Total GLE/PIB (N=2,369)	GLE/PIB Phase 2/3 N=2369					
		GT1 (N=998)	GT2 (N=466)	GT3 (N=643)	GT4 (N=182)	GT5 (N=32)	GT6 (N=48)
Cirrhosis							
No	2061 (87.0%)	872	431	527	160	30 (93.8%)	41 (85.4%)
Yes	308 (13.0%)	(87.3%) 126 (12.7%)	(92.5%) 35 (7.5%)	(82.0%) 116 (18.0%)	(87.9%) 22 (12.1%)	2 (6.2%)	7 (14.6%)
IL28B							
CC	766 (32.3%)	245	211	235	28 (15.3%)	11 (34.4%)	36 (75.0%)
CT	1224 (51.7%)	(24.5%)	(45.3%)	(36.5%)	111	12 (37.5%)	10 (20.8%)
TT	377 (15.9%)	579	180	332	(61.0%)	9 (28.1%)	2 (4.2%)
Missing	2 (0.1%)	(58.0%) 173 (17.3%) 1 (<0.1%)	(38.6%) 75 (16.1%) 0	(51.6%) 76 (11.8%) 0	42 (23.1%) 1 (<0.1%)	0	0
Baseline HCV RNA (log ₁₀ IU/mL)							
Mean (SD)	6.1 (0.8)	6.1 (0.7)	6.2 (0.9)	6.1 (0.8)	5.9 (0.7)	6.1 (0.6)	6.6 (0.8)
Median	6.2	6.1	6.5	6.2	5.9	6.2	6.8
Q1, Q3	5.7, 6.7	5.7, 6.6	5.8, 6.9	5.6, 6.8	5.4, 6.4	5.6, 6.5	6.4, 7.1
Min, Max	0.7, 7.6	1.1, 7.6	0.7, 7.8	1.2, 7.6	4.2, 7.2	5.0, 6.8	3.6, 7.5
< 6,000,000 IU/mL	1852 (78.2%)	854	303	478	168	27 (84.4%)	22 (45.8%)
≥ 6,000,000 IU/mL	517 (21.8%)	(85.6%) 144 (14.4%)	(65.0%) 163 (35.0%)	(74.3%) 165 (25.7%)	(92.3%) 14 (7.7%)	5 (15.6%)	26 (54.2%)
Baseline ALT							
≤ 1.5 x ULN	1331 (56.2%)	610	296	247	126	21 (65.6%)	31 (64.6%)
> 1.5 x ULN	1038 (43.8%)	(61.1%) 388 (38.9%)	(63.5%) 170 (36.5%)	(38.4%) 396 (61.6%)	(69.2%) 56 (30.8%)	11 (34.4%)	17 (35.4%)
Prior HCV trt history							
TN	1640 (69.2%)	561	369	521	122	26 (81.3%)	41 (85.4%)
PR-exp	546 (23.0%)	(56.2%)	(79.2%)	(81.0%)	(67.0%)	6 (18.7%)	7 (14.6%)
DAA-exp	70 (3.0%)	318	80 (17.2%)	80 (12.4%)	55 (30.2%)	0	0
PI-exp*	38 (1.6%)	(31.9%)	17 (3.6%)	42 (6.5%)	1 (0.5%)	0	0
NS5A-exp*	38 (1.6%)	10 (1.0%)	0	0	1 (0.5%)	0	0
PI & NS5A-exp*	37 (1.6%)	37 (3.7%)	0	0	1 (0.5%)	0	0
		37 (3.7%)	0	0	2 (1.1%)		
		35 (3.5%)					

Source: Produced by Dr. Usher; ADSL database

Reviewer Comment: Demographically age and sex were adequately represented, however,

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

there were very few non-white subjects (6% Black or African American, 12% Asian and 2% Other) enrolled in trials submitted with this Application. Ideally, the study population would be more representative of the intended treatment population. However, as shown below, SVR12 was high and there is no suggestion even in the limited data (and amongst subjects with virologic failures) submitted with this Application that efficacy differs by race. There were also few subjects with GT 5 and 6 infection and prior DAA experience. This was a significant review issues and is discussed extensively below.

Efficacy Results – Primary Endpoint

Among HCV GT1-6 subjects, excluding subjects enrolled in MAGELLAN-1 (subjects with prior NS3/4A PI or NS5A inhibitor treatment experience), GLE/PIB treatment for 8-16 weeks resulted in high SVR12 rates, often approaching 100%. The table below provides a pooled summary of SVR12 and virologic failure (VF) rates across all Phase 2 and 3 trials that included NS3/4A PI- and NS5A inhibitor-naïve subjects (including subjects with severe renal impairment). Efficacy for NS3/4A PI or NS5A inhibitor treatment experienced subjects enrolled MAGELLAN-1 is discussed in Section 6.2.

The Phase 2 and 3 Efficacy Data support the FDA indicated GLE/PIB treatment regimens in the following patient populations:

Treatment-naïve

- *GT1 ,2, 3, or 4 subjects without cirrhosis for 8 weeks*
- *GT1, 2, 3, or 4 with compensated Cirrhosis (Child-Pugh A) for 12 weeks*
- *GT5 or 6 with or without Compensated cirrhosis 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)

- *GT1, 2 or 4 without cirrhosis for 8 weeks*
- *GT1, 2 or 4 with compensated cirrhosis for 12 weeks*
- *GT3 with or without cirrhosis for 16 weeks*
- *GT5 or 6 with or without compensated cirrhosis 12 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 (and 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 (and no prior NS5A inhibitor) for 12 weeks*

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

The following sections provide discussion of the efficacy and clinical virology data to support the above indications, by genotype, cirrhosis status and prior treatment history.

Table 8 Pooled SVR12 and virologic failure results for Treatment-naïve and Treatment-experienced- PRS subjects (excluding NS5A and/or NS3/4A PI inhibitor experienced subjects from MAGELLAN-1) who received GLE/PIB to-be-marketed dose levels in Phase 2 and 3 trials.
(Highlighted rows show data for regimens initially proposed by the sponsor for the label).

HCV GT	Cirrhosis?	Tx History	Regimen	SVR12	VF Rate	On-Tx VF	Relapse	Non-VF	
GT1	N	Naïve	GLE/PIB 8W	99% (245/248)	0% (0/248)	0	0	3	
			GLE/PIB 12W	99.6% (241/242)	0% (0/242)	0	0	1	
		IFN- or P/R- exp	GLE/PIB 8W	99% (137/138)	1% (1/138)	1	0	0	
			GLE/PIB 12W	100% (155/155)	0% (0/155)	0	0	0	
	Y	SOF + RBV or P/R exp	GLE/PIB 8W	1/1	0/1	0	0	0	
			GLE/PIB 12W	100% (4/4)	0% (0/4)	0	0	0	
			Naïve	GLE/PIB 12W	97% (69/71)	0% (0/71)	0	0	2
GT2	N	Naïve	GLE/PIB 8W	99% (172/174)	0% (0/174)	0	0	2	
			GLE/PIB 12W	99% (167/169)	0% (0/169)	0	0	2	
		IFN- or P/R- exp	GLE/PIB 8W	94% (16/17)	6% (1/17)	0	1	0	
			GLE/PIB 12W	100% (60/60)	0% (0/60)	0	0	0	
	Y	SOF + RBV or P/R exp	GLE/PIB 8W	83% (5/6)	17% (1/6)	0	1	0	
			GLE/PIB 12W	100% (5/5)	0% (0/5)	0	0	0	
GT3	N	Naïve	GLE/PIB 8W	95% (177/186)	3% (6/186)	1	5	3	
			GLE/PIB 12W	96% (258/270)	1% (4/270)	1	3	8	
			SOF+DCV 12W	97% (111/115)	1% (1/115)	0	1	3	
		IFN- or P/R- exp	GLE/PIB 12W	88% (36/41)	12% (5/41)	1	4	0	
			GLE/PIB 16W	92% (12/13)	8% (1/13)	0	1	0	
		SOF + RBV or P/R exp	GLE/PIB 12W	100% (7/7)	0% (0/7)	0	0	0	
	GLE/PIB 16W		100% (9/9)	0% (0/9)	0	0	0		
	Y	SOF/LDV exp	GLE/PIB 12W	1/1	0/1	0	0	0	
			Naïve	GLE/PIB 12W	98% (64/65)	0% (0/65)	0	0	1
			GLE/PIB + RBV 12W	100% (24/24)	0% (0/24)	0	0	0	
			IFN- or P/R- exp	GLE/PIB 16W	92% (24/26)	8% (2/26)	1	1	0
GLE/PIB + RBV 12W			100% (3/3)	0% (0/3)	0	0	0		
GT4	N	Naïve	GLE/PIB 8W	92% (36/39)	0% (0/39)	0	0	3	
			GLE/PIB 12W	100% (71/71)	0% (0/71)	0	0	0	
		IFN- or P/R- exp	GLE/PIB 8W	100% (7/7)	0% (0/7)	0	0	0	
	GLE/PIB 12W		98% (40/41)	0% (0/41)	0	0	1		
	Y	IFN- or P/R- exp	Naïve	GLE/PIB 12W	100% (12/12)	0% (0/12)	0	0	0
			IFN- or P/R- exp	GLE/PIB 12W	100% (7/7)	0% (0/7)	0	0	0

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

HCV GT	Cirrhosis?	Tx History	Regimen	SVR12	VF Rate	On-Tx VF	Relapse	Non-VF	
		exp							
		SOF + RBV or P/R exp	GLE/PIB 12W	1/1	0/1	0	0	0	
GT5	N	Naïve	GLE/PIB 8W	100% (2/2)	0% (0/2)	0	0	0	
			GLE/PIB 12W	100% (22/22)	0% (0/22)	0	0	0	
	Y	Naïve	GLE/PIB 12W	100% (6/6)	0% (0/6)	0	0	0	
			IFN- or P/R-exp	GLE/PIB 12W	100% (2/2)	0% (0/2)	0	0	0
GT6	N	Naïve	GLE/PIB 8W	88% (7/8)	0% (0/8)	0	0	1	
			GLE/PIB 12W	100% (27/27)	0% (0/27)	0	0	0	
			IFN- or P/R-exp	GLE/PIB 8W	100% (2/2)	0% (0/2)	0	0	0
	Y	Naïve	GLE/PIB 12W	100% (4/4)	0% (0/4)	0	0	0	
			IFN- or P/R-exp	GLE/PIB 12W	100% (6/6)	0% (0/6)	0	0	0
			IFN- or P/R-exp	GLE/PIB 12W	1/1	0/1	0	0	0

INF= interferon, P/R= pegylated interferon ribavirin, SOF=sofosbuvir, PI=protease inhibitor Source: This table was produced by Dr. Harington

Efficacy by Genotype

The efficacy discussion focuses on a genotype-based analysis and is meant to complement the thorough trial by trial statistical review and the detailed virology reviews from a clinical perspective. Discussion of each genotype, by treatment experience, cirrhosis status and treatment duration culminates in a reviewer comment that includes the final clinical assessment of the reviewer and the overall review team regarding the indication by genotype. The reviewer concurred with the review team on all below issues regarding efficacy. The efficacy by genotype discussion excludes the NS3/4A PI- and/or NS5A Inhibitor- DAA-experienced population, which is covered separately in Section 6.2 in the review of MAGELLAN-1. An additional, separate discussion of efficacy for patients with severe renal impairment is also presented in Section 6.3 in the review of EXPEDITION-4, although data from EXPEDITION-4 are also included in the below genotype discussion, as efficacy did not differ in this sub-population.

GENOTYPE 1

Overall Genotype 1(GT1) Data: As shown in Table 8, there were a total of 889 HCV GT1, NS3/4A PI- and NS5A Inhibitor-Naïve subjects in the Phase 2/3 dataset treated for 8 or 12 weeks duration. Of these, 101 (11.4%) were subjects with compensated cirrhosis and 561 (63.1%) were treatment naïve. Subjects with treatment experience either had interferon (INF) or pegylated interferon, and ribavirin (P/R) experience or experience with sofosbuvir and ribavirin or P/R (TE-PRS). Thirty-three GT-1 subjects were co-infected with HIV, including 18 subjects in the GLE/PIB 12 week arm and 15 in the 8 week arm.

In total, across all 889 GT1 subjects treated for 8 or 12 weeks duration, there were two virologic failures, both in ENDURANCE-1. One non-cirrhotic subject who received 8 weeks duration

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

experienced on-treatment virologic failure, and one cirrhotic subject who received 12 weeks duration experienced relapse; neither subject was co-infected with HIV. In addition, six subjects did not achieve SVR12 for non-virologic reasons including discontinuation of treatment (3) or missing SVR12 values (3). One of these 6 subjects was treatment naïve and non-cirrhotic and received the 12 week treatment duration, which was not proposed for labeling.

Statistical Considerations of GT1 Data: HCV GT1, TN and TE-PRS subjects were enrolled in ENDURANCE-1, ENDURANCE-2, SURVEYOR-1, SURVEYOR-2, EXPEDITION-1 and EXPEDITION-4. Each trial met its statistical thresholds for GT1 analysis, and all trials were adequately conducted. Overall, GT1 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Table 9 Genotype 1 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, excluding NS3/4A PI- and NS5A Inhibitor-DAA Experienced Subjects enrolled in MAGELLAN -1 (data supporting final FDA recommended durations shown in red)

GT	Trial	Prior Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*	
				GLE/PIB x 8 w	GLE/PIB x 12 w
1	ENDURANCE-1	TN	NC	99.1 (217/219) 96.7, 99.7	99.5 (216/217) 97.4, 99.9
1	SURVEYOR-1	TN	NC	96.5 (28/29) 82.8, 99.4	NS
1	EXPEDITION-4	TN	NC	NS	100 (43/43) 91.8, 100
1	Treatment Naïve Non-Cirrhotic-Pooled	TN	NC	98.8 (245/248) 96.5, 99.6	99.6 (259/260) 97.8, 99.9
1	EXPEDITION-1	TN	C	NS	100 (66/66) 94.5, 100
1	EXPEDITION-4	TN	C	NS	81.8 (9/11) 52.3, 94.9
1	Treatment Naïve Cirrhotic – Pooled	TN	C	NS	97.4 (75/77) 91, 99.3
1	ENDURANCE-1	TE-PRS	NC	99.2 (131/132) 95.8, 100.0	100 (135/135) 97.2, 100
1	SURVEYOR-1	TE-PRS	NC	100 (5/5) 56.6, 100	NS
1	SURVEYOR-2	TE-PRS	NC	100 (2/2)	NS
1	ENDURANCE-2	TE-PRS	NC	NS	100 (3/3)
1	Treatment Experienced	TE-PRS	NC	99.3 (137/138) 96.0, 100.0	100 (138/138) 97.3, 100

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	Non-Cirrhotic Pooled				
1	EXPEDITION-1	TE-PRS	C	NS	95.8 (23/24) 79.8, 99.3

Adapted from a table produced by Drs. Tracy and Usher. 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.

Treatment-Naïve or PRS- Treatment Experienced Without Cirrhosis for 8 weeks or 12 weeks

ENDURANCE-1 enrolled the largest proportion of TN and TE-PRS GT1 non-cirrhotic subjects [(703/889), 79.1%]. ENDURANCE-1 was a Phase 3, randomized, open-label, parallel-group, multicenter study, in TN and TE-PRS GT1 HCV or HCV/HIV-1 co-infected adult subjects, without cirrhosis, to evaluate the safety and efficacy of 8- and 12-weeks of GLE/PIB. Randomization to either an 8- or 12-week regimen was performed in a 1:1 ratio, stratified by screening viral load (< or ≥6 million IU/mL) and HCV GT1 subtype (1a or 1b). Safety assessments were planned out to 24 weeks post-end of treatment.

The primary trial objective was to demonstrate non-inferiority of the 12-week GLE/PIB regimen to a historical control of 97% SVR12 using a 6% NI margin. The justification for the 97% pre-specified clinical threshold was based on data from a Phase 3 trial among GT1 HCV DAA-naïve subjects who were non-cirrhotic receiving ombitasvir/paritaprevir/ritonavir+dasabuvir+/-RBV in addition to findings from previous trials of SOF/LDV (ION-1, ION-2, and ION-3), which demonstrated a high 97% SVR12. However, Phase 3 trials leading to this estimate included a SOC, at that time, of an IFN-based regimen. The SVR in TN subjects who received an IFN-based regimen was approximately 78%. Therefore, the difference, or M1, was 19% (i.e. 97%-78%). Thus, with a 6% margin, the lower bound that must be exceeded in ENDURANCE-1 was 91%.

The SVR12 in 8 week and 12 week GLE/PIB groups was 99.1% 95%CI: (97.5, 99.7) and 99.7% 95% CI: (98.4, 100), respectively in the ITT population of ENDURANCE-1. One subject in the GLE/PIB 8 week arm was an on-treatment failure, two subjects were missing the SVR12 assessment and one subject prematurely discontinued treatment on study Day 2. The lower bound around the SVR12 in the GLE/PIB 12 week regimen was 98.3% well above the pre-specified 91% target. The difference between treatment groups was -0.6% (8-12 weeks) with a lower bound of -2% above the -5% pre-specified NI margin. Therefore, the data supported an 8 week treatment duration in GT1 treatment-naïve or treatment-experienced-PRS subjects without cirrhosis.

However, the FDA statistical review team did not agree with the Applicant’s non-inferiority approach, without inclusion of an active comparator regimen in the trial. Therefore, their analysis was one of superiority, evaluating the lower bound of the 95%CI compared to the

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

clinically acceptable threshold of 91%. As discussed above, both the 8 and 12 week arms demonstrated superiority, with a lower bound of the 95%CI of 97.5% and 98.4% for the 8 and 12 week arms, respectively.

Of note, additional supportive data were evaluated from SURVEYOR-1 (n=5) and SURVEYOR-2 (n=2), both evaluating GLE/PIB for 8 weeks duration and ENDURANCE-2 (n=3), evaluating 12 weeks duration supporting the treatment of TE-PRS subjects without cirrhosis (see table above). All 10 subjects achieved SVR.

Treatment-Naïve and Treatment Experienced-PRS With Compensated Cirrhosis for 12 weeks

Data to support treatment-naïve subjects with compensated cirrhosis for 12 weeks were derived from EXPEDITION-1 and EXPEDITION-4. Both trials were non-randomized, single arm, non-comparative trials; and therefore statistical results were described via a two-sided 95% CI calculated using the Wilson method, due to the high rate of SVR12 (see table above and statistical review for details). Most [(87/101), 86.1%] of the GT1 subjects with compensated cirrhosis were enrolled in EXPEDITION-1.

In treatment-naïve subjects with cirrhosis from EXPEDITION-1 and EXPEDITION-4, the SVR12 rates were 100% (66/66) with a 95%CI (94.5, 100), and 81.8% (9/11) with a 95%CI (52.3, 94.9), respectively. Both subjects who did not achieve SVR12 had non-virologic failure. The SRV12 rate was 95.8% (23/24) with a 95%CI of (79.8, 99.3) in treatment-experienced-PRS subjects with cirrhosis from EXPEDITION-1; the one subject who did not achieve SVR12 had virologic relapse.

Subgroup analyses were not conducted given the very high SVR 12 in this population. There were no major additional statistics considerations. Please see the statistics review for further details.

Clinical Virology Considerations:

Among noncirrhotic HCV GT1 infected subjects without cirrhosis treated with GLE/PIB for 8 weeks, 1/387 (0.3%) subjects experienced virologic failure. The single virologic failure subject experienced on-treatment failure and not relapse. A longer treatment duration would not have influenced treatment outcome in this single subject with on-treatment virologic failure. 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, 1/101 (1%) experienced virologic failure (relapse).

The near 100% efficacy of GLE/PIB indicates that natural baseline HCV resistance-associated polymorphisms did not significantly influence treatment efficacy for HCV GT1 infected subjects. Considering 9 resistance-associated amino acid positions in NS5A, amino acid polymorphisms

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

were detected at the $\geq 15\%$ nucleotide sequence level in 21% (78/380) and 32% (147/461) of GT1a- and GT1b-infected subjects, respectively, who had no previous exposure to NS3 protease and NS5A inhibitors. Both virologic failure subjects had GT1a virus with two resistance-associated polymorphisms, although only one polymorphism was detected in one subject at the $\geq 15\%$ level. Ten subjects with HCV GT1a infection had ≥ 2 NS5A resistance-associated polymorphisms detected at the $\geq 15\%$ level, and all 10 achieved SVR12. Both virologic failure subjects also 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.

Additional Clinical Data/ Considerations: Additional details regarding the subjects with on treatment failure and relapse are briefly described below. Although data were limited given that there was only one on treatment failure and one virologic relapse, there was no indication that age, sex or race played a role in these virologic failures.

Subject 106104 is a 60 year old non-cirrhotic white male with a previous treatment history of P/R experienced virologic break-through on day 29 and subsequently withdrew from the study.

Subject 203501 is a 62 year old white female with cirrhosis and a baseline CTP 5 and MELD 7 and a previous history of treatment with P/R who failed to achieve SVR12.

Reviewer Comment: Given the high SVR rates and robust data for GT1 TN and TE-PRS in this application, the review team supports the indication of 8 weeks of therapy for subjects without cirrhosis and 12 weeks of therapy for subjects with compensated cirrhosis (CTP A liver disease) in this population. From a general safety standpoint, this indication also minimizes the exposure time to GLE/PIB, decreasing the possibility of any associated adverse events and possibility for drug-drug interactions without sacrificing efficacy.

Although the numbers of HIV-co-infected subjects were small (n=33), there were no virologic failures in this subpopulation. Further, as HIV status is not expected to have a direct effect on efficacy, recommendations for treatment of HIV-co-infected subjects should mirror the overall treatment recommendations by genotype and treatment experience. This recommendation is bolstered by additional summary data provided by the Applicant at midcycle showing SVR12 results of 100% from an additional 21 HCV GT3 infected subjects with HIV-1 coinfection, who received GLE/PIB for 8 weeks in an ongoing trial, EXPEDITION-2 (M14-730).

GENOTYPE 2

Overall Genotype 2 (GT2) Data: As shown in Table 8, there were a total of 466 HCV GT2, TN and TE-PRS subjects in the Phase 2/3 efficacy dataset. Of these, 35 (7.5%) were subjects with

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

compensated cirrhosis and 369 (79.2%) were treatment-naïve. Subjects with treatment experience either had INF or P/R experience or experience with SOF and RBV or P/R. Two non-cirrhotic subjects experienced virologic failures; both subjects experienced relapse. Four subjects did not achieve SVR12 for non-virologic reasons including missing SVR12 data (1) and discontinuation of treatment (3).

Statistical Considerations: HCV GT2, TN and TE-PRS subjects were enrolled in ENDURANCE-2, SURVEYOR-2, EXPEDITION-1 and EXPEDITION-4. Each trial met its statistical thresholds for GT2 analysis and the trials were adequately conducted. Overall, GT2 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Table 10 Genotype 2 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, (pooled data supporting final FDA recommended durations shown in red)

GT	Trial	Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*	
				GLE/PIB x 8 w	GLE/PIB x 12 w
2	SURVEYOR-2	TN	NC	98.8 (172/174) 95.9, 99.7	95.5 (21/22) 78.2, 99.2
2	ENDURANCE-2	TN	NC	NS	99.3 (140/141) 96.1, 99.9
2	EXPEDITION-4	TN	NC	NS	100 (13/13) 77.2, 100
2	Pooled	TN	NC	98.8 (172/174) 95.9, 99.7	98.9 (174/176) 95.9, 99.7
2	EXPEDITION-1	TN	C	NS	100 (24/24) 86.2, 100
2	EXPEDITION-4	TN	C	NS	100 (4/4) 51.0, 100
2	Pooled	TN	C	NS	100 (28/28) 87.9, 100
2	ENDURANCE-2	TE-PRS	NC	NS	100 (58/58) 93.8, 100
2	SURVEYOR-2	TE-PRS	NC	91.3 (21/23) 73.2, 97.6	100 (3/3)
2	Pooled	TE-PRS	NC	91.3 (21/23) 73.2, 97.6	100 (61/61) 94.1, 100
2	EXPEDITION-1	TE-PRS	C	NS	100 (7/7) 64.6, 100

Adapted from a table produced by Drs. Tracy and Usher. 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.

Treatment-Naïve and PRS-Experienced GT2 Subjects Without Cirrhosis

Genotype 2 TN and TE-PRS subjects were enrolled predominately in ENDURANCE-2 and CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

SURVEYOR-2. Approximately 43% (202/466) of the overall G2 subjects were enrolled in ENDURANCE-2, which was a Phase 3, randomized, double-blind, placebo-controlled (delayed treatment) multicenter study to evaluate the safety and efficacy of GLE/PIB for 12 weeks in HCV GT2-infected subjects without cirrhosis (either TN or TE-PRS). Among this sample of HCV GT2-infected, non-cirrhotic (NC) subjects, the SVR12 was 99.5% with a 95% CI of (97.2, 100), with only one subject failing to achieve SVR12 due to missing the post-treatment 12 week assessment; there were no virologic failures. The SVR12 results among GT2-infected subjects treated with 12 weeks of GLE/PIB was 100%, providing strong support for a 12 week duration, but not the requested 8 week duration.

Support for the 8-week duration in GT-2 non-cirrhotic subjects comes from SURVEYOR-2 Part 4 and Part 2. SURVEYOR-2 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety and efficacy of GLE/PIB, co-administered or combined, with or without ribavirin (RBV) in adults with HCV GT 2, 3, 4, 5, or 6 infection who are TN or TE-PRS with or without cirrhosis for 8 and 12 weeks duration.

Within SURVEYOR-2, 143 TN or PRS-TE non-cirrhotic GT2 subjects were enrolled in Part 4, and 54 TN or PRS-TE non-cirrhotic GT2 subjects were enrolled in Part 2; all 197 subjects received GLE/PIB for 8 weeks.

The SVR12 rate from SURVEYOR-2 for combined Parts 2 and 4, in TN and TE-PRS subjects without cirrhosis was 97.9% (193/197) with a 95%CI of (94.5, 99.2) ; 2 subjects experienced virologic failure. The efficacy determination for SURVEYOR-2 Part 4 alone, was a comparison to the external threshold SVR12 rate of 89%. This historical threshold is considered clinically relevant as it was based on the SVR12 rate from the currently approved standard-of-care, SOF+ RBV for 12 weeks, at the time of the trial initiation. The SVR rate was 98.5% (135/137) with a Wilson method 95% CI of (94.8%, 99.6%); with the lower bound of the 95%CI well above the 89% threshold.

TN and PRS-Experienced GT2 Subjects With Compensated Cirrhosis

Most [31/35] 88.6%] GT2 subjects with compensated cirrhosis were enrolled in EXPEDITION-1. This was a single-arm, open-label, multicenter study to evaluate the safety and efficacy of a 12-week regimen of GLE/PIB for treating GT 1, 2, 4, 5 or 6 HCV-infected adult subjects with compensated cirrhosis who are either TN or TE-PRS. Although the Applicant claimed this trial was a Phase 3 trial, this open label single arm trial lacked a formal hypothesis, and hence was evaluated as a Phase 2 study by the FDA statistics team. The SVR12 rate was 100% (31/31), and there were no GT-2 virologic failures in this study. There were no major additional statistics considerations. Please see the statistics review for further details.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

The remaining 4 GT2 cirrhotic subjects were enrolled in EXPEDITION-4, and received 12 weeks of GLE/PIB. All 4 subjects achieved SVR12.

Clinical Virology Considerations:

Within the population of HCV GT2 infected subjects without cirrhosis, virologic failure occurred in 2/197 (1%) subjects treated with GLE/PIB for 8 weeks. The two failures were due to relapse and occurred in treatment-experienced subjects. One of these subjects had low GLE exposure possibly related to a medical history of gastric bypass.

As in HCV GT1 infected subjects, the near 100% efficacy of GLE/PIB for subjects with HCV GT2 infection indicates that natural baseline resistance-associated polymorphisms did not significantly affect treatment outcome. Several HCV GT2 subtypes were represented, with subtypes 2a, 2b and 2c being most common. 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 1% (2/197) relapse rate with no evidence of baseline or treatment-emergent resistance in the 2 subjects that relapsed support recommending GLE/PIB for 8 weeks for noncirrhotic, HCV GT2 infected patients. Furthermore, all 35 cirrhotic HCV GT2 infected subjects treated with GLE/PIB for 12 weeks achieved SVR12.

Additional Clinical Data/ Considerations: Additional details regarding the two subjects who experienced relapse are briefly described below. Although data were limited given that there were only two subjects with virologic failure, there was no indication that age, sex or race played a role in these virologic failures.

Subject 2917 is a 56 year old white female with a relevant history of gastric bypass, without cirrhosis who experienced a relapse at post treatment week 12. She had a history of prior treatment with SOF and RBV. The subject experienced no AEs on treatment but was found to have exposures of GLE on Day 1 and Week 4 that were > 75% lower than other subjects in the same treatment arm. The exposures of PIB in this subject were comparable to other subjects in the cohort .

Subject 7016 is a 55 year old non-cirrhotic white male with prior P/R treatment experience who experienced relapse at post treatment week 12. The subject experienced no adverse events and had normal drug levels.

Reviewer Comment: Given the high SVR rates and robust data for GT2 TN and TE-PRS subjects in this application, the review team supports the indication of 8 weeks of therapy for

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

subjects without cirrhosis and 12 weeks of therapy for subjects with compensated cirrhosis (CTP A liver disease) in this population. As was noted for GT1 subjects, from a general safety standpoint, this indication also minimizes the exposure time to GLE/PIB, decreasing the possibility of any associated adverse events and possibility for drug-drug interactions without sacrificing efficacy.

GENOTYPE 3

Overall Genotype 3(GT3) Data:

As shown in Table 8, there were a total of 643 HCV GT3, TN and PRS-TE subjects who were treated with GLE/PIB in the Phase 2/3 dataset. Of these, 116 (18.0%) were subjects with compensated cirrhosis and 521 (81.0%) were treatment naïve. Subjects with treatment experience either had INF or P/R experience or experience with SOF and RBV or P/R. All were treated with GLE/PIB with or without RBV for 8, 12 or 16 weeks duration. Overall, three non-cirrhotic subjects and one cirrhotic subject experienced on-treatment virologic failure and 14 non-cirrhotic subjects and 2 cirrhotic subjects experienced relapse. Fifteen subjects did not achieve SVR12 for non-virologic reasons, eight were missing SVR12 data and seven discontinued treatment. For the statistical evaluations, only treatment regimens without RBV were considered.

Statistical Considerations:

HCV GT3, TN and TE-PRS subjects were enrolled in ENDURANCE-3, SURVEYOR-2, and EXPEDITION-4. Overall, GT3 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Table 11 Genotype 3 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, (data supporting final FDA recommended durations shown in red)

GT	Trial	Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*		
				GLE/PIB x 8 w	GLE/PIB x 12 w	GLE/PIB x 16 w
3	ENDURANCE-3	TN	NC	94.9 (149/157) 90.3, 97.4	95.3 (222/233) 91.7, 97.3	NS
3	SURVEYOR-2	TN	NC	96.5 (28/29) 82.8, 99.4	96.3 (26/27) 81.7, 99.3	NS
3	EXPEDITION-4	TN	NC	NS	100 (10/10)	NS
3	Pooled	TN	NC	95.2 (177/186) 91.1, 97.4	95.5 (258/270) 92.4, 97.4	NS
3	SURVEYOR-2	TN	C	NS	98.4 (63/64) 91.7, 99.7	NS

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

3	EXPEDITION-4	TN	C	NS	100 (1/1)	NS
3	Pooled	TN	C	NS	98.5 (64/65) 91.8, 99.7	NS
3	SURVEYOR-2	TE-PRS	NC	NS	87.8 (36/41) 74.5, 94.7	95.5 (21/22) 78.2, 99.2
3	SURVYOR-2	TE-PRS	C	NS	NS	94.1 (48/51) 84.1, 98.0

Adapted from a table produced by Drs. Tracy and Usher. 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.

ENDURANCE-3- Treatment Naïve without cirrhosis

The majority, (74%, 390/527) of non-cirrhotic GT 3 subjects in the Phase 2/3 efficacy dataset were enrolled in ENDURANCE-3. This was a Phase 3, randomized, open-label, active-controlled (SOF/DCV), multicenter, non-inferiority trial to assess the efficacy and safety of GLE/PIB in GT3-infected, TN subjects without cirrhosis.

This trial included three treatment arms, GLE/PIB for 12 weeks (arm A, N=233), SOF/DCV for 12 weeks (arm B, N=116) and GLE/PIB for 8 weeks (arm C, N=157). 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 was added to the trial design following review of Phase 2 data, input from the Division, and after the trial was initiated. The trial objectives were first to test for non-inferiority of GLE/PIB for 12 weeks versus SOF/DCV based on a 6% margin, followed by a test for superiority of the 12 week arm to the active control.

The Applicant's algorithm for evaluating efficacy of the GLE/PIB 8w regimen involved assessing the lower bound of the CI around the 8w SVR12 and also of the CI around the difference (8w-12w). Since the lower bound the CI around the point estimate of the 8w SVR12 was 91.5% (applicant's analysis), the applicant calculated the adjusted 97.5% CI (-5.4, 4.6) around the difference (-0.4%) between GLE/PIB groups.

The FDA statistical reviewer's assessment of the 8w arms' efficacy differed from the applicant's. Specifically, the reviewer focused on the lower bound of the confidence interval around the SVR12 of 90.3% (Wilson method), which is slightly below than the target historical SVR12 rate of 92%. Secondly, the reviewer's analysis of the difference (8W-SOF/DCV) in SVR12 generated a difference of -1.6% and corresponding 97.5% confidence interval (adjusted for multiple testing) of -7.7% to 5.1%. These results do not meet the -6%NI margin; however, these findings suggest that the 8w regimen confers *a clinically acceptable SVR12 rate ranging from 90% to 97%* and as much as 8% worse than the active-comparator, SOF/DCV, but fails to demonstrate superiority over the historical threshold of 92%.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 12 ENDURANCE-3 Statistical Comparisons of SVR12

	GLE/PIB 12w (n=233)	SOF/DCV 12w (n=115)	GLE/PIB 8w (n=157)
SVR12	222 (95.3)	111 (96.5)	149 (94.9)
95% CI (Wald) (Applicant's)	92.6, 98.0	93.2, 99.9	91.5, 98.3
95% CI (Wilson) (Reviewer's)	91.7, 97.3	91.4, 98.6	90.3, 97.4
Difference (CI) in SVR12			
1st Primary Comparison: GLE/PIB 12 w vs. SOF/DCV			
GLE/PIB 12 w –SOF/DCV (95% CI Wald) (Applicant's)			-1.2 (-5.6, 3.1)
GLE/PIB 12 w –SOF/DCV (95% CI Wilson) (Statistics Reviewer's)			-1.2 (-5.4, 4.2)
2nd Primary Comparison: GLE/PIB 8w vs. GLE/PIB 12w or vs. SOF/DCV			
GLE/PIB 8 w - GLE/PIB 12 w (97.5% CI Wald) (Applicant's)			-0.4 (-5.4, 4.6)
GLE/PIB 8 w – SOF/DCV 12 w (97.5% CI Wilson) (Statistics Reviewer's)			-1.6 (-7.7, 5.1)

Table created by Drs. Usher and Tracy.

Treatment Experienced-PRS With and Without Compensated Cirrhosis

PRS-treatment experienced GT 3 subjects with and without compensated cirrhosis were enrolled in SURVEYOR-2. As described above, SURVEYOR-2 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety and efficacy of GLE/PIB, co-administered or combined, with or without ribavirin (RBV) in subjects with HCV GT 2, 3, 4, 5, or 6 infection who were TN or TE-PRS with or without cirrhosis. This study was not designed to test a formal hypothesis. SVR 12 results for GT3 subjects enrolled in SURVEYOR-2 are shown in the below table. SVR12 results ranged from 90.9% to 96.6%.

Table 13 SURVEYOR-2 Genotype 3 SVR12 by Treatment Arm

	SVR12	OTVF	Relapse	Other
Arm D GT3, TN and TE without cirrhosis 12 weeks	28/30 (93.3) (95% CI: 78.7, 98.2)	0	1/30 (3.3)	1/30 (3.3)
Arm L GT3 TN without cirrhosis 8 weeks	28/29 (96.6) (95% CI: 82.8, 99.4)	0	0	1/29 (3.4)
Arm L GT3 TE without cirrhosis 12 weeks	22/24 (91.7) (95% CI: 74.2, 97.7)	1/24 (4.2)	1/23 (4.3)	0

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Arm O GT3, TN with cirrhosis 12 weeks	27/28 (96.4) (95% CI: 82.3, 99.4)	0	1/28 (3.6)	0
Arm Q GT3, TN with cirrhosis 12 weeks	39/40 (97.5) (95% CI: 87.1, 99.6)	0	0	1/40 (2.5)
Arm Q GT3, TE, without cirrhosis 12 weeks	20/22 (90.9) (95% CI: 72.2, 97.5)	0	2/22 (9.1)	0
Arm R GT3, TE, without cirrhosis 16 weeks	21/22 (95.5) (95% CI: 78.2, 99.2)	0	1/22 (4.5)	0
Arm R GT3 TE with cirrhosis 16 weeks	45/48 (93.8) (95% CI: 83.2, 97.9)	1/48 (2.1)	1/46 (2.2)	1/48 (2.1)

Adapted from table produced by Drs. Usher and Tracy OTVF= on treatment virologic failure

Clinical Virology Considerations:

Pooled SVR12 rates for HCV GT3 infected subjects ranged from approximately 90 to 100% across various GLE/PIB durations and patient populations. For treatment-naïve, noncirrhotic HCV GT3 infected subjects, pooled SVR12 rates (non-VF-censored) were 97% (177/183) and 99% (258/261) for those who received GLE/PIB for 8 or 12 weeks, respectively, with a 1.9% higher relapse rate [(n=5) 2.7% vs. (n=3) 0.8%] with the 8-week versus 12-week duration. No treatment-naïve, HCV GT3 infected subjects with cirrhosis who received GLE/PIB for 12 weeks experienced virologic failure (n=64, non-VF-censored).

For treatment-experienced (IFN- or SOF-based), HCV GT3 infected subjects without cirrhosis, relapse rates were 8.3% (4/48) and 4.5% (1/22) with 12- and 16-week GLE/PIB durations, respectively. Similarly, a 4% (2/50) relapse rate was observed for treatment-experienced, HCV GT3 infected subjects with cirrhosis who received GLE/PIB for 16 weeks. Therefore, from a virologic standpoint a conservative 16-week GLE/PIB duration was recommended for treatment-experienced (IFN- or SOF-based), HCV GT3 infected subjects with or without cirrhosis in order to reduce the risk of relapse.

Across all GLE/PIB treatment regimens, 98% of HCV GT3 infected subjects had a subtype 3a infection. There was not a clear association between the detection of NS3 resistance-associated polymorphisms and treatment outcome with GLE/PIB for subjects with GT3 infection. However, it was found that baseline and treatment-emergent resistance data

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

indicate that certain NS5A resistance-associated polymorphisms, particularly A30K, may influence GLE/PIB efficacy for GT3. The A30K polymorphism was detected at a $\geq 15\%$ nucleotide sequence level in 6% of GT3a baseline sequences.

Among treatment-naïve, noncirrhotic subjects treated with GLE/PIB for 8 or 12 weeks, 9 subjects experienced virologic failure (excluding 1 suspected reinfection), of whom 5 (56%) had subtype 3a virus with an NS5A A30K polymorphism. 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. The A30K or Y93H polymorphisms were also enriched among treatment-experienced, HCV GT3 infected subjects who experienced virologic failure with GLE/PIB for 12 or 16 weeks, although insufficient data were available to assess the impact of these polymorphisms specifically on the efficacy of the 16-week duration recommended in the label (n=1 each for A30K or Y93H).

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, including Y56H/N, Q80K/R, A156G, and Q186L/R. In NS5A, Y93H was the predominant treatment-emergent resistance pathway, occurring in 15/18 (83%) subjects. Importantly, there was no obvious indication that treatment duration (8-16 weeks) influenced the likelihood of detecting NS3 and NS5A RASs at the time of virologic failure. Therefore, one should expect a high likelihood of treatment-emergent RASs in patients who fail treatment with any GLE/PIB treatment duration ≥ 8 weeks.

Additional Clinical Data/ Considerations: Additional details regarding subjects who experienced virologic failure are briefly summarized in the below table. Although data were limited given that there were relatively few subjects with virologic failures (n=19), there was no indication that age, sex or race played a role in these virologic failures.

Table 14 GT3 Virologic Failures

Unique Subject Identifier	Virologic Breakthrough Flag	Study Day of 1st Virologic Breakthrough	Relapse 12	Assigned Treatment Duration	Age	Sex	Race	Previous Virologic Response Category
174309	N	NA	Y	8 weeks	40	M	ASIAN	Naïve
162318	N	NA	Y	8 weeks	53	M	WHITE	Naïve
123305	N	NA	Y	8 weeks	50	M	WHITE	Naïve
129306	N	NA	Y	8 weeks	55	M	WHITE	Naïve
161301	N	NA	Y	12 weeks	37	M	WHITE	Naïve
145301	N	NA	Y	12 weeks	51	M	ASIAN	Naïve

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

141305	N	NA	Y	12 weeks	49	M	WHITE	Naïve
140310	N	NA	Y	8 weeks	59	F	WHITE	Naïve
1301	N	NA	Y	12 weeks	61	F	WHITE	P/R RELAPSER
7003	N	NA	Y	8 weeks	59	M	WHITE	P/R RELAPSER
3409	N	NA	Y	12 weeks	57	M	WHITE	P/R OTHER
6119	N	NA	Y	16 weeks	58	M	WHITE	SOF/RBV RELAPSE
1909	N	NA	Y	12 weeks	55	M	WHITE	P/R RELAPSE
4806	N	NA	Y	12 weeks	59	M	WHITE	P/R RELAPSER
2809	N	NA	Y	16 weeks	64	M	WHITE	P/R RELAPSE
137304	Y	56	NA	NA	42	M	WHITE	Naïve
139305	Y	85	NA	NA	47	M	WHITE	Naïve
6801	Y	50	NA	NA	51	M	WHITE	P/R ON-TREATMENT FAILURE
-6809	Y	62	NA	NA	56	M	WHITE	P/R NON-RESPONDER

Source: ADEFFP23 database.

Reviewer Comment: *Given the totality of data for GT3 TN and TE-PRS subjects in this application, the review team supports the indication of 8 weeks of therapy for treatment naïve patients without cirrhosis, 12 weeks of therapy for treatment naïve subjects with compensated cirrhosis (CTP A liver disease) and 16 weeks of therapy for patients with PRS-treatment experience.*

For treatment-naïve, noncirrhotic HCV GT3 infected subjects, the decision to recommend GLE/PIB for 8 weeks versus 12 weeks was a major review issue due to the slightly higher 2% relapse rate observed with the 8 versus 12-week duration. Additional statistical and virology analyses did not identify a specific subgroup that clearly benefited from a 12-week versus 8-week treatment duration. The Applicant also provided additional summary data at the mid-cycle to support the 8 week indication in this population, which included SVR12 results from an additional 21 HCV GT3 infected subjects with HCV/HIV-1 coinfection who received GLE/PIB for 8 weeks in an ongoing trial (EXPEDITION-2, M14-730). All 21 subjects achieved SVR12. In addition, the Applicant 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, addressing the question of possible re-treatment options. The review team therefore concluded that GLE/PIB for 8 weeks for treatment-naïve, noncirrhotic HCV GT3 infected patients is well supported based on the high SVR12 rate, and low relapse rate (<3%) observed in clinical trials, with an adequate sample size (n=186 in NDA who received GLE/PIB for 8 weeks).

The review team concluded that twelve weeks of therapy for treatment naïve cirrhotic subjects is also well supported given the lack of virologic failures in this adequately sized subset (N=65 in the NDA who received GLE/PIB for 12 weeks). The decision to recommend a conservative 16-week GLE/PIB duration for treatment-experienced (IFN- or SOF-based), HCV

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

GT3 infected patients with or without cirrhosis was made in order to address the risk of relapse which was about 4% higher (8.3% versus 4.5%) in subjects treated with 12- and 16-week GLE/PIB durations, respectively.

GENOTYPE 4

Overall Genotype 4(GT4) Data:

As shown in Table 8, there were a total of 178 HCV GT4, NS3/4A PI- and NS5A Inhibitor-Naïve subjects in the Phase 2/3 dataset treated for 8 or 12 week durations. Of these, 20 (11.2%) were subjects with compensated cirrhosis and 122 (68.5%) were treatment naïve. Subjects with treatment experience either had INF or P/R experience or experience with SOF and RBV or P/R. No subjects experienced virologic failure. Four subjects did not achieve SVR12 for reasons not related to virologic failure, including missing SVR12 data and discontinuation of treatment.

Statistical Considerations:

HCV GT4, NS3/4A PI- and NS5A Inhibitor-Naïve subjects were enrolled in ENDURANCE-4, SURVEYOR-1, SURVEYOR-2, EXPEDITION-1 and EXPEDITION-4. Trials were adequately conducted. Overall, GT4 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Table 15 Genotype 4 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, excluding NS3/4A PI- and NS5A Inhibitor-DAA Experienced Subjects enrolled in MAGELLAN -1 (data supporting final FDA recommended durations shown in red)

GT	Trial	Prior Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*	
				GLE/PIB x 8 w	GLE/PIB x 12 w
4	ENDURANCE-4	TN	NC	NS	100 (45/45) 92.1, 100
4	SURVEYOR-1	TN	NC	NS	100 (18/18) 82.4, 100
4	SURVEYOR-2	TN	NC	92.3 (36/39) 79.7, 97.3	NS
4	EXPEDITION-4	TN	NC	NS	100 (16/16) 80.6, 100
4	Pooled	TN	NC	92.3 (36/39) 79.7, 97.3	100 (79/79) 95.4, 100
4	EXPEDITION-1	TN	C	NS	100 (12/12) 75.7, 100
4	EXPEDITION-4	TN	C	NS	100 (4/4)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

					51, 100
4	Pooled	TN	C	NS	100 (16/16) 80.6, 100
4	ENDURANCE-4	TE-PRS	NC	NS	96.8 (30/31) 83.8, 99.4
4	SURVEYOR-1	TE-PRS	NC	NS	100 (4/4)
4	SURVEYOR-2	TE-PRS	NC	100 (7/7) 64.6, 100	NS
4	Pooled	TE-PRS	NC	100 (7/7) 64.6, 100	97.1 (34/35) 85.5, 99.5
4	EXPEDITION-1	TE-PRS	C	NS	100 (4/4)

Adapted from a table produced by Drs. Tracy and Usher. . 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.

All data for GT4 comes from single arm trials. GT4 subject had high SVR12 rates (92-100%) across the various subgroups and there were no virologic failures. Therefore, a brief summary of the trials and overall SVR results are provided below.

Treatment-Naive and Treatment Experienced-PRS Subjects Without Cirrhosis- 12 week duration

Approximately half of non-cirrhotic GT4 subjects (76/158 or 48%) were enrolled in ENDURANCE-4. This study was a single-arm, open label Phase 3 trial that evaluated the safety and efficacy of 12 weeks GLE/PIB in TN and PRS-TE subjects with HCV GT 4, 5, or 6 infection without cirrhosis. In total, 76 HCV GT4 subjects enrolled into ENDURANCE-4, of which, 45 subjects were TN and 31 subjects were PRS-TE. This single arm trial had no formal hypothesis testing. The number and percentage of subjects in the overall ITT population that achieved SVR12 were summarized and the 95% CI was calculated. Please see the statistical review for the overall assessment of ENDURANCE-4. Seventy-five of 76 GT4 subjects (98.7%) in ENDURANCE-4 achieved SVR12, one GT4 subject withdrew early from the trial due to an adverse reaction of TIA (discussed in detail in Section 8.4.2).

Treatment-Naive and Treatment Experienced-PRS Subjects Without Cirrhosis- 8 week duration

Non-cirrhotic subjects (TN and PRS-TE) enrolled in SURVEYOR-2 received 8 weeks of therapy (Arm S, GT4 only, n=46). As described above, SURVEYOR-2 was a multi-arm, multi-part, open label Phase 2 trial. There were seven GT4 PRS-TE subjects in this study and 39 TN subjects in this study. There were no virologic failures. SVR 12 was 100% in the TE population and 92% in TN ITT-PS population (4 subjects did not achieve SVR12 due to other reasons).

Treatment-Naive and Treatment Experienced-PRS Subjects With Cirrhosis-12 week duration

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

The majority of the GT-4 subjects with cirrhosis (14/16) were enrolled in EXPEDITION-1. As described above, EXPEDITION-1 was a Phase 2, single-arm, open-label, multicenter study to evaluate the safety and efficacy of a 12-week regimen of GLE/PIB for treating GT 1, 2, 4, 5 or 6 HCV-infected adult subjects with compensated cirrhosis who are either TN or TE-PRS. There were 12 GT 4 TN subjects and four TE subjects enrolled in the trial. All subjects achieved SVR12; there were no GT4 virologic failures in this trial.

Clinical Virology Considerations:

No cases of virologic failure occurred among HCV GT4 infected, noncirrhotic subjects who received GLE/PIB for 8 weeks (n=46) or 12 weeks (n=112), or among cirrhotic subjects who received GLE/PIB for 12 weeks (n=20). Although the number of HCV GT4 infected subjects who received the 8-week duration was relatively limited (n=46), the lack of any relapses with this duration, as well as the consistent efficacy overall for HCV GT4 infected subjects, support the use of GLE/PIB for 8 weeks for noncirrhotic, HCV GT4 infected patients.

Several HCV GT4 subtypes were represented, although subtypes 4a and 4d were predominant, consistent with previous DAA trials. Among HCV GT4 infected subjects enrolled at U.S. study sites, 40/47 (85%) had a subtype 4a infection. Given the 0% virologic failure rate for HCV GT4 infected subjects, there was no evidence that baseline polymorphisms in NS3 or NS5A affected treatment outcome.

Reviewer Comment:

Given the high SVR rates and lack of virologic failure in GT4 TN and PRS-TE subjects in this application, the review team supports the indication of 8 weeks of therapy for subjects without cirrhosis and 12 weeks of therapy for subjects with compensated cirrhosis (CTP A liver disease) in this population.

GENOTYPE 5

Overall Genotype 5(GT5) Data:

As shown in Table 8, there were a total of only 32 HCV GT5, TN and TE-PRS subjects in the Phase 2/3 dataset. Of these, 2 (6.3%) were subjects with compensated cirrhosis and 26 (81.3%) were treatment naïve. Subjects with treatment experience either had INF or P/R experience. No subjects experienced virologic failure and all subjects achieved SVR 12.

Statistical Considerations:

Data from ENDURANCE-4 (n=26), SURVEYOR-1 (Part 2)(n=1), SURVEYOR-2 (n=2), EXPEDITION-1 (n=2) and EXPEDITION-4 (n=1) supports GLE/PIB for treatment of TN and PRS-TE HCV GT5 subjects. Overall, GT5 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 16 Genotype 5 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, (data supporting final FDA recommended durations shown in red)

GT	Trial	Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*	
				GLE/PIB x 8 w	GLE/PIB x 12 w
5	ENDURANCE-4	TN	NC	NS	100 (20/20) 83.9, 100
5	SURVEYOR-1	TN	NC	NS	100 (1/1)
5	SURVEYOR-2	TN	NC	100 (2/2)	NS
5	EXPEDITION-4	TN	NC	NS	1/1 (100)
5	Pooled	TN	NC	100 (2/2)	100 (22/22) 85.1, 100
5	EXPEDITION-1	TN	C	NS	100 (2/2)
5	ENDURANCE4	TE-PRS	NC	NS	100 (6/6) 61.0, 100

Adapted from a table produced by Drs. Tracy and Usher. 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

The majority of GT5 subjects (26/32) in this application were enrolled in ENDURANCE-4. As described above, ENDURANCE-4 was a single-arm, open label Phase 3 trial that evaluated the safety and efficacy of 12 weeks of GLE/PIB in TN or PRS-TE subjects with HCV GT 4- 6 infection without cirrhosis. In total, there were 26 GT5 TN or PRS-TE subjects enrolled in ENDURANCE-4 and one GT5 subject enrolled in SURVEYOR-1 Part 2; all were treated for 12 weeks. The SVR12 rate was 100%; there were no GT5 virologic failures from either trial. Only 2 non-cirrhotic subjects were enrolled in SURVEYOR-2 and received 8 weeks of therapy. Both subjects achieved SVR12. Similarly, there were 2 GT5 subjects with cirrhosis enrolled in EXPEDITION-1, however, they received 12 weeks of therapy; both subjects achieved SVR12.

Clinical Virology Considerations:

Of the 32 HCV GT5 infected subjects who received GLE/PIB for 8 or 12 weeks in clinical trials, no subjects experienced virologic failure. However, only 2 subjects received GLE/PIB for 8 weeks, and these 2 subjects did not appear to be representative of the broader GT5 population. Both subjects who received the 8-week duration had low baseline HCV RNA levels; these subjects had the second and third lowest HCV RNA levels of all 32 HCV GT5 infected subjects. The other 30 HCV GT5 infected subjects (28 noncirrhotic, 2 with cirrhosis) received GLE/PIB for 12 weeks.

An NS3 D168E polymorphism, which has potential for clinically significant protease inhibitor resistance, was also detected in 13/31 (42%) of HCV GT5a infected subjects with available data, but all 13 subjects received GLE/PIB for 12 weeks.

Reviewer Comment: Given the high SVR12 rate in this population, and the small but adequate

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

sample size of GT5 TN and PRS-TE subjects studied for 12 weeks, the review team supports the indication of 12 weeks of therapy for patients without cirrhosis and with compensated cirrhosis (CTP A liver disease) in this population. A significant review issue was the adequacy of data to support an 8 week duration for non-cirrhotic GT5 subjects. Given that there were only 2 subjects who were treated for the 8 week duration, and that they did not appear to be representative of the broader GT5 population (neither had a D168 mutation and both had low baseline HCV viral load), the review team did not support this indication. While the Division generally has allowed for some extrapolation of results for lower prevalence HCV GTs like GT5 and GT6, even with the 12-week duration some extrapolation of available data needs to be considered to support treatment recommendations for GT5 -infected patients with compensated cirrhosis or prior sofosbuvir- or interferon-based treatment experience. The sponsor has an ongoing trial, M16-126, that will assess the efficacy of the 8-week duration in additional noncirrhotic subjects with HCV GT5 or GT6 infection. This study could provide sufficient data to support recommending GLE/PIB for 8 weeks for this population with a future submission.

GENOTYPE 6

Overall Genotype 6 (GT6) Data:

As shown in Table 8, there were a total of 48 HCV GT6, TN and TE-PRS subjects in the Phase 2/3 dataset. Of these, 7 (14.6%) were subjects with compensated cirrhosis and 41 (85.4%) were treatment naïve. Subjects with treatment experience either had INF or P/R experience. Subjects were treated with GLE/PIB for 8 or 12 weeks; no subjects experienced virologic failure. One subject did not achieve SVR12 for reasons not related to virologic failure; this subject was missing SVR12 data.

Statistical Considerations:

GT6 subjects were enrolled in ENDURANCE-4, SURVEYOR 1, SURVEYOR-2, EXPEDITION-1 and EXPIDITION-4. Overall, GT6 SVR12 data by trial, treatment experience, cirrhosis status and treatment duration are shown in the below table.

Table 17 Genotype 6 SVR 12 by Trial, Treatment Experience, Cirrhosis Status and Study Duration, (data supporting final FDA recommended durations shown in red)

GT	Trial	Treatment Experience	Cirrhosis Status	% SVR12 (n/N), 95% CI*	
				GLE/PIB x 8 w	GLE/PIB x 12 w
6	ENDURANCE-4	TN	NC	NS	100 (17/17) 81.6, 100
6	SURVEYOR-1	TN	NC	NS	100 (10/10) 72.2, 100
6	SURVEYOR-2	TN	NC	87.5 (7/8)	NS

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

				61, 100	
6	EXPEDITION-4	TN	NC	NS	100 (1/1)
6	Pooled	TN	NC	87.5 (7/8) 61, 100	100 (28/28) 87.9, 100
6	EXPEDITION-1	TN	C	NS	100 (6/6) 61, 100
6	ENDURANCE-4	TE-PRS	NC	NS	100 (2/2)
6	SURVEYOR-1	TE-PRS	NC	NS	100 (1/1)
6	SURVEYOR-2	TE-PRS	NC	100 (2/2)	NS
6	Pooled	TE-PRS	NC	100 (2/2)	100 (3/3)
6	EXPEDITION-1	TE-PRS	C	NS	100 (1/1)

Adapted from a table produced by Drs. Tracy and Usher. 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

The majority of non-cirrhotic subjects 56.1% (23/41) were enrolled in ENDURANCE-4. As described above, ENDURANCE-4 was a single-arm, open label Phase 3 trial that evaluated the safety and efficacy of 12 weeks of GLE/PIB in TN or TE subjects with HCV GT 4- 6 infection without cirrhosis. There were no GT6 virologic failures in this trial.

Eight TN noncirrhotic and 2 TE noncirrhotic subjects were enrolled in SURVEYOR-2. Seven (6 TN and 1 TE subjects with cirrhosis) were enrolled in EXPEDITION-1. The single GT6 subject who did not achieve SVR12 (non-virologic failure) was enrolled in SURVEYOR-2.

Clinical Virology Considerations:

HCV GT6 is extremely genetically diverse with at least 28 reported subtypes and wild-type amino acid sequences at multiple key positions in NS5A, including at positions 28, 30 and 93, vary across different subtypes within GT6, and also between GT6 and other HCV genotypes. Based on the limited sample size and SVR data, it is not possible to draw any firm conclusions regarding the potential impact of HCV GT6 genetic diversity or baseline polymorphisms on the efficacy of an 8-week treatment duration of GLE/PIB.

Reviewer Comment: Given the high SVR12 rate in this population, and the small but adequate sample size of GT6 TN and TE-PRS subjects studied for 12 weeks, the review team supports the indication of 12 weeks of therapy for patients without cirrhosis and with compensated cirrhosis (CTP A liver disease) for this population.

Like for GT5, the significant review issue was the adequacy of data to support an 8 week duration for non-cirrhotic subjects. Only 8 non-cirrhotic treatment naïve and 2 INF or P/R treatment experienced subjects who were treated for 8 weeks duration were a part of this application. As stated above, while the Division has allowed for some extrapolation of results for lower prevalence HCV GTs like GT5 and GT6, even with the 12-week duration some extrapolation of available data needs to be considered to support treatment

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

recommendations for GT6-infected patients with compensated cirrhosis or prior sofosbuvir- or interferon-based treatment experience. The ongoing trial, M16-126, addressing the efficacy of the 8-week duration in additional subjects with HCV GT5 or GT6 infection, may provide data to potentially support an 8 week duration of GLE/PIB for GT 5 or 6 patients without cirrhosis in the future.

6.2. MAGELLAN-1 (M15-410)

6.2.1. Study Design

Overview and Objective

MAGELLAN-1 was a multi-arm, multi-part, open label Phase 2 trial that evaluated GLE/PIB, co-administered or fixed-dose combination, with or without RBV in adults with HCV GT 1, 4, 5, and 6 infection who failed a prior anti-HCV DAA-containing regimen. The primary objectives in Part 1 of this study were to assess the efficacy and safety of ABT-493 and ABT-530, and the contribution of RBV in adults with chronic HCV GT1 infection who previously failed treatment with a DAA-containing regimen. The arm(s) in Part 1 of the study, which met the pre-specified efficacy and safety criteria, were studied in Part 2 of the study, where the efficacy and safety of the regimen were confirmed by evaluating it in a broader and larger subject population.

Trial Design

The trial contained two parts, with Part 2 initiated based on achieving safety and efficacy criteria in Part 1. Those with HCV GT 4, 5, or 6 were included in Part 2 only. Only data from Arm C (N=22) in Part 1 and Arms D (N=44) and E (N=47) in Part 2 used the selected Phase 3 dosage and thus were submitted for review. Randomization occurred in a 1:1 ratio between Arms D and E. Randomization was stratified by HCV genotype (GT1 or GT4 – GT6) and by previous experience to the following 2 DAA regimen classes:

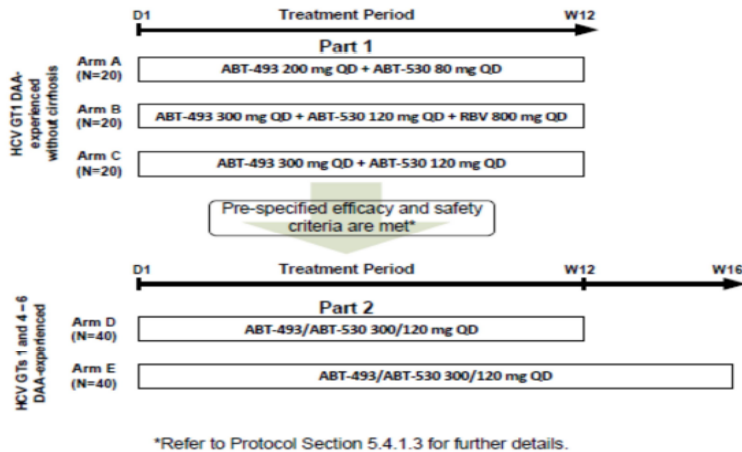
1. NS5A inhibitor ($\pm$ PI)-experienced, limited to DCV-, LDV-, or OBV-containing combination regimens; or
2. NS5A inhibitor-naïve/NS3/4A PI-experienced, limited to: PTV/r-, SMV-, TVR-, or BOC-containing combination regimens.

This study was not designed to test a formal hypothesis, although hypothesis testing is conducted. See Figure 1 below.

Figure 1 M15-610 MAGELLAN-1 Trial Design

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Figure 1. Study M15-410 Schematic



D = day; DAA = direct-acting antiviral agent; GT = genotype; HCV = hepatitis C virus; RBV = ribavirin; QD = once daily; W = week

Source: Magellan-1 protocol

Study Endpoints

The primary efficacy endpoint was the percentage of subjects who achieved SVR12 (HCV RNA < LLOQ 12 weeks after the last actual dose of study drug).

Statistical Analysis Plan

For each treatment arm, the number and percentage of subjects achieving SVR12 were summarized along with a 95% confidence interval using the Wilson score. In addition, the difference in SVR12 rates between treatment arms was analyzed using the stratum-adjusted Mantel-Haenszel proportion with a continuity correction for variance, adjusting for each of the randomization stratum. Data from Arms A and B are included in total calculations, but are not presented separately as they did not use the proposed dose of GLE/PIB.

6.2.2. Study Results

Patient Disposition

A total of 50 subjects were randomized and received ≥ 1 dose of study drug in Part 1. Two subjects discontinued study drug prematurely (1 subject due to virologic failure and 1 subject was lost to follow-up). In Part 2 of the study, a total of 91 subjects were randomized and received ≥ 1 dose of study drug in Part 2. Four subjects (all in Arm E) discontinued study drug prematurely due to virologic failure.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Protocol Violations/Deviations

A total of 3 protocol deviations occurred for 3 subjects. Two were violations of exclusion criteria and one subject took a prohibited medication (Senna Plus/Sennosides SOD) containing an herbal derivative from Days 35-37. These protocol violations had no bearing on the interpretability of the trial results.

Table of Demographic Characteristics

Table 18 summarizes baseline demographic and disease characteristics.

Table 18 MAGELLAN-1 Baseline Characteristics/Demographics

	<i>Total</i> (n=141)	<i>GLE/PIB</i> 12 wk (C) (n=22)	<i>GLE/PIB</i> 12 wk (D) (n=44)	<i>GLE/PIB</i> 16 wk (E) (n=47)
Males	105 (74.5)	18 (81.8)	31 (70.5)	33 (70.2)
Mean (sd) age	55.9 (7.9)	58.5 (6.6)	55.6 (8.6)	55.6 (8.3)
Race				
White	102 (72.3)	12 (54.5)	34 (77.3)	35 (74.5)
Black	37 (26.2)	10 (45.5)	9 (20.5)	11 (23.4)
Asian	2 (1.4)	0	1 (2.3)	1 (2.1)
HCV genotype				
GT 1	137 (97.2)	22 (100)	43 (97.7)	44 (93.6)
GT 4	4 (2.8)	0	1 (2.3)	3 (6.4)
Treatment Experience				
NS5A & NS3/4A PI Experienced	47 (33.3)	7 (31.8)	14 (31.8)	16 (34.0)
NS5A Experienced & NS3/4A PI Naïve	42 (29.8)	4 (18.2)	16 (36.4)	18 (38.3)
NS3/4A Experienced & NS5A Naïve	52 (36.9)	11 (50.0)	14 (31.8)	13 (27.7)
Cirrhotic Status				
Non-Cirrhotic	114 (80.9)	22 (100)	29 (65.9)	35 (74.5)
Cirrhotic	27 (19.1)	0	15 (34.1)	12 (25.5)
Mean (sd) log ₁₀ HCV RNA	6.27 (0.62)	6.55 (0.51)	6.01 (0.66)	6.24 (0.56)
IL28 Genotype				
CC	22 (15.6)	3 (13.6)	6 (13.6)	5 (10.6)
CT	87 (61.7)	14 (63.6)	27 (61.4)	30 (63.8)
TT	31 (22.0)	5 (22.7)	11 (25.0)	11 (23.4)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	Unknown	1 (0.7)	0	0	1 (2.1)
Region*					
North America	97 (68.8)		22 (100)	23 (52.3)	24 (51.1)
Europe	20 (14.2)		0	8 (18.2)	12 (25.5)
Rest of the World	24 (17.0)		0	13 (29.5)	11 (23.4)

Table Created by Drs. Usher and Tracy.

Reviewer Comment: The vast majority [137/141 (97%)] of subjects were infected with HCV genotype 1 and therefore only genotype 1 was considered for an indication by the FDA review team. One-third, 33%, of the subjects were both NS5A and NS3/4A PI-experienced. A little more than a third, 37%, of subjects were NS5A-naïve and NS3/4A PI-experienced and 30% were NS5A-experienced and NS3/4A PI-naïve. Approximately 19% of the subjects had cirrhosis.

Mean age was approximately 56 years at base and approximately three quarters of the study population was white or male. Because subject randomization occurred within Parts 1 and 2 separately, it is expected that Arms D and E have balanced distributions of characteristics and demographics and most of the characteristics are balanced between Arms D and E. However, Arm E had a lower percentage of cirrhotic subjects, a slightly higher mean log₋₁₀ HCV RNA at baseline, and a slightly higher percentage of NS5A-experienced subjects compared to Arm D.

Efficacy Results - Primary Endpoint

Table 19 provides SVR 12 results for MAGELLAN-1 as submitted by the Applicant and reproduced by the FDA review team. Of the 141 subjects, 128 subjects achieved SVR12. Six subjects experienced on-treatment virologic failure, five subjects experienced post-treatment relapse, and two subjects had missing SVR12 values. Ten of the subjects with virologic failure were GT1a, and one additional subject was GT1b. Eight of the 11 subjects were both NS3/4A PI- and NS5A-experienced.

Table 19 MAGELLAN-1 SVR12

	GLE+PIB 12 wk (C) (n=22)	GLE/PIB 12 wk (D) (n=44)	GLE/PIB 16 wk (E) (n=47)
SVR12	ITT: 19/22 (86.4) (95% CI: 66.7, 95.3)	ITT: 39/44 (88.6) (95% CI: 76.0, 95.0)	ITT: 43/47 (91.5) (95% CI: 80.1, 96.6)
OTVF	1/22 (4.5)	1/44 (2.3)	4/47 (8.5)
Relapse	0/22 (0)	4/44 (9.1)	0/43 (0)
Other	2/22 (9.1)	0/44 (0)	0/47 (0)
	Mantel-Haenszel	-3.2%	

CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	(95% CI: -16.7, 10.3)
Fisher's Exact Test	p=0.734
Logistic Regression	p=0.341

Table Created by Dr. Usher and Tracy. OTVF= on treatment virologic failure

Table 20 provides the SVR12 rate and SVR12 failures by treatment experience and treatment duration for those subjects who have NS5A and/or NS3/4A PI experience. These calculations were not provided by the Applicant but were included in the description of MAGELLAN-1.

Table 20 SVR12 for NS5A and/or NS3/4A PI Experienced Subjects by Treatment Duration

<i>Treatment Experience</i>	<i>GLE/PIB 12 wk (n=65)</i>	<i>GLE/PIB 16 wk (n=44)</i>
NS5A & NS3/4A PI-experienced	16/20 (80.0) (95% CI: 58.4, 91.9) OTVF: 1/20 (5.0) Relapse: 3/20 (15.0)	12/15 (80.0) (95% CI: 54.8, 93.0) OTVF: 3/15 (20.0)
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)
NS5A-naïve & NS3/4A PI-experienced	23/25 (92.0) (95% CI: 75.0, 97.8) 2 missing SVR12	12/12 (100) (95% CI: 75.8, 100)

Table created by Dr. Usher and Tracy. OTVF= on treatment virologic failure

Virology Analysis

Complementary, but slightly different from the statistics approach shown above, the Clinical Virology reviewer pooled subjects who received GLE/PIB for 12 weeks across Arms A, C and D since the only differences in treatments administered were the DAA formulations used and the slightly lower GLE and PIB dose levels administered in Arm A (n=6, all achieved SVR12). Arm B subjects received GLE/PIB plus RBV for 12 weeks, and Arm E subjects received GLE/PIB for 16 weeks.

Using this approach, overall SVR12 rates ranged from 86-100% across treatment arms. Virologic failure occurred in 10/107 (9%) and 1/26 (4%) subjects with HCV GT1a or GT1b infection, respectively (non-VF-censored population). All 11 subjects who experienced virologic failure had treatment experience with an NS5A inhibitor-containing regimen. Results on the

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

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.

Among HCV GT1 infected subjects who were **NS3/4A PI-experienced and NS5A inhibitor-naïve**, GLE/PIB for 12 weeks resulted in an SVR12 rate of 26/26 (100%, non-VF-censored), with no obvious benefit of dosing GLE/PIB for >12 weeks or in combination with RBV, supporting the use of GLE/PIB for 12 weeks in this population.

Among HCV GT1 infected, **NS5A inhibitor-experienced, NS3/4A PI-naïve subjects**, non-VF-censored 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 prior **NS5A inhibitor and NS3/4A PI experience**, with SVR12 rates of 83% (19/23) and 80% (12/15) with the 12- and 16-week durations, respectively. Although SVR12 rates were similar with the 12- and 16-week durations, all 4 instances of virologic failure with the 16-week duration occurred on-treatment, while all instances of relapse occurred among subjects who received the 12-week duration, providing some evidence that a 16-week duration may reduce the risk of relapse. In general, the numbers of subjects who received GLE/PIB + RBV were insufficient to determine if RBV improves treatment efficacy.

Prior NS5A inhibitor experience was associated with the presence of baseline NS5A resistance-associated substitutions (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, and baseline NS3 D168 RASs were also associated with virologic failure for subjects with prior NS5A inhibitor and NS3/4A PI experience. Most virologic failure subjects had treatment-emergent or evolving RASs in NS3 or NS5A, or in both targets, indicating the potential for further treatment-emergent resistance selection with GLE/PIB failure. Please see virology review for further details.

Reviewer Comment: Based on the above statistical and virology analysis, the review team supports a 12 week treatment indication for NS3/4A PI-experienced and NS5A inhibitor-naïve patients with GT1 HCV infection. An important review issue related to the MAGELLAN-1 trial was if the sponsor had sufficient evidence to support a treatment recommendation for HCV GT1 infected, NS5A inhibitor-experienced patients. Based on the analysis shown above, the review team concluded that the data supports a treatment recommendation for GLE/PIB for 16 weeks for HCV GT1 infected patients who are NS5A inhibitor-experienced and NS3/4A PI-naïve. In particular, this represents a RBV-free, 2DAA treatment regimen for patients who currently have no approved treatment options, which is also important for patients with moderate to severe renal failure who cannot take a SOF-based regimen. However, the data were not supportive of a treatment recommendation for GT1 infected patients with

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

experience to both NS5A inhibitors and NS3/4A PIs due to higher rates of treatment failure and the potential for further treatment-emergent resistance selection with GLE/PIB failure in this subpopulation.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses

A subgroup analysis was conducted by the FDA statistics team and is shown in the below table.

Table 21 MAGELLAN-1 Subgroup Analysis

		Total (n=141)	GLE/PIB 12 wk (C) (n=22)	GLE/PIB 12 wk (D) (n=44)	GLE/PIB 16 wk (E) (n=47)
Age	< 65 years	116/126 (92.1) 5 relapses, 4 on-trt VF, 1 missing	16/18 (88.9) 1 on-trt VF, 1 missing	37/41 (90.2) 4 relapse	36/39 (92.3) 3 on-trt VF
	≥ 65 years	12/15 (80.0) 2 on-trt VF, 1 missing	3/4 (75.0) 1 missing	2/3 (66.7) 1 on-trt VF	7/8 (87.5) 1 on-trt VF
Race	White	91/102 (89.2) 5 on-trt VF, 4 relapses, 2 missing	9/12 (75.0) 1 on-trt VF, 2 missing	30/34 (88.2) 3 relapse, 1 on-trt VF	32/35 (91.4) 3 on-trt VF
	Black	36/37 (97.3) 1 on-trt VF	10/10 (100)	9/9 (100)	10/11 (90.9) 1 on-trt VF
	Asian	1/2 (50.0) 1 relapse	0 subjects	0/1 (0) 1 relapse	1/1 (100)
Gender	Male	96/105 (91.4) 4 on-trt VF, 3 relapses, 2 missing	15/18 (83.3) 1 on-trt VF, 2 missing	27/31 (87.1) 3 relapse, 1 on-trt VF	31/33 (93.9) 2 on-trt VF
	Female	32/36 (88.9) 2 on-trt VF, 2 relapses	4/4 (100)	12/13 (92.3) 1 relapse	12/14 (85.7) 2 on-trt VF
BL HCV RNA	< 1 mil c/mL	41/42 (97.6) 1 relapse	4/4 (100)	19/20 (95) 1 relapse	14/14 (100)
	≥ 1 mil c/mL	87/99 (87.9) 6 on-trt VF, 4 relapse, 2 missing	15/18 (83.3) 1 on-trt VF, 2 missing	20/24 (83.3) 3 relapse, 1 on-trt VF	29/33 (87.9) 4 on-trt VF
	< 6 mil c/mL	99/107 (92.5)	11/12 (91.7)	35/40 (87.5)	36/38 (94.7)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

		4 relapse, 3 on-trt VF, 1 missing	1 missing	4 relapse, 1 missing	2 on-trt VF
	≥ 6 mil c/mL	29/34 (85.3)	8/10 (80.0)	4/4 (100)	7/9 (77.8)
		3 on-trt VF, 1 relapse, 1 missing	1 on-trt VF, 1 missing		2 on-trt VF
	< 10 mil c/mL	115/125 (92.0)	15/16 (93.8)	37/42 (88.1)	41/45 (91.1)
		5 on-trt VF, 4 relapse, 1 missing	1 missing	4 relapse, 1 on-trt VF	4 on-trt VF
	≥ 10 mil c/mL	13/16 (81.3)	4/6 (66.7)	2/2 (100)	2/2 (100)
		1 on-trt VF, 1 relapse, 1 missing	1 on-trt VF, 1 missing		
HCV Genotype					
	GT 1	124/137 (90.5)	19/22 (86.4)	38/43 (88.4)	40/44 (90.9)
		6 on-trt VF, 5 relapse, 2 missing	1 on-trt VF, 2 missing	4 relapse, 1 on-trt VF	4 on-trt VF
	GT 4	4/4 (100)	0 subjects	1/1 (100)	3/3 (100)
Treatment Experience					
	NS5A & NS3/4A PI Experienced	39/47 (82.9)	6/7 (85.7)	11/14 (78.6)	13/16 (81.3)
		4 on-trt VF, 4 relapse	1 on-trt VF	3 relapse	3 on-trt VF
	NS5A Experienced & NS3/4A PI Naïve	39/42 (92.9)	4/4 (100)	14/16 (87.5)	17/18 (94.4)
		2 on-trt VF, 1 relapse		1 on-trt VF, 1 relapse	1 on-trt VF
	NS3/4A Experienced & NS5A Naïve	50/52 (96.1)	9/11 (81.8)	14/14 (100)	13/13 (100)
		2 missing	2 missing		
Cirrhotic Status					
	Non-Cirrhotic	105/114 (92.1)	19/22 (86.4)	25/29 (86.2)	34/35 (97.1)
		5 relapse, 2 on-trt VF, 2 missing	1 on-trt VF, 2 missing	4 relapse	1 on-trt VF
	Cirrhotic	23/27 (85.2)	0	14/15 (93.3)	9/12 (75.0)
		4 on-trt VF		1 on-trt VF	3 on-trt VF
IL28 Genotype					
	CC	22/22 (100)	3/3 (100)	6/6 (100)	5/5 (100)
	CT	76/87 (87.4)	11/14 (78.6)	22/27 (81.5)	28/30 (93.3)
		5 relapse, 4 on-trt VF, 2 missing	1 on-trt VF, 2 missing	4 relapse, 1 on-trt VF	2 on-trt VF
	TT	30/31 (96.8)	5/5 (100)	11/11 (100)	10/11 (90.9)
		1 on-trt VF			1 on-trt VF
	Unknown	0/1 (0)	0 subjects	0 subjects	0/1 (0)
		1 on-trt VF			1 on-trt VF
Region					
	North America	88/97 (90.7)	19/22 (86.4)	21/23 (91.3)	21/24 (87.5)
		5 on-trt VF, 2 relapse, 2 missing	1 on-trt VF, 2 missing	1 on-trt VF, 1 relapse	3 on-trt VF
	Europe	19/20 (95.0)	0 subjects	7/8 (87.5)	12/12 (100)
		1 relapse		1 relapse	
	Rest of the World	21/24 (87.5)	0 subjects	11/13 (84.6)	10/11 (90.9)
		2 relapse, 1 on-trt		2 relapse	1 on-trt VF

Reviewer Comment: As expected, given the overall high SVR12 rate, the SVR12 rate among the various subgroups was also high. The small sample sizes for some subgroups with more variation were difficult to interpret. Please refer to the statistics review for further details.

6.3. EXPEDITION-4 (M15-462)

6.3.1. Study Design

Overview and Objective

EXPEDITION-4 (M15-462) was a single-arm, open-label study to evaluate the efficacy and safety of GLE/PIB in renally-impaired adults with chronic hepatitis C (CHC) virus genotype 1 – 6 infection. The primary objectives of the trial were to evaluate the efficacy and safety of 12 weeks of GLE/PIB in adults with CHC genotype 1-6 infection and chronic renal impairment.

This trial began December 21, 2015 and the last subject's last visit for the primary analysis occurred on September 28, 2016. Enrollment was conducted across 30 sites in Australia, Belgium, Canada, France, Greece, Italy, New Zealand, the United Kingdom, and the United States. At the time of trial initiation, there were no HCV DAA regimens approved for use in patients with severe renal impairment. Subsequently on January 28, 2016, grazoprevir/elbasvir (GZR/EBR) was approved for use in HCV genotype 1 and 4 infected patients with severe renal impairment. There remains an unmet medical need for DAA regimens for treatment of patients with severe renal impairment and HCV genotype 2, 3, 5, or 6 infections.

Trial Design

Subjects enrolled in this single-arm, open label trial received GLE/PIB 300 mg/120 mg daily for 12 weeks and were then followed for an additional 24 weeks. At the time of NDA submission the study was ongoing. The analysis included in the submission is an interim analysis where all subjects have completed at least 12 weeks of follow-up. The study design included virologic stopping criteria, such that the study drug was discontinued if there was 1) a confirmed increase from nadir in HCV RNA (2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir); or 2) a confirmed HCV RNA ≥ 100 IU/mL after HCV RNA $<$ lower limit of quantification (LLOQ) during treatment.

The 300 mg/120 mg dose was chosen to maximize efficacy and minimize toxicity across HCV genotypes and patient populations. This dose was well tolerated in Phase 2b trials among subjects with genotype 1- 6 infection without severe renal impairment. Further, the regimen

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

achieved SVR12 in $\geq 95\%$ of subjects in most Phase 2b trial arms. GLE/PIB is minimally excreted from the kidneys and pharmacokinetic studies have shown that renal impairment does not impact drug exposure. Therefore, the use of the same dose of study drug in subjects with and without renal impairment was considered appropriate.

The trial was designed to enroll up to 100 adult subjects with CHC and severe renal impairment. Severe renal impairment was defined as an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73². Of these 100 subjects, the Sponsor planned for approximately 80 subjects to require dialysis. Subjects infected with HCV genotypes 1-6 were eligible for study participation. The Sponsor intended for approximately 50 of the subjects to be infected with genotype 1, while the remaining study population would include a mix of genotype 2, 3, 4, 5, and 6-infected subjects. Treatment-naïve and treatment-experienced subjects were eligible for study participation. However, only prior exposure to interferon, ribavirin, and sofosbuvir was permitted among treatment-experienced subjects. Subjects who had failed prior treatment with a protease inhibitor and/or an NS5A inhibitor were excluded. Additionally, genotype 3-infected patients with any prior HCV treatment experience were excluded from the trial as there were insufficient efficacy data to support a 12 week treatment duration in this population.

The study included the enrollment of subjects with and without compensated cirrhosis. Cirrhosis was defined as any one of the following: 1) liver biopsy showing cirrhosis (e.g., Metavir fibrosis score > 3 or Ishak score > 4); 2) FibroTest® score ≥ 0.75 and an aspartate aminotransferase: platelet ratio index (APRI) > 2 during screening; or 3) Fibroscan® result ≥ 14.6 kPa. Any subject with signs or symptoms of hepatic decompensation or a Child-Pugh score > 6 was excluded from the trial. The sponsor intended for approximately 25 of the enrolled subjects to be cirrhotic.

Subjects with a history of hepatocellular carcinoma, active hepatitis B coinfection (i.e. positive hepatitis B surface antigen), HIV coinfection, coinfection with multiple HCV genotypes, previous solid organ transplantation, any uncontrolled medical conditions, acute renal failure within prior three months, or any cause of liver disease other than CHC were excluded from study participation.

Overall, the Division was in agreement with the trial design as described above.

Study Endpoints

The primary efficacy endpoint was SVR12. This was defined as HCV RNA $< \text{LLOQ}$ 12 weeks after the last actual dose of study drug. The secondary efficacy endpoints were on treatment virologic failure and post-treatment relapse. .

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Statistical Analysis Plan

The primary efficacy and safety analyses were performed on the intent-to-treat (ITT) population. This included all enrolled subjects who received at least one dose of study drug. The number and proportion of subjects achieving SVR12 were determined and a two-sided 95% confidence interval (CI) was calculated. For subjects missing visit values, backward imputation was applied for the analysis of SVR when possible. If backward imputation was not possible, then an HCV RNA value from a local laboratory was imputed if available. If neither of these approaches to imputation were possible, the subject was imputed as a failure. No formal hypothesis was tested in this single arm trial. Please refer to statistics review of Dr. Laree Tracy and Dr. Therri Usher for complete details.

Protocol Amendments

There were two amendments to this protocol. Amendment 1 was received on November 24, 2015. The purpose of this amendment was to exclude treatment-experienced genotype 3 infected subjects due to a lack of established efficacy in this population. The Division agreed that the exclusion of these subjects was appropriate. Amendment 2 was received on March 23, 2016. Notable changes implemented in this amendment include revised contraception use requirements and updated exclusion criteria allowing for the enrollment of subjects on peritoneal dialysis. The changes in Amendment 2 did not significantly affect the conduct of the trial.

6.3.2. Study Results

Patient Disposition

This study was ongoing at the time of NDA submission. The database was locked on October 7, 2016 and data through the post-treatment week 12 visit was submitted. There were 140 subjects screened and 104 subjects enrolled in EXPEDITION-4. All 104 enrolled subjects received at least one dose of study drug. Therefore all 104 subjects were included in the intention to treat (ITT) population for efficacy analyses and in the safety population for safety analyses. Four subjects discontinued study drug prematurely due to an AE and the remaining 100 subjects completed 12 weeks of study drug as planned. Regarding study disposition, 1 subject discontinued the study prematurely due to death, 2 subjects completed the full 24 weeks of follow up, and the remaining 101 subjects were ongoing in the study at the time of data lock.

Protocol Violations/Deviations

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Protocol deviations were uncommon in EXPEDITION-4. Six (5.8%) subjects experienced 7 protocol deviations. Six of these deviations pertained to inclusion/exclusion criteria and one deviation pertained to a prohibited concomitant medication.

Reviewer comment: This reviewer agrees with the Applicant that the noted protocol deviations are not likely to have impacted the study results.

Table of Demographic Characteristics

EXPEDITION-4 was a multinational trial, enrolling subjects from 30 sites across 9 countries. Subjects were predominately male (76%) and the median age was 57 years. As intended, approximately half of the subjects were infected with HCV genotype 1 and the remaining subjects were distributed across genotypes 2-6, with only a single genotype 5 subject and a single genotype 6 subject enrolled. Nearly 20% of subjects were cirrhotic, and just over 80% of subjects were on dialysis. See Table 22 for additional details regarding subject demographics and baseline characteristics.

Table 22 EXPEDITION-4 Demographic and Baseline Disease Characteristics (ITT)(N=104)

Characteristic	N (%)*
Age, years	
Median (range)	57 (28 – 83)
≥ 65 years	28 (26.9%)
Gender (Male)	79 (76.0%)
Race	
White	64 (61.5%)
Black	25 (24.0%)
Asian	9 (8.7%)
Other	6 (5.8%)
Ethnicity	
Hispanic	4 (3.9%)
Non-Hispanic	100 (96.1%)
Region	
US	15 (14.4%)
Non-US	89 (85.6%)
Baseline HCV RNA Log₁₀ (IU/mL)	
Mean (SD)	5.85 (0.74)
Median (range)	5.91 (3.40 – 7.54)
HCV Genotype/Subtype	
1	54 (51.9%)
1a	23 (22.1%)
1b	29 (27.9%)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

1 other	2 (1.9%)
2	17 (16.4%)
3	11 (10.6%)
4	20 (19.2%)
5	1 (1.0%)
6	1 (1.0%)
IL28B Genotype	
CC	24 (23.1%)
CT	56 (53.8%)
TT	24 (23.1%)
Cirrhosis (Yes)	20 (19.2%)
Dialysis (Yes)	85 (81.7%)
Diabetes (Yes)	43 (41.4%)
Treatment History	
Treatment-Naïve	60 (57.7%)
Treatment-Experienced	44 (42.3%)

*Presented as n (%) unless otherwise noted.

Source: DM and ADSL datasets

Efficacy Results - Primary Endpoint

Overall SVR12 results are summarized in the below table. Of 104 subjects in the ITT population, 102 (98.1%) achieved SVR12. Among the two subjects who failed to achieve SVR12, 1 subject had missing data (subject died from intracerebral hemorrhage in the post-treatment follow-up period before reaching SVR12 visit) and one subject had discontinued treatment on Day 27 due to an adverse event (Grade 2 diarrhea). There were no virologic failures.

Table 23 Proportion of Subjects Achieving SVR12 in EXPEDITION-4

	% (n/N)	[95% CI]
SVR Achieved (%)	98.1 (102/104)	(93.3%, 99.5%)
SVR Not Achieved	1.9 (2/104)	(0.5%, 6.7%)
Virologic Failure	0 (0/104)	(0%, 3.6%)
Non-virologic Failure	1.9 (2/104)	(0.5%, 6.7%)

Source: Created in JReview using LB and ADEFFOUT datasets
 95% CIs calculated by statistical reviewer

In addition to the primary efficacy endpoint of SVR12, this trial included three key secondary efficacy endpoints: number of subjects experiencing on-treatment virologic failure and number of subjects experiencing relapse by post-treatment Week 12. No subjects met either secondary efficacy endpoint.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Reviewer comment: Based on the findings of this trial, GLE-PIB for 12 weeks appears highly efficacious in subjects with severe renal impairment regardless of HCV genotype, cirrhosis status, or HCV treatment history. It should be noted that many of these subgroups contained very small numbers of subjects (particularly for genotypes 5 and 6 and for prior sofosbuvir-experienced subgroups). However, based on the observed SVR12 data, it is not anticipated that the presence or absence of renal impairment will impact SVR12 rates; therefore, recommendations for treatment durations in the various subgroups will be made based on the overall data for each particular subgroup.

Subgroup Analyses of the Primary Endpoint

Subgroup analyses were performed to evaluate the impact of various demographic and baseline disease characteristics on efficacy. Both HCV disease characteristics and CKD disease characteristics, including HCV genotype, cirrhosis status, and HCV treatment experience were assessed. Please refer to the statistics review for the results of the subgroup analyses. The two subjects who failed to achieve SVR12 were both HCV genotype 1 infected and both were cirrhotic and on dialysis at enrollment.

Reviewer comment: Given that there were only 2 subjects who did not achieve SVR12, it is not possible to draw any conclusions regarding potential differences in efficacy across the various subgroups.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Results the Phase 2/3 dataset from were pooled to compile a summary table describing SVR12 rates by HCV genotype, treatment experience, for the FDA recommended treatment durations. GLE/PIB is highly effective across all 6 evaluated HCV GTs, in treatment experienced subjects with prior exposures to INF, P/R, SOF and RBV or P/R, and in GT1 subjects with prior exposure to NS5A or NS3/4A PI inhibitors.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 24 SVR 12 by Recommended Treatment Duration, Pooled Analysis Phase 2/3 Efficacy Dataset

% SVR12 (n/N), 95% CI*					
GT	Treatment Experience	Cirrhotic Status	GLE/PIB x 8 w	GLE/PIB x 12 w	GLE/PIB x 16 w
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) 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(22/22) 85.1, 100	
	TE	NC		100 (6/6) 61.0, 100	
	TN/TE†	C		100(2/2)	
6	TN	NC		100(28/28) 87.9, 100	
	TE	NC		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.

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

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

7.1.2. Subpopulations

SVR12 in the Phase 2/3 dataset did not vary substantially based on age, race, or sex. As previously noted, there were very few treatment failures across the trials, and the small numbers complicated attempts to identify meaningful trends based on age, race, or sex. SVR12 in subjects with severe renal impairment was high and did not differ from SVR in the overall Phase 2/3 dataset.

7.1.3. Dose and Dose-Response

In Phase 2 dose-ranging studies, lower virologic failure rates were observed in GT3-infected subjects receiving the GLE + PIB 300 mg + 120 mg dose compared to those in lower GLE and PIB dose groups (i.e., 200 mg + 120 mg and 200 mg + 40 mg (Study M14-868). Including RBV in the GLE/PIB regimen did not improve the SVR rate based on SVR12 results in GLE and PIB, and therefore, RBV containing treatment arms were not considered for an indication.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The goal of HCV treatment is total viral eradication, as measured by SVR. Therefore the duration of therapy needed before HCV viral load becomes undetectable therapy (the onset of efficacy) is less important than maintenance of an undetectable viral load off therapy, which is measured as SVR12 and SVR24. Historically, SVR24 was considered a cure and was used as the regulatory endpoint. However, data from 15 phase 2 and 3 clinical HCV trials demonstrated high correlation between SVR12 and SVR24, thereby prompting DAVP to use SVR12 as the primary endpoint for marketing applications rather than SVR24[9]. Complete SVR24 data were not available for all the Phase 2/3 trials but these data will be submitted upon trial completion.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

GLE/PIB would be the first DAA HCV treatment regimen that yields high SVR rates across HCV GT 1-6 with an indicated treatment duration as short as 8 weeks for non-cirrhotic, treatment-naive or PRS-experienced patients with GT 1-4. This represents a large portion of the US population with chronic HCV. GLE/PIB would also be the first all-DAA regimen indicated in the population of subjects with severe renal impairment for genotypes 2, 3, 5 and 6. In addition GLE/PIB, provides an important DAA-only, RBV-free treatment option for GT1-infected patients with prior treatment experience with NS5A (16 weeks duration) or NS3/4A PIs (12 weeks duration).

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

7.3. Integrated Assessment of Effectiveness

The efficacy of GLE/PIB for the treatment of CHC infection in subjects without cirrhosis and with compensated (CTP A) cirrhosis has been established by the results of the nine pivotal Phase 2 and 3 trials discussed in Section 6. Overall SVR12 rates in the Phase 2 /3 trials were 91 to 100% across all genotypes for the recommended treatment durations of 8 to 16 weeks, as shown above.

Significant efficacy review issues included the duration of treatment (8 versus 12 weeks) for GT3 treatment naïve subjects without cirrhosis, traditionally viewed as the most difficult to treat genotype. However, pooled SVR12 rates (non-VF-censored) were high for both durations 97% (177/183) and 99% (258/261) for those who received GLE/PIB for 8 or 12 weeks, respectively, with only a 1.9% higher relapse rate (2.7% vs. 0.8%) with the 8-week versus 12-week duration. The review team favored the 8 week duration given the small, and non-statistical, difference in efficacy (only 2 subjects more had virologic relapse, relapse of n=5 vs. n=3 for 8 vs 12 weeks, respectively) and the large numbers of persons that would be needed to be treated at 12 weeks to see the small incremental benefit in overall efficacy. There are also numerous obvious and practical benefits of a shorter treatment duration including overall patient treatment experience, less possibility for drug-drug interactions and related adverse events, as well as the public-health benefits of reduced health system burden, including fewer treatment-related visits.

For GTs 5 and 6, given the high SVR12 rate in this population, and the small but adequate sample size of GT5 NS3/4A PI- and NS5A Inhibitor-Naïve subjects studied for 12 weeks, the review team supported the indication of 12 weeks of therapy for patients without cirrhosis and with compensated cirrhosis (CTP A liver disease) in this population. While the Division generally has allowed for some extrapolation of results for lower prevalence HCV GTs like GT5 and GT6, even with the 12-week duration, some extrapolation of available data needed to be considered to support treatment recommendations for GT5 -infected patients with compensated cirrhosis or prior sofosbuvir- or interferon-based treatment experience. The sponsor has an ongoing trial, M16-126, that will assess the efficacy of the 8-week and 12-week durations in treatment-naïve and treatment-experienced-PRS subjects with HCV GT5 or GT6 infection, with and without compensated cirrhosis. This study could provide sufficient data to support a future recommendation of GLE/PIB for 8 weeks for treatment-naïve and treatment-experienced PRS patients without cirrhosis.

The review team recommended a 12 week treatment indication for NS3/4A PI-experienced and NS5A inhibitor-naïve patients with GT1 HCV infection, based on a high SVR12. However, an important review issue related to the MAGELLAN-1 trial was whether the Applicant had provided sufficient evidence to support a treatment recommendation for HCV GT1 infected,

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

NS5A inhibitor-experienced patients. The review team concluded that the data support a treatment recommendation for GLE/PIB for 16 weeks for HCV GT1 infected, NS5A inhibitor-experienced, NS3/4A PI-naïve patients, based on the non-VF-censored SVR12 of 94% in this population, when treated for 16 weeks. However, the data were not supportive of a treatment recommendation for GT1 infected patients with experience to both NS5A inhibitors and NS3/4A PIs, due to higher rates of treatment failure and lower SVR12 in this subpopulation (SVR 80%).

GLE-PIB for 12 weeks also appeared highly efficacious in subjects with severe renal impairment regardless of HCV genotype, cirrhosis status, or HCV treatment history. It should be noted in the trial of subjects with severe renal impairment many of the genotype and patient subpopulations contained very small numbers of subjects (particularly for genotypes 5 and 6 and for prior sofosbuvir-experienced subgroups). However, based on both the metabolism of GLE/PIB and the observed SVR12 data, it is not anticipated that the presence or absence of renal impairment will impact SVR12 rates, therefore recommendations for treatment durations in the various genotypes and subpopulations of patients with severe renal impairment will follow the overall data supported indication for each particular genotype or subgroup.

SVR12 was 100% with no virologic failures GT1 HCV/HIV co-infected subpopulation. As it is also not anticipated that the presence or absence of HIV infection will impact SVR12 rates, recommendations for treatment durations in the various genotypes and subpopulations of patients with HIV-co-infection will follow the overall data for each particular genotype or subgroup.

In summary, this is the first regimen with pan-genotypic efficacy, which can be used for as little as 8 weeks in non-cirrhotic, treatment-naïve subjects with GT 1-4 infection, or in non-cirrhotic, PRS-treatment-experienced subjects with GTs 1, 2 or 4. This would also be the first approved regimen of any kind for subjects with HCV GT 2, 3, 5, or 6 infection and severe renal impairment. Additionally, the regimen provides an important treatment option for some HCV GT1 DAA- experienced patients.

8 Review of Safety

Safety Review Approach

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/Phase3 pooled safety dataset included data from 2,265 subjects with or without cirrhosis who received at least

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

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 database excluded subjects with severe renal impairment enrolled in EXPEDITION-4 (M15-462), as subjects with severe renal impairment have different baseline health status. Throughout the safety review, the Phase 2/3 safety database will be used to define the total safety population, excluding EXPEDITION-4 subjects (n=2,265) as this trial was reviewed separately and is discussed further below in Section 8.7.

Individual analysis of ENDURANCE-2, the placebo controlled trial, and EDURANCE-3, the active controlled trial are also presented. The Phase 2/Phase3 pooled safety dataset was analyzed by duration and cirrhosis status and these data are also presented. A thorough hepatic safety review was conducted given adverse events of hepatic decompensation associated with earlier generation marketed HCV NS3/4A PIs. Deaths occurring in any submitted Phase 2 or Phase 3 trial were reviewed and assessed.

Dr. Lara Stabinski conducted the above safety analyses which are presented in Section 8. Unless otherwise specified, clinical trial data were independently analyzed using the SDTM datasets as well as the ISS datasets in JReview. Any differences in findings by the FDA reviewer compared to the Applicant were relatively minor and attributable to variable methods of pooling and subgroup analyses. All of the safety assessments and conclusions are those of the FDA reviewer unless otherwise specified.

Dr. Aimee Hodowanec conducted the primary safety analysis of EXPEDITION-4, which is presented in Section 8.7. As stated above, EXPEDITION-4 was not pooled with any other trial for analyses presented in Section 8 because subjects with severe renal impairment (CKD Stage 4 or 5) represent a considerably different patient population and thereby have potentially different safety concerns.

The Applicant also submitted a Safety Update Report (SUR) four months after the original NDA submission. Deaths, SAEs, potential cases of hepatotoxicity, hepatic decompensation and events of hepatocellular carcinoma, reported in the SUR are included in the relevant safety sections.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The following table describes the overall exposure to GLE/PIB in the GLE/PIB development program. Excluding subjects who received deferred treatment in the placebo controlled trial (ENDURANCE-2), 2,369 subjects 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.

CDER Clinical Review Template 2015 Edition

87

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 25 Development Program: Population and Size

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N=3,311			
Clinical Trial Groups	New Drug (GLE 300 mg QD and PIB 120 mg QD) (n= 3,311)	Active Control (SOF/DCV) (n=115)	Placebo (n=100)
Normal Volunteers	942	NA	NA
Placebo Controlled Trial conducted for this indication ²	202	NA	100
Active Controlled trial conducted for this indication ³	233	115	NA
Open label trials conducted for this indication ⁴	1,934	NA	NA

¹ *study drug* means the drug being considered for approval.

8.2.2. Relevant characteristics of the safety population:

Demographic characteristics of subjects in the pooled Phase 2/Phase 3 dataset are summarized in the below table. Baseline characteristics for each of the pivotal trials are described in Section 6.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 26 Summary Demographic Characteristics, Phase 2/Phase 3 Safety Dataset, excluding M15-462 (severe renal impairment)

Age	Phase 2/Phase 3 Safety Dataset N= 2,265
Mean (SD)	52.3 (11.82)
≥ 65 years N (%)	300 (13.2)
Sex N (%)	
Male	1,239 (54.7)
Female	1,026 (45.3)
Race N (%)	
White	1,834 (81.1)
Black	124 (5.5)
Asian	263 (11.6)
Other/ No info	44(1.9)
Location N (%)	
North America	937 (41.4)
Europe	826 (36.5)
Rest of world	502 (22.2)
HCV/HIV Co-infection N (%)	
HCV Genotype 1/HIV Co-infection	33(1.4)
Baseline Fibrosis Stage	
F0-F1	1,593 (70.5)
F2	154 (6.8)
F3	228 (10.1)
F4	286 (12.6)
Cirrhosis Status N (%)	
No Cirrhosis	1,977 (87.3)
Compensated Cirrhosis	288 (12.7)
Baseline Mean Child Turcotte Pugh Score Mean (SD)	
Compensated Cirrhosis	5.1 (0.3)
Baseline Mean MELD Score Mean (SD)	
No Cirrhosis	6.5(1.1)
Compensated Cirrhosis	7.3(1.6)
Baseline FIB-4 Score (SD)	
No Cirrhosis	1.5 (1.0)
Compensated Cirrhosis	4.4 (2.6)
HCV Genotype N(%)	
Genotype 1	943 (41.6)
Genotype 2	632 (27.9)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Genotype 3	450 (19.9)
Genotype 4	162 (7.2)
Genotype 5	47 (2.1)
Genotype 6	31(1.4)
Prior Treatment Experience N (%)	
Experienced	685 (30.2)
Naïve	1,580 (69.8)

Source: ISS2 dataset

- a. Excluding Study M15-462
- b. Fibrosis stage was based on the algorithm that used biopsy, Fibroscan, or Fibrotest results at baseline. Four subjects were missing fibrosis stage at baseline.
- c. Cirrhosis status was based on Investigator assessment of cirrhotic or noncirrhotic at screening.

8.2.3. Adequacy of the safety database:

The safety database for both products is comprehensive and adequate to assess the safety of GLE/PIB for the proposed indication, dosage regimen, duration of treatment, and patient population. The Phase 2/3 trials evaluated over 2,300 subjects treated at the proposed dose and duration of GLE/PIB, which exceeds FDA’s recommendation for a 1000-1500 subject safety database for treatment of patients with compensated liver disease.[10]

8.3. Adequacy of Applicant’s Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For Phase 2 and 3 trials, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant’s summary and assessment.

8.3.2. Categorization of Adverse Events

No issues were identified with respect to recording, coding, and categorizing of adverse events (AEs). The Applicant categorized AEs and serious adverse events (SAEs) in accordance with standard regulatory definitions. AEs were defined in Common Terminology Criteria for Adverse Events (CTCAE). The Investigator rated the severity of each AE according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 4. The clinical reviewers verified the Applicant’s translation of verbatim terms to preferred terms for events reported in the Phase 2/3 Safety dataset.

8.3.3. Routine Clinical Tests

Routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Treatment Weeks (TW) 1, 2, 4, 6, 8, 12 and 16, as applicable and follow-up weeks 4 and 24. The frequency

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurements, physical examinations, 12-lead ECGs (at baseline and end of treatment), and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the Investigator during the trials.

8.4. **Safety Results**

The Phase 2/3 safety analysis dataset was used for all analyses unless otherwise specified. All subjects who received at least one dose of study medication at the indicated dosage without ribavirin were included in this dataset, excluding those with severe renal disease (EXPEDITION-4; M15-462). For the purposes of comparison, and where relevant, data from the placebo (ENDURANCE-2; M15-464) and active controlled (ENDURANCE-3; M13-594) trials are presented. In addition, in certain cases, for illustrative purposes, data are presented by duration and cirrhosis status.

An overall summary of safety events in the placebo controlled, active controlled, severe renal impairment population and Phase 2/3 safety analysis dataset by duration and cirrhosis status are presented in the below tables.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 27 Overall Safety Events by Duration

	Treatment Group, n (%)								
	ENDURANCE-2 M15-464, GT2 (Placebo-Controlled)		ENDURANCE-3 M13-594, GT3 (Active-Controlled)			EXPEDITION-4 M15-462 (Severe Renal Impairment)	Pooled Studies ENDURANCE-1 (M13-590), SURVEYOR-1 (M14-867), ENDURANCE-2 (M15-464), SURVEYOR-2 (M14-868), ENDURANCE-3 (M13-594), ENDURANCE-4 (M13-583), EXPEDITION-1 (M14-172), MAGELLAN-1 (M15-410) (Study drug arm registration studies, excludes subjects with renal impairment)		
	Placebo 12 weeks (N = 100)	GLE/PIB 12 weeks (N = 202)	SOF/DCV 12 weeks (N = 115)	GLE/PIB 12 weeks (N = 233)	GLE/PIB 8 weeks (N = 157)	GLE/PIB 12 weeks (N = 104)	GLE/PIB 8 weeks (N = 850)	GLE/PIB 12 weeks (N = 1295)	GLE/PIB 16 weeks (N = 120)
Any AE	58 (58.0)	131 (64.9)	80 (69.6)	177 (76.0)	98 (62.4)	74 (71.2)	542 (63.8)	901 (69.6)	86 (71.7)
Any DAA-related AE ^{b,c}	33 (33.0)	64 (31.7)	50 (43.5)	112 (48.1)	63 (40.1)	51 (49.0)	315 (37.1)	552 (42.6)	62 (51.7)
An AE Grade $\geq$ 3	1 (1.0)	5 (2.5)	2 (1.7)	11 (4.7)	3 (1.9)	25 (24.0)	17 (2.0)	39 (3.0)	9 (7.5)
Any DAA-related AE Grade $\geq$ 3 ^{b,c}	0	1 (0.5)	1 (0.9)	1 (0.4)	0	5 (4.8)	0	3 (0.2)	1 (0.8)
Any SAE	1 (1.0)	3 (1.5)	2 (1.7)	5 (2.1)	3 (1.9)	25 (24.0)	12 (1.4)	29 (2.2)	7 (5.8)
Any DAA-related SAE ^{b,c}	0	0	0	0	0	0	0	1 (< 0.1)	0
Discontinuation of study drug due to:									
Any AE	0	0	1 (0.9)	3 (1.3)	0	4 (3.8)	1 (0.1)	7 (0.5)	0
Any DAA- related AE ^{b,c}	0	0	1 (0.9)	1 (0.4)	0	2 (1.9)	0	3 (0.2)	0
Any fatal AE	0	0	0	0	0	1 (1.0)	1 (0.1)	1 (< 0.1)	0
All deaths ^d	0	0	1 (0.9)	0	1 (0.6)	1 (1.0)	3 (0.4)	3 (0.2)	0

AE = adverse event; DAA = direct-acting antiviral agent; DCV = daclatasvir; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event; SOF = sofosbuvir

- For the placebo arm, treatment-emergent AEs were defined as any event that began or worsened in severity after the first dose of placebo through 30 days after the last dose of placebo and prior to open-label Day 1.
- DAA = GLE, PIB, GLE/PIB, DCV, or SOF.
- Investigator assessment.
- Includes nontreatment-emergent deaths.

Source: Clinical IR 2/17/17; data verified

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 28 Overall Safety Events by Cirrhosis Status

	Treatment Group, n (%)						
	EXPEDITION-4 M15-462, (Severe Renal Impairment)		Pooled Studies ENDURANCE-1 (M13-590), SURVEYOR-1 (M14-867), ENDURANCE-2 (M15-464), SURVEYOR-2 (M14-868), ENDURANCE-3 (M13-594), ENDURANCE-4 (M13-583), EXPEDITION-1 (M14-172), MAGELLAN-1 (M15-410) (Study drug arm registration studies, excludes subjects with renal impairment)				
	<u>GLE/PIB</u> <u>12 weeks</u> No cirrhosis (N = 84)	<u>GLE/PIB</u> <u>12 weeks</u> Cirrhosis (N = 20)	<u>GLE/PIB</u> <u>8 weeks</u> No Cirrhosis (N = 850)	<u>GLE/PIB</u> <u>12 weeks</u> No Cirrhosis (N = 1070)	<u>GLE/PIB</u> <u>12 weeks</u> Cirrhosis (N = 225)	<u>GLE/PIB</u> <u>16 weeks</u> No Cirrhosis (N = 57)	<u>GLE/PIB</u> <u>16 weeks</u> Cirrhosis (N = 63)
Any AE	54 (64.3)	20 (100)	542 (63.8)	735 (68.7)	166 (73.8)	39 (68.4)	47 (74.6)
Any DAA-related AE ^{a,b}	39 (46.4)	12 (60.0)	315 (37.1)	454 (42.4)	98 (43.6)	28 (49.1)	34 (54.0)
An AE Grade ≥ 3	14 (16.7)	11 (55.0)	17 (2.0)	25 (2.3)	14 (6.2)	3 (5.3)	6 (9.5)
Any DAA-related AE Grade ≥ 3 ^{a,b}	2 (2.4)	3 (15.0)	0	3 (0.3)	0	1 (1.8)	0
Any SAE	14 (16.7)	11 (55.0)	12 (1.4)	16 (1.5)	13 (5.8)	3 (5.3)	4 (6.3)
Any DAA-related SAE ^{a,b}	0	0	0	1 (< 0.1)	0	0	0
Discontinuation of study drug due to:							
Any AE	2 (2.4)	2 (10.0)	1 (0.1)	7 (0.7)	0	0	0
Any DAA-related AE ^{a,b}	0	2 (10.0)	0	3 (0.3)	0	0	0
Any fatal AE	0	1 (5.0)	1 (0.1)	1 (< 0.1)	0	0	0
All deaths ^c	0	1 (5.0)	3 (0.4)	2 (0.2)	1 (0.4)	0	0

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event

a. DAAs = GLE, PIB, or GLE/PIB.

b. Investigator assessment.

c. Includes nontreatment-emergent deaths.

Source: Clinical IR 2/17/17; data verified

Reviewer Comment: AEs, SAEs and Grade 3 or higher AEs occurred at higher frequency in groups with expected poorer baseline health status including in the study of severe renal impairment, in those with cirrhosis and those receiving 16 weeks of therapy (who were more likely to have cirrhosis, HCV genotype 3 and to be treatment experienced). However, AEs considered by the Applicant/Investigator as possibly related occurred at more similar frequencies across these subgroups; DAA-related AEs occurred at similar frequencies to AEs in the placebo and active control arms. There was only one SAE and one Grade 3 or higher AE considered by the Applicant to be possibly related to the study drug. The overall AE summary is favorable with few subjects discontinuing GLE/PIB due to AEs (0.5% overall).

8.4.1. Deaths

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

A total of 6 deaths occurred amongst all the subjects in the Phase 2 and Phase 3 Safety Analysis Set at the time of the database lock. One additional death occurred in a subject with severe renal impairment (EXPEDITION-4) and is described in further detail in Section 8.7. All subjects received coformulated GLE/PIB 300 mg/120 mg QD or coadministered GLE 300 mg QD and PIB 120 mg QD. Adverse events that led to death included cerebral hemorrhage (2 subjects; including 1 in the study of severe renal impairment), hepatic cancer metastatic, pneumonia, accidental overdose, and adenocarcinoma. One subject died due to unknown cause (preferred term death). No deaths were assessed as related to DAA study drug by the Investigator or Applicant. The below table provides a summary of each death in the Phase 2/3 safety dataset provided with reviewer comments.

Table 29 Deaths in Phase 2 and 3 Safety Analysis Set

Subject ID	Age/Sex/Race	Total GLE/PIB Exposure (Days)	Study Day Onset Study Day (Days post last dose)	Baseline Cirrhosis/Liver Status	Applicant Associated Preferred Term	Other reported AEs	Significant Medical History/Circumstances of Death	Reviewer Comment
162309(USA)	23/M/W	56	133 (77)	No Cirrhosis F0-F1 FIB 4: 0.4 NAÏVE	Accidental overdose	SAE-Dependence (Day 51)- methadone and heroin relapse Hypokalemia (Day63)	Anxiety, panic attacks, suicidal ideation, seizures./ Found dead in car. Presumed overdose. Autopsy report and death certificate "unobtainable". Considered unrelated to study drug by Applicant and Investigator.	<i>The paucity of information regarding the subject's death complicates causality assessment. However, given that the death occurred 77 days after the last dose of study drug, the reviewer agrees with the Applicant and Investigator assessment of causality.</i>
103505 (BEL)	40/M/W	84	143 (59)	Cirrhosis F4 FIB 4: 2.2 CTP 5 MELD 7 NAÏVE	Cerebral hemorrhage	SAE- Epistaxis (Day 9) Other AEs on treatment- Edema, Petechaie, Fatigue. MELD week 2 up to 8 the normalized week 16. Plts, INR, PTT relatively stable. Week 2 experienced max	History of Epilepsy and von Willebrand disease Type III and 2 major previous remote bleeding episodes (2009, 1976). / Spontaneous massive cerebral hemorrhage. Considered unrelated to study drug by Applicant and Investigator.	<i>This subject, who had few previous major bleeding events, experienced bleeding on study drug. However, his INR and PTT remained stable. The event leading to his death</i>

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

						from baseline blood pressure elevation systolic 25, diastolic 26. (Baseline BP 137/77, week 2 162/103. Elevation was not sustained)		<i>occurred 60 days after the last dose of study drug and the reviewer agrees that his underlying condition could have been the cause of his death.</i>
133102 (CAN)	43/F/B	85	99 (14)	No Cirrhosis FO-F1 FIB 4: 5.3 NAÏVE	Death	SAE –Aspiration pneumonia (Day 54) Found “shaking, agitated” Hypocalcemia, Opiates in urine	History of gastric bypass, heartburn, hypothyroidism, osteomyelitis, on methadone, smoker. / Died on bus ride home from EOT visit. HCV viral load was negative. Autopsy pending. Considered unrelated to study drug by Applicant and Investigator.	<i>The paucity of information regarding the subject’s death complicates causality assessment. Given gastrointestinal AEs seen in many other subjects, this subjects underlying absorption limitation symptom, her AE of hypocalcemia and seizure like activity it is possible that her death was partially attributable to the study drug. However, there is not sufficient information for a full assessment</i>

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

								<i>and therefore the reviewer classifies the cause of death as unknown.</i>
2305 (USA)	63/M/W	86	227 (141)	No Cirrhosis F3 FIB 4: 2.5 CTP 5 NAÏVE	Pneumonia	AEs- Localized infection, back pain. BL MELD 18 (on anticoagulation).	History of Asthma, COPD, Emphysema, DVT, CHF, DM, arrhythmia. / Subject died in long term care facility. Cause of death on death certificate was "pneumonia". Considered unrelated to study drug by Applicant and Investigator.	<i>The reviewer agrees that the subject's death was likely due to pneumonia and his underlying chronic disease conditions.</i>
1301 (USA)	65/M/W	85	156 (71)	No cirrhosis FO-F1 FIB4: 2.4 MELD 6 (Experienced-RBV, pegIFN, TVR)	Hepatic cancer metastatic	SAE Pathologic Fracture, other AEs headache, night sweats, hypoesthesia, photosensitivity reaction, pruritus generalized, anxiety, arthralgia, neuralgia.	H/o Depression, Anxiety, DJD, Insomnia, remote history of benign knee soft tissue tumor. / Presented with pathologic fracture and weakness. Considered unrelated to study drug by Applicant and Investigator.	<i>Hepatocellular carcinoma in HCV infected persons is more likely to present in subjects with cirrhosis, and in this case treatment of HCV did not prevent the development of HCC. However, the role of HCV treatment and its association with the development of HCC has not been established.</i>

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

3408(USA)	67/F/W	29	29, (89 died)	No cirrhosis F3 FIB4: 2.4 NAÏVE	Adenocarcinoma	Other AE nausea	“Benign” hypochoic lymph node portahepatis with multiple smaller nodes one year prior. Day 29 abdominal wall mass numerous nodules, liver, spleen, lung and peripancreatic nodes. Pathology “favoring” gynecologic origin. Pt had hysterectomy in 1983. Considered unrelated to study drug by Applicant and Investigator.	<i>The reviewer agrees with the Investigator’s assessment that this likely death was a result of the subject’s malignancy.</i>

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Safety Update: Three additional subjects died since the primary analysis database lock for the NDA submission and through the data cutoff date for this update. The deaths of these 3 subjects occurred at least 135 days after the completion of treatment and no death was considered related to study drug. All 3 subjects achieved SVR12. They are briefly presented below.

Subject 1019 is a 60 year old white male with a history of depression, anxiety, insomnia, and drug abuse/suicide who died of an intentional self- injury on Day 202, 145 days after the last dose of study drug, shortly after a discharge from a rehabilitation facility.

Subject 302508 is a 76 year old white male with a history of hypertension who died of an ischemic stroke on Day 221, 136 days after the last dose of study drug.

Subject 609505 is a 61 year old white male with a history of peripheral vascular disease who died of cardiopulmonary failure on Day 219, 135 days after the last dose of study drug.

Reviewer Comment: *The reviewer agrees that the cause of death in these subjects was not related to study drug, but rather to subjects' underlying risk factors and disease states.*

8.4.2 Serious Adverse Events

Treatment Emergent SAEs were infrequent overall, occurring in approximately 2% of subjects overall and in 1.6% of non-cirrhotic subjects. SAEs occurred in approximately 6% of cirrhotic subjects. There was one (1%) SAE in the placebo group and there were 2 (2%) SAEs the SOF/DCV active comparator group. The below table provides a summary of Treatment Emergent SAEs in the Phase 2/3 Safety Dataset by system organ class (SOC) and cirrhosis status.

Table 30 Treatment-emergent SAEs by SOC and Cirrhosis Status in the Phase 2/3 Safety Dataset, excluding subjects with severe renal impairment

Primary System Organ Class	No Cirrhosis N=1,977	Cirrhosis N=288	Total Subjects N=2,265
Infections and infestations	8 (0.4%)	3 (1.0%)	11 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.2%)	5 (1.7%)	8 (0.3%)
Injury, poisoning and procedural complications	5 (0.3%)	1 (0.3%)	6 (0.2%)
Gastrointestinal disorders	2 (0.1%)	3 (1.0%)	5 (0.2%)
Psychiatric disorders	3 (0.2%)	1 (0.3%)	4 (0.2%)
Respiratory, thoracic and mediastinal disorders	3 (0.2%)	1 (0.3%)	4 (0.2%)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Primary System Organ Class	No Cirrhosis N=1,977	Cirrhosis N=288	Total Subjects N=2,265
Cardiac disorders	2 (0.1%)	1 (0.3%)	3 (0.1%)
Nervous system disorders	2 (0.1%)	1 (0.3%)	3 (0.1%)
Hepatobiliary disorders	2 (0.1%)	0 (0.0%)	2 (0.1%)
Metabolism and nutrition disorders	0 (0.0%)	2 (0.7%)	2 (0.1%)
General disorders and administration site conditions	1 (0.1%)	0 (0.0%)	1 (0.0%)
Eye disorders	1 (0.1%)	0 (0.0%)	1 (0.0%)
Investigations	0 (0.0%)	1 (0.3%)	1 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	0 (0.0%)	1 (0.0%)
Pregnancy and perinatal conditions ^a	1 (0.1%)	0 (0.0%)	1 (0.0%)
Total Subjects	31 (1.6%)	17 (5.9%)	48 (2.1%)

a. All pregnancies discussed in Section 8.8.2

Source: ADEA Database

Overall and amongst the non-cirrhotic, all SAE SOC categories contained less than 1% of subjects. Amongst cirrhotic the SOCs “Neoplasms benign, malignant and unspecified”, “Infections and infestations”, “Gastrointestinal Disorders” and “Metabolism and Nutrition”(with rounding), contained 1% or more subjects. Dictionary Defined terms for these events are listed below.

Table 31 Treatment-emergent SAEs by SOC and Dictionary Derived Term, where SOC >= 1% of the Cirrhotic sub-population

Primary System Organ Class	Dictionary Derived Term	No Cirrhosis N=1,977	Cirrhosis N=288	Total Subjects N=2,265	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma	1 (0.1%)	0 (0.0%)	1 (0.0%)	
	Colon cancer	0 (0.0%)	1 (0.3%)	1 (0.0%)	
	Hepatic neoplasm	0 (0.0%)	1 (0.3%)	1 (0.0%)	
	Hepatocellular carcinoma	0 (0.0%)	2 (0.7%)	2 (0.1%)	
	Paranasal sinus and nasal cavity malignant neoplasm recurrent	1 (0.1%)	0 (0.0%)	1 (0.0%)	
	Squamous cell carcinoma of skin	0 (0.0%)	1 (0.3%)	1 (0.0%)	
	Uterine leiomyoma	1 (0.1%)	0 (0.0%)	1 (0.0%)	
	Infections and infestations	Appendicitis	1 (0.1%)	0 (0.0%)	1 (0.0%)
		Bronchitis	1 (0.1%)	0 (0.0%)	1 (0.0%)
		Cellulitis	1 (0.1%)	0 (0.0%)	1 (0.0%)
Endophthalmitis		0 (0.0%)	1 (0.3%)	1 (0.0%)	
	Gastrointestinal viral infection	1 (0.1%)	0 (0.0%)	1 (0.0%)	

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	Ophthalmic herpes simplex	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Pneumonia	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Rectal abscess	0 (0.0%)	1 (0.3%)	1 (0.0%)
	Urinary tract infection	0 (0.0%)	1 (0.3%)	1 (0.0%)
	Urosepsis	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Wound infection	1 (0.1%)	0 (0.0%)	1 (0.0%)
Gastrointestinal disorders	Gastric ulcer	0 (0.0%)	1 (0.3%)	1 (0.0%)
	Hemorrhoids	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Irritable bowel syndrome	1 (0.1%)	0 (0.0%)	1 (0.0%)
	Esophageal varices hemorrhage	0 (0.0%)	1 (0.3%)	1 (0.0%)
	Umbilical hernia	0 (0.0%)	1 (0.3%)	1 (0.0%)
Metabolism and nutrition disorders	Hyperglycemia	0 (0.0%)	1 (0.3%)	1 (0.0%)
	Hypoglycemia	0 (0.0%)	1 (0.3%)	1 (0.0%)

Source: ADAE database

Reviewer comment: Overall, acute infections comprised a largest number of the treatment emergent SAEs observed, which are unlikely to be related to either the underlying disease condition (in this population with well compensated liver disease) or study medication.

Numbers in the Neoplasms SOC were driven by hepatocellular carcinoma in the cirrhotic sub-population. These 3 hepatocellular carcinomas represent 3 of 6 total hepatocellular carcinoma cases seen in the GLE/PIB arms of this study (3 cases were not classified as treatment emergent SAEs). All hepatocellular carcinoma cases are discussed in detail in Section 8.5.1. In brief, hepatocellular carcinoma is a known complication of chronic HCV infection, usually seen in patients with cirrhosis. The effect of DAA therapy on the development or prevention of hepatocellular carcinoma is not completely understood; however in this study of well compensated cirrhotics (mean CTP 5.1) successful therapy with GLE/PIB did not eliminate the risk of hepatocellular carcinoma.

Other than hepatocellular carcinoma, “transient ischemic attack” was the only one other Dictionary Defined Term Treatment Emergent SAE that occurred in more than one subject. One of these events, was the only SAE considered possibly related to study drug by the Investigator. Both subjects and their SAEs are described briefly below.

- **Subject 303402** is a 49 year old non-cirrhotic white male with a history of smoking cigarettes (0.5 packs/day for 30 years), obesity (baseline BMI 31), and cardiac conduction abnormality on Screening electrocardiogram (ECG), and elevated hemoglobin (18.1 g/dL) and hematocrit at Screening, experienced two events of transient ischemic attack (TIA) on Day 11 and 36. On Day 11, the subject experienced right hand clumsiness and Broca’s aphasia. On Day 11, a carotid ultrasound, cerebral magnetic resonance imaging

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

(MRI), cerebral computerized tomography, and ECG were within normal limits. Study drug was withdrawn, with the last dose administered on Day 12. The subject was treated with enoxaparin and acetylsalicylic acid and experienced another event of dysarthria on Day 36. Blood pressure readings were not provided for the duration of the events, but the subject was normotensive at screening and baseline with a baseline with a blood pressure of 127/80. At Week 2 the subject had an elevated diastolic blood pressure of 133/93 (no further readings were available as the subject discontinued treatment). Cerebral MRI was normal. The Investigator considered the events of TIA as having a reasonable possibility of being related to study drug. The Sponsor considered the events as having no reasonable possibility of being related to study drug, and more likely related to a history of obesity, smoking, and a cardiac conduction abnormality as noted on Screening ECG, as well as elevated hemoglobin and hematocrit.

Reviewer Comment: The reviewer agrees with the Investigator that the younger age, race, elevated diastolic blood pressure (albeit a single reading) on treatment and temporal association between onset of study medication and onset of TIA are suggestive for an adverse drug reaction; although this subject had some possible baseline stroke risk factors including smoking (the baseline conduction abnormality was not mentioned on subsequent ECGs). According to recent studies, the risk of death from ischemic heart disease and stroke doubles with every sustained 20 mm Hg systolic or 10 mm Hg diastolic increase among people from age 40 to 89.[11]

- **Subject 326104** is a 62 year old non-cirrhotic Asian female with relevant medical history of right carotid transient ischemic attack approximately 8 months prior (b) (6) and fatty liver, experienced a transient ischemic attack. On Day 4, the subject experienced a sudden onset of dysphagia, difficult speech, and right upper arm weakness for a few minutes and was admitted to the hospital. Computed tomography and magnetic resonance imaging showed no acute abnormalities. Color Doppler sonography of the extracranial carotid showed intimal thickening and sparse mural plaques along the course of bilateral extracranial common and internal carotid arterial and vertebral artery; there was no identifiable significant stenosis. Cardiac echo showed left ventricle diastolic dysfunction or aging process, no intra-cardiac shunt or mass detected, mild mitral reflux, tricuspid regurgitation, pulmonic regurgitation, and no mention of intra-cardiac thrombus. Blood pressure readings were not available during this event but the subject was normotensive at baseline and all subsequent visits; she did have elevated diastolic blood pressure on her screening visit. The subject was treated with acetylsalicylic acid, piracetam, and mecobalamin. The subject's upper limb weakness and speech function improved on the following day after the event. Study drug was not interrupted or discontinued due to this event. The Investigator considered the event of

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

transient ischemic attack as having no reasonable possibility of being related to study drug and more likely related to medical history of right carotid transient ischemic attack. The Sponsor considered the event as having no reasonable possibility of being related to study drug and more likely related to cerebrovascular disease and her personal history of previous TIA.

Reviewer Comment: Although the timing of this event is suggestive of an adverse drug reaction, this event occurred in a subject with a recent history of transient ischemic attack (within one year). This reviewer agrees with the Investigator and Applicant that there is no evidence that this event was related to study medication.

In EXPEDITION-4; M15-462, the study population with severe renal impairment, one subject experienced a cerebral hemorrhage resulting in death and one subject experienced facial paresis. Both subjects experienced on-treatment increases and fluctuations in blood pressure proximal to their events, but these fluctuations are difficult to interpret in the context of underlying severe renal impairment. (See Section 8.7 for further details).

Given these cardiovascular SAEs, further analysis of cardiac-related SAEs was conducted. Angina coded as “Angina Pectoris” and “Angina Unstable” Treatment Emergent SAEs occurred in two subjects. They are described briefly below.

Subject 7010 experienced Angina Pectoris. This subject is a 51 year old white male with hypertension noted at screening (150/75) and baseline (169/79) and a history of intermittent chest pain within a year of treatment, who presented on Day 9 -10 with stabbing chest pain, tingling in left arm and headache. In the hospital on Day 10, blood pressure was 160/80 mm/Hg (not clear if this was before or after anti-hypertensives were administered), troponin T level was 5 NG/L (reference range: 0 – 14 NG/L), and an exercise tolerance test (ETT) showed some ST depression noted at late stage during ETT, 1 – 2 mm stage III onwards, with no limiting chest pain; angiogram was normal. Study drug was not interrupted or discontinued due to this event. On Day 14, the subject was discharged from the hospital and the event of angina pectoris was considered resolved. Blood pressure at the 2 week visit (Day 15) was 186/84 but decreased to his baseline at subsequent visits. His hypertension was treated after his event with two antihypertensive drugs (metoprolol day 10-14 and felodipine day 10 -ongoing). The Investigator and Applicant evaluated the event as unrelated to study drug.

Reviewer Comment: Although the timing of this event is suggestive of an adverse drug reaction and at least one on-treatment measurement showed a worsening of blood pressure around the time of the event, the event occurred in a subject with a recent history of intermittent chest pain (within one year). This reviewer agrees with the Investigator and Applicant that there is limited direct evidence that this event was related to study medication

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

and could be related to his underlying poorly controlled (or possibly previously untreated) hypertension.

Subject 172105 experienced Angina Unstable. This subject is 65 year old white male with a relevant history of hypertension (screening blood pressure was 158/96 and baseline blood pressure was 156/111) and psoriatic arthritis. The subject experienced an adverse event of hypokalemia (grade 1) first noted on Day 16. The subject's blood pressure significantly decreased on treatment, notably on the Week 1 visit it was 136/80 and on the Week 4 visit it was 122/88. The subject was on doxazosin and lercanapidine during this time period and there were no noted changes to his antihypertensives. On Day 26, the subject felt chest pain secondary to unstable angina and was urgently admitted to the hospital. Limited laboratory results were negative for myocardial infarction including creatine kinase level of 39 IU/mL (reference range: 39 – 308 IU/mL). No other laboratory results were reported. The subject was treated with enoxaparin, acetylsalicylic acid, clopidogrel, co-diovan, and amlodipine. Electrocardiogram (ECG) showed T-wave abnormality with no sign of myocardial infarction. Coronography showed stenosis of the left anterior descending (LAD) artery and 60 percent stenosis of first diagonal branch. Percutaneous coronary intervention (PCI) of the LAD artery was performed with good circulation observed after PCI. Study drug was not interrupted or discontinued due to this event. The Investigator and Applicant assessed this event as unrelated to the study drug.

Reviewer Comment: Although the dramatic fluctuation in blood pressure is suggestive of an adverse drug reaction (or drug-drug interaction), the event occurred in a subject with underlying coronary artery disease. This reviewer agrees with the Investigator and Applicant that there is no direct evidence that this event was related to study medication.

In addition, 3 subjects experienced SAEs of "Acute myocardial Infarction" or "Myocardial Infarction" coded as non-Treatment Emergent occurring on Study Days 116-132, Post Treatment Days 32-76. There was also one subject who experienced a non-Treatment Emergent SAE of "Coronary Artery Disease" on Day 132 or Post Treatment Day 38. With the exception of one subject with myocardial infarction, all had known histories of cardiovascular disease.

Reviewer Comment: The subject with the "Coronary Artery Disease" event experienced an AE of hypertension on treatment, but overall there was no clear pattern preceding these non-treatment emergent events.

Safety Update:

One additional **Subject 8719** was reported as having a treatment emergent SAE of hiatal hernia. The subject is a 61 year old white female, with ongoing alcohol use (less than 2 drinks per day), former smoker, with relevant history of chronic hepatitis C virus infection without cirrhosis,

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

hiatal hernia, gastritis, esophagitis, diffuse abdominal tenderness, nausea, bloating and belching, vomiting, and gastroesophageal reflux disease experienced an event of hiatus hernia. She also developed multiple treatment emergent gastrointestinal side effects including abdominal pain, nausea, vomiting, fatigue and dizziness starting on Day 1 of treatment.

Reviewer Comment: The most common cause of a hiatal hernia is an increase in pressure in the abdominal cavity. Pressure can come from vomiting or abdominal distension. Therefore the subject's on treatment clinical course including multiple gastrointestinal symptoms could be reasonably partially attributable to the development of the SAE of hiatal hernia, but is confounded by her history of gastrointestinal illness and pre-existing hernia.

8.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

Overall, discontinuations due to AEs were infrequent. All provided narratives were reviewed for discontinuations due to AEs. Overall 7 subjects, 0.3% of those in the Phase 2/3 safety dataset, excluding those in the population with severe renal disease, discontinued due to any AE. Of these, three subjects (0.1%) prematurely discontinued study medication due to AE considered related to study drug (Subjects 142305, 303402, 1004020). See **Table 32** for summary of all adverse events in subjects with discontinuations due to adverse events.

Table 32 Subjects with Discontinuations Due to Adverse Events in the Phase 2/3 Safety Data-Set, excluding subjects with severe renal impairment (shading indicates events considered causal)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Study/Unique Identifier	Dictionary Derived Term	Standard Toxicity Grade	Serious Event	Causality Reasonable Possibility?	AE Start Day	AE End Day	Last Day of Treatment
M13583-45227-100402	Depression	1	N	N	70	126	73
	Dyspepsia	1	N	Y	5	69	
	Dyspepsia	2	N	Y	70	117	
	Fatigue	1	N	Y	30	117	
	Headache	1	N	Y	30	117	
	Myalgia	1	N	Y	70	126	
	Sinusitis	1	N	N	47	57	
M13583-51078-303402	Anxiety	1	N	N	12	.	12
	Transient ischemic attack	2	Y	Y	11	11	
	Transient ischemic attack	2	Y	Y	36	36	
M13590-04355-130104	Amnesia	1	N	N	68	121	78
	Anxiety	2	N	N	68	121	
	Dandruff	1	N	N	68	121	
M13594-09818-162308	Alcohol abuse	3	N	N	1	54	53
	Cough	1	N	N	2	10	
	Nausea	1	N	Y	20	28	
M13594-44319-120301	Asthenia	1	N	N	8	18	77
	Dyspepsia	1	N	N	2	.	
	Facial pain	3	N	N	47	.	
	Graft complication	2	N	N	18	.	
	Irritability	1	N	Y	8	15	
	Paranasal sinus and nasal cavity malignant neoplasm recurrent	3	Y	N	72	.	
M13594-45610-142305	Abdominal pain	2	N	Y	4	9	5
	Diarrhea	2	N	Y	4	9	5
	Dizziness	2	N	Y	4	9	
	Fatigue	2	N	Y	4	9	
	Headache	2	N	Y	4	9	
	Malaise	2	N	Y	4	9	
	Nausea	2	N	Y	4	9	
M14867-42730-3408	Adenocarcinoma	5	Y	N	29	89	29
	Nausea	1	N	Y	8	.	

Reviewer Comment: As shown in the table, there were few discontinuations due to AEs. However, most subjects that discontinued treatment due to AEs experienced multiple AEs. All but one subject had at least one AE that was considered related even if this was not the stated reason for treatment discontinuation. Gastrointestinal symptoms occurred in 5 of 7 subjects with treatment discontinuations due to AEs.

8.4.3. Significant Adverse Events

This section describes Grade 3 and 4 adverse events that occurred in the treatment-emergent period. Some of these events were also considered SAEs; hence, there is some overlap between events reported in this section and in section 8.4.2. A total of 67 (3.0%) subjects in the Phase 2/3 safety dataset, excluding subjects with severe renal disease, experienced Treatment Emergent Grade 3 or Grade 4 Adverse Events; 62 (2.7%) experienced Grade 3 events and 10 (0.4%) experienced Grade 4 events (some subjects experiencing both Grade 3 and 4 events). A larger proportion of cirrhotics, 7.6% experienced Grade 3 or 4 AEs. Approximately 60% of the Treatment Emergent Grade 3 and 4 events were SAEs (See section 8.4.2). A total of four subjects experienced Grade 3 or 4 AEs considered by the Investigator as possibly related to study drug; none of these events were considered SAEs, all events resolved and study drug was not discontinued.

Treatment Emergent Grade 3 or 4 AEs considered related included:

- **Abdominal Pain Upper:** 48 year old white male, Grade 3, Day 39-71
- **Asthenia:** 61 year old white male, Grade 3, Day 44-85
- **Migraine:** 61 year old white female, Grade 3, Day 23-30
- **Alanine aminotransferase Increase, Aspartate aminotransferase Increase, Gamma-Glutamyltransferase Increase:** 58 year old white male, Grade 3, Day 87-101/116

Grade 3 or 4 Treatment Emergent Events occurring in more than one subject are listed in the below table. Only one event of increased gamma-glutamyltransferase was assessed by the Investigator as possibly related to study drug. Both hepatocellular carcinoma events, one pneumonia, one alcohol abuse and one syncope event were considered SAEs

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 33 Grade 3 and 4 Adverse Events Occurring in More than One Subject by Cirrhosis Status in the Phase 2/3 Safety Data-Set, excluding subjects with severe renal impairment

Dictionary Derived Term	No Cirrhosis N=1,977	Cirrhosis N=288	Subjects N=2,265
Pneumonia	3 (0.2%)	0 (0.0%)	3 (0.1%)
Back pain	2 (0.1%)	1 (0.3%)	3 (0.1%)
Syncope	1 (0.1%)	1 (0.3%)	2 (0.1%)
Hepatocellular carcinoma	0 (0.0%)	2 (0.7%)	2 (0.1%)
Gastroenteritis	1 (0.1%)	1 (0.3%)	2 (0.1%)
Alcohol abuse	1 (0.1%)	1 (0.3%)	2 (0.1%)
Gamma-glutamyltransferase increased	2 (0.1%)	0 (0.0%)	2 (0.1%)
Anemia	1 (0.1%)	1 (0.3%)	2 (0.1%)
Hypertension	2 (0.1%)	0 (0.0%)	2 (0.1%)
Aspartate aminotransferase increased	2 (0.1%)	0 (0.0%)	2 (0.1%)

Source: ADAE database.

Liver related events and laboratories are discussed further in Section 8.5.1. A brief description of subjects with back-pain, syncope, anemia gastroenteritis and hypertension are below:

Back pain- Subject 348103 - 56 year non cirrhotic white female, with grade 3 back pain starting the second week of treatment lasting through treatment week 5. She also experienced subsequent AEs of nasopharyngitis, abdominal distension and constipation and had a 1.9 g/DL drop in hemoglobin from baseline to week 4.

Back pain- 120102 -74 year old non-cirrhotic white female with grade 3 back pain and extremity pain starting at Week 10. Laboratories were stable with the exception of hemoglobin which decreased by approximately 1.6 g/dL from baseline to Week 12.

Back pain- Subject 2923 -48 year old white male with cirrhosis and baseline CTP 5, MELD 7 experienced grade 3 back pain on treatment Week 15/16. Other AEs on treatment included dizziness, fatigue, arthralgia, myalgia, vomiting, back pain and muscular weakness. Hemoglobin and other laboratories were stable.

Syncope-Subject 242108 -25 year old non-cirrhotic white male experienced grade 3 syncope and abdominal pain 3 weeks after the end of a 12 week treatment course. He also experienced the AEs of headache and pharyngitis on treatment. Bilirubin and INR were increased slightly at the end of treatment. Vital signs were stable.

Syncope- Subject 606503 -88 year old cirrhotic male with baseline CTP 5, MELD 6 experienced endophthalmitis, grade 3 syncope and hypertension within 3 weeks after completion of a 12 week treatment course of study drug. The syncopal episode was considered an SAE.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Gastroenteritis – Subject 3701-44 year old non-cirrhotic female Native Hawaiian or other Pacific Islander developed a grade 3 gastroenteritis during Treatment Week 2, lasting approximately one week. She had no other adverse events. Her hemoglobin decreased 1.4 g/dL from baseline to Treatment Week 6.

Gastroenteritis- Subject 4007- 46 year old cirrhotic male with baseline CTP 5, MELD 6 experienced a grade 3 gastroenteritis lasting from Treatment Week 6 to Treatment Week 10. He also experienced an AE of oral herpes on therapy. His hemoglobin decreased 1.5 g/dL from baseline to Treatment Week 8.

Anemia- Subject 1012- 60 year old white non-cirrhotic female with a baseline hemoglobin of 12.8 experienced AEs of headache, nausea and peripheral swelling starting Treatment Week 2. She developed bronchitis, stomatitis, pneumonia and anemia after Treatment Week 9. Her hemoglobin nadir was 9.7 with a total hemoglobin decline of 3.1 g/dL.

Anemia-Subject 203507- 64 year old cirrhotic male with baseline CTP 6, MELD 17 experienced on treatment AEs of abdominal distension, decreased appetite, constipation, esophageal varices hemorrhage and duodenal ulcer, before experiencing the AE of anemia on Treatment Week 4. His hemoglobin declined from 15.6 to 7.3 g/dL. AST, ALT, ALP and Bilirubin declined in the first 4 weeks of treatment. [Subject had baseline elevation of diastolic blood pressure (142/98), which improved on-treatment (possibly secondary to GI bleed) and worsened after the treatment course was completed.]

Hypertension- Subject 242106-64 year old non-cirrhotic female experienced grade 3 hypertension starting on Treatment Week 1; however maximum blood pressure captured on study vitals was 157/80 (baseline was 143/83). She had a history of moderate renal impairment.

Hypertension-Subject 174302- 66 year old non-cirrhotic male experienced grade 3 hypertension at the end of 12 weeks of treatment (Treatment Week 12); however, the subject also had a baseline reading of increased blood pressure and was experiencing headache and ongoing sinusitis on treatment.

Reviewer Comment: Overall a small proportion of subjects experienced Grade 3 and 4 Treatment Emergent Adverse Events. Few occurred in more than one subject, without any clear pattern. Amylase and Lipase were not routinely collected as safety laboratories and would be important to rule out pancreatitis in subjects with severe abdominal symptoms and/or back pain, especially in those with decreasing hemoglobin on treatment without another obvious source of bleeding. In addition, both cases coded as gastroenteritis, particularly the case with several weeks of symptoms, could represent another

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

gastrointestinal AE, as viral gastroenteritis usually persists a day or 2, occasionally lasting up to 10 days.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

The most common AEs (≥ 5%) reported across in the Phase 2/3 dataset, excluding subjects with severe renal impairment were headache, fatigue, nausea and diarrhea.

Table 34 summarizes common treatment-emergent AEs irrespective of severity and causality in the Endurance-2 (M15-464) the placebo controlled trial. In this trial the most common AEs of headache, fatigue and asthenia were reported in similar proportions in the study drug and placebo arms, while 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 34 Treatment-emergent AEs Reported ≥2*% of Subjects in Either Treatment Group Endurance-2 (M15-464), 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%)
Vomiting	3 (1.5%)	2 (2.0%)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Dictionary Derived Term	GLE/PIB 12 WEEKS N=202	PLACEBO FOR 12 WEEKS N=100
Abdominal pain upper	3 (1.5%)	2 (2.0%)
Toothache	3 (1.5%)	1 (1.0%)
Sinusitis	3 (1.5%)	0 (0.0%)
Rash pruritic	3 (1.5%)	1 (1.0%)
Pyrexia	3 (1.5%)	0 (0.0%)
Palpitations	3 (1.5%)	0 (0.0%)
Nasopharyngitis	3 (1.5%)	2 (2.0%)
Influenza like illness	3 (1.5%)	0 (0.0%)
Gastroesophageal reflux disease	3 (1.5%)	3 (3.0%)
Flatulence	3 (1.5%)	0 (0.0%)
Urinary tract infection	2 (1.0%)	2 (2.0%)
Rhinitis	2 (1.0%)	2 (2.0%)
Dyspnea	2 (1.0%)	2 (2.0%)
Hypertension	2 (1.0%)	5 (5.0%)
Dental caries	1 (0.5%)	2 (2.0%)
Thirst	1 (0.5%)	2 (2.0%)
Blood creatine phosphokinase increased	0 (0.0%)	3 (3.0%)
Dizziness postural	0 (0.0%)	2 (2.0%)
Otitis media	0 (0.0%)	2 (2.0%)

*When rounded to the nearest whole number (as it appears in the label).

Source: ADAE database

Table 35 summarizes related adverse events (hereafter, referred to as adverse drug reactions [ADR]) reported in $\geq 2\%$ of subjects, irrespective of severity across the safety population. The Investigator's determination of causality is the basis for classification. The red box highlights ADRs occurring at or above 5% frequency, as displayed in product labeling. The inaccuracies and biases of Investigator assessment of causality are acknowledged. Headache, fatigue nausea and diarrhea were the most common ADRs across the Phase 2/3 dataset also seen in a higher proportion of the GLE/PIB arm of the placebo controlled study (ENDURANCE-2).

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 35 Treatment-emergent ADRs Reported in ≥ 2%* of Subjects, All Grades

Dictionary Derived Term	ENDURANCE-2 M15-464, GT2 (Placebo controlled)		ENDURANCE-3 M15-594,GT3 (Active controlled)			Pooled Studies- Excluding EXPEDITION-4, M15-462, Severe Renal Impairment	
	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: ADAE, Asthenia, Dizziness, GERD and Myalgia more common in placebo therefore removed from table. Red box represents ADRs reported in ≥ 5% of subjects.

*When rounded to the nearest whole number.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Reviewer Comment: Both analyses (all AEs in the placebo controlled trial and ADRs) yield similar results terms, affirming that headache, fatigue, nausea, and diarrhea are the most frequently reported AEs with GLE/PIB. However, the occurrence of some of these events (especially headache and fatigue) was only slightly higher among GLE/PIB subjects, which suggests that the underlying HCV disease state may be contributing to the findings as well. Cirrhotic subjects were also more likely to experience the most common ADRs; however, the types of ADRs were similar to non-cirrhotic subjects. Exploratory analysis confirmed that ADRs were similar across all treatment durations. As shown in Section 10, headache, fatigue, nausea, and diarrhea were reflected in labelling recommendations as the most common ADRs, given that these ADRs were the most common adverse reactions occurring at higher frequency than placebo.

8.4.5. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in the placebo controlled study, ENDURANCE-2 (M15-464) and pooled Phase2/3 dataset, excluding those with renal failure. These analyses represent the worst change from baseline per subject. For most parameters, grade 3 and 4 abnormalities occurred infrequently and at a similar rate in subjects treated with GLE/PIB and placebo.

Table 36 Abnormalities in key chemistry parameters by highest toxicity grade, ENDURANCE -2 (M-15464), placebo controlled study

Laboratory Parameter	Highest Toxicity Grade*	GLE/PIB 12 Weeks N=202	Placebo 12 Weeks N=100
Alanine Aminotransferase (IU/L)			
Grade 1 (> ULN to 3.0 x ULN)	1	2 (1.0%)	9 (9.0%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	2	0 (0.0%)	6 (6.0%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	3	1 (0.5%)	2 (2.0%)
Alkaline Phosphatase (IU/L)			
Grade 1 (> ULN to 2.5 x ULN)	1	19 (9.4%)	1 (1.0%)
Aspartate Aminotransferase (IU/L)			
Grade 1 (> ULN to 3.0 x ULN)	1	4 (2.0%)	9 (9.0%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	2	0 (0.0%)	2 (2.0%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	3	2 (1.0%)	1 (1.0%)
Bilirubin (mg/dL)			
Grade 1 (> ULN to 1.5 x ULN)	1	16 (7.9%)	4 (4.0%)
Grade 2 (> 1.5 to 3.0 x ULN)	2	7 (3.5%)	0 (0.0%)
Grade 3 (> 3.0 to 10 x ULN)	3	1 (0.5%)	0 (0.0%)
Creatine Kinase (IU/L)			

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Laboratory Parameter	Highest Toxicity Grade*	GLE/PIB 12 Weeks N=202	Placebo 12 Weeks N=100
Grade1(>1 - 1.5 x baseline; >ULN - 1.5 x ULN)	1	20 (9.9%)	13 (13.0%)
Grade2 (>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	2	2 (1.0%)	3 (3.0%)
Grade 3(>3.0 baseline; >3.0 - 6.0 x ULN)	3	1 (0.5%)	1 (1.0%)
Creatinine (UMOL/L)			
Grade 1 (> 1 to 1.5 x baseline; or > ULN to 1.5 x ULN)	1	3 (1.5%)	1 (1.0%)
Gamma Glutamyl Transferase (IU/L)			
Grade 1(>ULN - 2.5 x ULN)	1	1 (0.5%)	3 (3.0%)
Grade2(>2.5 - 5.0 x ULN)	2	0 (0.0%)	1 (1.0%)
Grade3 (>5.0 - 20.0 x ULN)	3	1 (0.5%)	0 (0.0%)
Activated Partial Thomboplastin Time (Sec)			
Grade1 (>ULN - 1.5 x ULN)	1	2 (1.0%)	2 (2.0%)
Grade 2 (>1.5 - 2.5 x ULN)	2	0 (0.0%)	1 (1.0%)
Prothrombin Intl. Normalized Ratio			
Grade 1 (> 1 to 1.5 x ULN)	1	9 (4.5%)	2 (2.0%)
Grade 2 (> 1.5 to 2.5 x ULN)	2	1 (0.5%)	0 (0.0%)
Grade 3 (> 2.5 x ULN)	3	1 (0.5%)	1 (1.0%)

Table 37 Abnormalities in key chemistry parameters by highest toxicity grade, Phase 2/3 Safety Dataset

Laboratory Parameter	Highest Toxicity Grade*	No Cirrhosis N=1,977	Cirrhosis N=288
Alanine Aminotransferase (IU/L)			
Grade 1 (> ULN to 3.0 x ULN)	1	20 (1.0%)	1 (0.3%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	2	3 (0.2%)	2 (0.7%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	3	2 (0.1%)	0 (0.0%)
Alkaline Phosphatase (IU/L)			
Grade 1 (> ULN to 2.5 x ULN)	1	154 (7.8%)	32 (11.1%)
Aspartate Aminotransferase (IU/L)			
Grade 1 (> ULN to 3.0 x ULN)	1	35 (1.8%)	1 (0.3%)
Grade 2 (> 3.0 ULN to 5.0 x ULN)	2	1 (0.1%)	4 (1.4%)
Grade 3 (> 5.0 ULN to 20.0 x ULN)	3	6 (0.3%)	0 (0.0%)
Bilirubin (mg/dL)			

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Laboratory Parameter	Highest Toxicity Grade*	No Cirrhosis N=1,977	Cirrhosis N=288
Grade 1 (>ULN - 1.5 x ULN)	1	115 (5.8%)	39 (13.5%)
Grade 2 (>1.5 - 3.0 x ULN)	2	41 (2.1%)	10 (3.5%)
Grade 3 (>3.0 - 10.0 x ULN)	3	6 (0.3%)	2 (0.7%)
Creatine Kinase (IU/L)			
Grade1 (>ULN - 2.5 x ULN)	1	20 (1.0%)	0 (0.0%)
Grade 2 (>2.5 x ULN - 5 x ULN)	2	2 (0.1%)	0 (0.0%)
Grade 3 (>5 x ULN - 10 x ULN)	3	1 (0.1%)	0 (0.0%)
Creatinine phosphokinase (U/L)			
Grade 1 (>ULN - 2.5 x ULN)	1	16 (0.8%)	1 (0.3%)
Grade 2 (>2.5 x ULN - 5 x ULN)	2	3 (0.2%)	0 (0.0%)
Grade 3 (>5 x ULN - 10 x ULN)	3	1 (0.1%)	0 (0.0%)
Creatinine (UMOL/L)			
Grade 1 (>1 - 1.5 x baseline; >ULN - 1.5 x ULN)	1	46 (2.3%)	11 (3.8%)
Grade 2 (>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	2	3 (0.2%)	1 (0.3%)
Grade 3 (>3.0 baseline; >3.0 - 6.0 x ULN)	3	0 (0.0%)	1 (0.3%)
Gamma Glutamyl Transferase (IU/L)			
Grade 1 (>ULN - 2.5 x ULN)	1	11 (0.6%)	0 (0.0%)
Grade 2 (>2.5 - 5.0 x ULN)	2	5 (0.3%)	1 (0.3%)
Grade 3 (>5.0 - 20.0 x ULN)	3	2 (0.1%)	0 (0.0%)
Grade 4 (>20.0 x ULN)	4	1 (0.1%)	0 (0.0%)
Activated Partial Thromboplastin Time (Sec)			
Grade 1 (>ULN - 1.5 x ULN)	1	51 (2.6%)	5 (1.7%)
Grade 2 (>1.5 - 2.5 x ULN)	2	6 (0.3%)	0 (0.0%)
Grade 3 (>2.5 x ULN; hemorrhage)	3	1 (0.1%)	1 (0.3%)
Prothrombin Intl. Normalized Ratio			
Grade 1 (> 1 to 1.5 x ULN)	1	146 (7.4%)	42 (14.6%)
Grade 2 (> 1.5 to 2.5 x ULN)	2	12 (0.6%)	2 (0.7%)
Grade 3 (> 2.5 x ULN)	3	9 (0.5%)	0 (0.0%)

Uric Acid levels were not available for ENDURANCE-2 and most of the subjects in the Phase 2/3 safety studies. However, of 561 non-cirrhrotic subjects in studies where this value was routinely collected, 6 subjects (1%) and 13 of 288 cirrhrotic subjects (5%) experienced Grade 4 Uric Acid Levels (Grade 4: >10mg/dL). Two non-cirrhrotic subjects and four cirrhrotic subjects with Grade 4 elevations had normal baseline values (Grade 0 at baseline). Of those with Grade 4 elevations, 2 subjects, both with cirrhrosis, experienced non-investigational AEs that could be at least partially attributed to increased levels of uric acid; one subject experienced nephrolithiasis (Week 2, Grade1) and one subject experienced gout(Week 5, Grade 1). Neither event was considered related to GLE/PIB by the Investigator or Applicant, both subjects had confounding Grade 3

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

elevations of Uric Acid at baseline.

Reviewer Comment: Grade 3 and 4 chemistry laboratory abnormalities were uncommon across study groups. ALT and AST trended down rapidly in the active treatment groups as HCV viral load decreased. Hence, it is not surprising that elevated ALT and AST and alkaline phosphatase were observed most frequently among subjects in the placebo group, who had ongoing HCV replication. On the other hand, minor alkaline phosphatase, bilirubin elevations and increases in INR were uncommon, but seen more in the GLE/PIB treatment arm of the placebo controlled study, ENDURANCE -2. Grade 2 and 3 INR elevations were mostly transient with a single spike occurring between TW 1 and 8, associated with a concurrent increase in PTT and but not associated with any obvious bleeding events. Of the subjects with Grade 1 INR elevations, 6 subjects experienced the following events which could reasonably be a consequence of bleeding or hemolysis: Anemia, Hematoma, Ecchymosis, Hematemesis, Blood Urine present, Gout and Blood Uric Acid Increased. No laboratory events were considered appropriate for labelling given the low frequency of abnormalities and lack of clear association with study drug. However, laboratory abnormalities will continue to be monitored for trends in the post marketing setting.

Table 38 Abnormalities in key hematology parameters by highest toxicity grade, ENDURANCE -2 (M-15464), placebo controlled

Laboratory Parameter	Highest Toxicity Grade*	GLE/PIB 12 Weeks N=202	Placebo 12 Weeks N=100
Hemoglobin (g/dL)			
Grade 1 (< LLN to 10.0 g/dL)	1	3 (1.5%)	5 (5.0%)
Leukocytes (10 ³ /μL)			
Grade 1 (< LLN to 3000/mm ³)	1	16 (7.9%)	8 (8.0%)
Lymphocytes (10 ³ /μL)			
Grade 1 (< LLN to 800/mm ³)	1	0 (0.0%)	1 (1.0%)
Grade 2 (< 800 to 500/mm ³)	2	3 (1.5%)	0 (0.0%)
Neutrophils (10 ³ /μL)			
Grade 1 (< LLN to 1500/mm ³)	1	19 (9.4%)	8 (8.0%)
Grade 2 (< 1500 to 1000/mm ³)	2	11 (5.4%)	12 (12.0%)
Grade 3 (< 1000 to 500/mm ³)	3	3 (1.5%)	0 (0.0%)
Platelet (10 ³ /μL)			
Grade 1 (< LLN to 75,000/mm ³)	1	9 (4.5%)	7 (7.0%)
Grade 2 (< 75,000 to 50,000/mm ³)	2	0 (0.0%)	2 (2.0%)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 39 Abnormalities in key chemistry parameters by highest toxicity grade, Phase 2/3 Safety Dataset, excluding subjects with severe renal disease

Laboratory Parameter	Highest Toxicity Grade*	No Cirrhosis N=1,977	Cirrhosis N=288
Hemoglobin (g/dL)			
Grade 1 (< LLN to 10.0 g/dL)	1	66 (3.3%)	17 (5.9%)
Grade 2 (< 10 to 8.0 g/dL)	2	3 (0.2%)	1 (0.3%)
Grade 3 (< 8.0 g/dL)	3	1 (0.1%)	1 (0.3%)
Leukocytes (10 ³ /μL)			
Grade 1 (< LLN to 3000/mm ³)	1	93 (4.7%)	16 (5.6%)
Grade 2 (< 3000 to 2000/mm ³)	2	22 (1.1%)	11 (3.8%)
Grade 3 (< 2000 to 1000/mm ³)	3	1 (0.1%)	0 (0.0%)
Lymphocytes (10 ³ /μL)			
Grade 1 (< LLN to 800/mm ³)	1	12 (0.6%)	3 (1.0%)
Grade 2 (< 800 to 500/mm ³)	2	19 (1.0%)	8 (2.8%)
Grade 3 (< 500 to 200/mm ³)	3	4 (0.2%)	1 (0.3%)
Neutrophils (10 ³ /μL)			
Grade 1 (< LLN to 1500/mm ³)	1	130 (6.6%)	26 (9.0%)
Grade 2 (< 1500 to 1000/mm ³)	2	52 (2.6%)	12 (4.2%)
Grade 3 (< 1000 to 500/mm ³)	3	10 (0.5%)	1 (0.3%)
Platelet (10 ³ /μL)			
Grade 1 (< LLN to 75,000/mm ³)	1	78 (3.9%)	24 (8.3%)
Grade 2 (< 75,000 to 50,000/mm ³)	2	2 (0.1%)	21 (7.3%)
Grade 3 (<50,000 - 25,000/mm ³ ; <50.0 - 25.0 x 10e9 /L)	3	0 (0.0%)	4 (1.4%)

Reviewer Comment: Grade 3 and 4 hematology laboratory abnormalities were uncommon and in most cases seen in similar proportion of placebo subjects. No hematology laboratory events were considered appropriate for labelling given the low frequency of abnormalities and lack of clear association with study drug. However, laboratory abnormalities will continue to be monitored for trends in the post marketing setting.

8.4.6. Vital Signs

Significant fluctuations in blood pressure were observed in several individual subjects. Within the analysis datasets, the sponsor provided flags for subjects experiencing on-treatment extremes in systolic or diastolic blood pressure in the Phase 2/3 safety dataset. The numbers of subjects who met these criteria for at least one study visit, excluding those in EXPEDITION-4

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

(subjects with renal failure) are presented below.

Extreme Values of Blood Pressure Elevation

- Systolic blood pressure ≥ 180 mmHg AND an increase of ≥ 20 mmHg from baseline, n=17 (0.8%)
- Diastolic blood pressure ≥ 105 mmHg AND an increase of ≥ 15 mmHg from baseline, n= 28 (1.2%)

Extreme Values of Low Blood Pressure

- Systolic blood pressure ≤ 90 mmHg AND a decrease of ≥ 20 mmHg from baseline, n= 19 (1.3%)
- Diastolic blood pressure ≤ 50 mmHg AND a decrease of ≥ 15 mmHg from baseline, n= 24 (1.1%)

Treatment Emergent Hypertension

In addition, 42 subjects (1.9%) experienced on-treatment adverse events of hypertension. Twenty four of 42 subjects did not have a previous diagnosis of hypertension. Twenty seven of 42 subjects experienced a grade 1 event of hypertension, 13 subjects experienced a grade 2 event of hypertension and 2 subjects experienced grade 3 events of hypertension. (**Subjects 242106** and **174302** who experienced grade 3 events of hypertension and are described in Section 8.43 on Significant Adverse Events.) There were no treatment emergent adverse events of hypertension that were considered serious.

Fourteen subjects with hypertension AEs were considered related to GLE/PIB by the Investigator. These 14 subjects are presented in Appendix C. Of the 14 subjects with hypertension considered related to study drug, 7 had pre-existing hypertension, were on antihypertensive medications, and appeared to experience a worsening of blood pressure on treatment requiring dosage adjustments and/or additional blood pressure medications. Maximum elevation from baseline blood systolic pressure ranged 5 mmHg to 59 mmHg and maximum elevation in diastolic blood pressure ranged from 5 mmHg to 22 mmHg; mean blood pressure elevations and trends were significantly confounded by the treatment of blood pressure.

Seven subjects did not have a previous diagnosis of hypertension and were reported to have new onset hypertension starting as early as Day 8 to Day 29, all were considered ongoing events. Four subjects were started on one or more anti-hypertensives. Maximum elevation from baseline blood systolic pressure ranged 7mmHg to 55mmHg and maximum elevation in diastolic blood pressure ranged from 6mmHg to 23 mmHg; mean blood pressure elevations and trends were significantly confounded by the treatment of blood pressure.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

One non-serious but clinically significant AE of hypertensive heart disease and one clinically significant AE of hypertensive crisis were also reported. The event of hypertensive crisis was considered reasonably related and occurred on Day 39 in a subject (**4021**) without a previous documented history of hypertension (study vitals are normal indicating that this may have been an event diagnosed by an outside practitioner and treated between the study visits; Day 39 was between 2 study visits and the subject was started on 2 antihypertensive Days 42 and 43 also before returning for a study visit). This subject is also described in Appendix C.

As discussed in Section 8.4.2 (Serious Adverse Events), there are some subjects in which blood pressure fluctuations may have played at least a partial role in precipitating the event including in the subjects listed below:

Subject 303402 303402 Transient Ischemic Attack- 49 year old non-cirrhotic white male, with elevated hemoglobin and ongoing tobacco use, with no known history of hypertension, and normotensive at baseline with a single recorded elevated diastolic blood pressure increase of 13 mmHg proximal to the event of TIA (blood pressure 133/93 - no further readings were available as the subject discontinued treatment). This was the only SAE in the Phase 2/3 dataset with an event considered by the Investigator as related to GLE/PIB.

Subject 7010 Angina Pectoris – 51 year old with baseline hypertension and on moderate on-treatment blood pressure (mainly diastolic) fluctuations (range 101/65 to 142/91). This subject also experienced a myocardial infarction at Week 18-19 (approximately 10 weeks after completing 8 weeks of treatment with GLE/PIB.)

Subject 172105 Angina Unstable – 65 year old white male with baseline hypertension with blood pressure fluctuations on treatment [diastolic range (111mmHg at baseline to 71mmHg) and systolic range (122 mmHg to 160mmHg)]. This subject also experienced hypokalemia.

Given these blood pressure events, an information request (IR) was sent to the Applicant and an blood pressure analysis was conducted including all subjects with the following possible cardiovascular events or symptoms: Events in the Body System or Organ Class *Cardiac Disorder* or Dictionary Derived Term *Chest Pain, Chest Discomfort, Dyspnea, Dyspnea Exertional, Edema, Edema Peripheral, Cerebral Hemorrhage, Facial paresis, Transient Ischemic Attack or Headache*.

Of all the subjects in the Phase 2/3 Safety dataset, excluding those with renal failure, 76 subjects experienced these potential cardiovascular events or symptoms defined in this way. Eleven of 76 were previously diagnosed with hypertension, and 40 carried either a diagnosis of hypertension or a medically relevant cardiovascular diagnosis at baseline.

Six of 76 subjects experienced maximum systolic blood pressure elevations of ≥ 40 mmHg; 9 subjects experienced maximum systolic elevations between 20-39 mmHg; and 11 experienced systolic elevations between 10-29 mmHg. There were also 8 subjects with maximum diastolic

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

elevations >20 mmHg and 25 with maximum diastolic elevations of 10-20 mmHg. The majority of subjects with increased blood pressures, particularly at the extremes, carried a previous diagnosis of hypertension or cardiovascular disease, and trends were difficult to discern over time given titration of antihypertensive medications in this population.

Tables describing subjects with these events and maximum systolic blood pressure elevations ≥ 20 mmHg from baseline and diastolic elevations of ≥ 10 mmHg are shown in the Appendix D and E.

Treatment Emergent Hypotension

In addition to the subjects who experienced extreme hypertensive blood pressure values discussed above, adverse events of treatment emergent hypotension were reported for 6 subjects and orthostatic hypotension was reported for one subject. Only the event of orthostatic hypotension was considered causal. No events were considered serious. Of note, of the six subjects with hypotension, 3 subjects (subjects **404403**, **700403** and **192104**) had baseline hypertension, were on concomitant anti-hypertensive and experienced no other adverse events that could explain their hypotension. The three remaining subjects who experienced hypotension also experienced infections that could reasonably lead to a lowering of blood pressure. The subject with orthostatic hypotension (subject **204205**), had a relevant medical history of intestinal occlusion, epigastralgia and Sjogren's syndrome and was on multiple concomitant medications.

Of those with extreme measured values hypotension or reported values of hypotension as AEs, a total of 13 of 57 subjects had baseline hypertensive diagnosis. Most were on concomitant medications including ACE-inhibitors, ARBs, beta blockers and calcium channel blockers. Two subjects experienced other adverse events that could be related to hypotension; the etiology of hypotension in the remaining subjects with a diagnosis of hypertension is not clear.

Overall Reviewer Comment: Overall approximately 84 (3.7%) of subjects experienced either an increased systolic or diastolic blood pressure readings and/or experienced an adverse event of hypertension. In addition, 57 (2.5%) subjects experienced either decreased systolic or diastolic blood pressure readings and/or experienced an adverse event of hypotension or orthostatic hypotension. This could suggest a possible blood pressure signal in both directions. However, the majority of the cases, especially amongst those with increased blood pressure had confounding medical histories and trends were difficult to follow given appropriate medical interventions (i.e. titrating or initiating antihypertensives) for blood pressure control. It is also possible that these values reflect natural variation and/or an unmasking of a chronic disease (particularly hypertension) in the context of the additional clinical scrutiny that subjects receive in a clinical trial.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Given that several cases of hypotension occurred in subjects with baseline hypertension on anti-hypertensives with no other explanation for low blood pressure, some of the hypotension may be explained by drug-drug interactions, although a specific interaction has not been identified by the review team to date. Similarly, for those with increased blood pressure, the majority of subjects were on concomitant medications at baseline, either for hypertension or other chronic diseases and drug-drug interactions, hepatic metabolism or hepatic transporters could also play a role in treatment emergent hypertension, in this context. Currently, there are no specific data that points to a specific drug-drug interaction, hepatic transporter or other mechanism to explain the hyper and hypo-tension events; additionally, no pre-clinical signals were identified. However, the clinical team continues to work with the clinical pharmacology team to ensure a thorough review of all the available data. If any additional information is discovered that helps to explain these findings, the issue will be updated.

8.4.7. Electrocardiograms (ECGs)

ECGs were assessed at screening and at the end of treatment. The Applicant reports four subjects with treatment-emergent abnormal ECGs deemed clinically significant by the Investigator:

Subject 167301, a 52-year-old white male, experienced an asymptomatic, non-serious, event of bundle branch block right (Grade 2) that began on Day 85, was considered not related to study drug, and was ongoing at the time of the report. No past cardiovascular medical history and no relevant concomitant medications were reported.

Subject 206503, a 57-year-old white male, had a clinically significant abnormal electrocardiogram finding noted at the End of Treatment Visit (Day 79) of atrial fibrillation with a controlled ventricular response; this finding was recorded as a Grade 1 AE of atrial fibrillation that resolved on Day 96. No other AEs were reported for this subject. No past cardiovascular medical history and no relevant concomitant medications were reported.

Subject 104501, a 58-year-old white male, had QTcF prolongation (498 msec and 497 msec) on Day 85 (1 day after the last dose of study drug) that was unchanged from the screening value of 498 msec. No associated AE was recorded.

Subject 6204, a 66-year-old white male, experienced atrial fibrillation with rapid ventricular response with premature ventricular or aberrantly conducted complexes on Day 58 that were recorded as AEs of atrial fibrillation and defect conduction intraventricular. These events were nonserious, lasted 2 days, and were considered to be not related to study drug. This subject had a history of hypertension, diabetes mellitus, and hyperlipidemia. Baseline electrocardiogram was normal.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

All four subjects with ECGs deemed clinically significant by the investigator were either generally asymptomatic at the time of abnormal ECGs and/or had either cardiac risk factors, abnormal screening/baseline ECGs, or findings consistent with age-related risk in this population that confounded the assessment. The primary review team concludes available reported ECG data do not support relevant labeling.

8.4.8. QT

The effect of fixed dose combination of glecaprevir and pibrentasvir on the QTc interval was evaluated in a Phase 1 randomized, single blind, placebo- and positive-controlled four-period crossover thorough QTc study in 48 healthy adult subjects. The FDA Interdisciplinary Review Team for QT Studies Consultation conducted a thorough QT review of these data. They concluded that the largest upper bounds of the 2-sided 90% CI for the mean difference between fixed-dose combinations (600 mg GLE+240 mg PIB; 400 mg GLE+120 mg PIB) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms and the moxifloxacin profile over time is adequately demonstrated in the below table, indicating that assay sensitivity was established.

Table 40 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ABT-493 400 MG + ABT-530 120 MG and ABT-493 600 MG + ABT-530 240 MG and the Largest Lower Bound for Moxifloxacin 400 mg (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
400 mg GLE (ABT-493) + 120 mg PIB (ABT-530)	5	2.3	(-1.0, 5.5)
600 mg GLE (ABT-493) + 240 mg PIB (ABT-530)	5	2.7	(-0.6, 5.9)
Moxifloxacin 400 mg*	2	12.2	(9.1, 15.4)

* Multiple endpoint adjustment was not applied.

In summary, the FDA review team concluded that at 20-fold of glecaprevir and 5-fold of pibrentasvir steady state therapeutic concentrations, the glecaprevir and pibrentasvir combination does not prolong the QTc interval to any clinically relevant extent.

8.4.9. Immunogenicity

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Because GLE and PIB are small molecules and not peptides, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

GLE is an NS3/4A Serine Protease Inhibitor (Chymotrypsin-like). Serine proteases are ubiquitous in eukaryotes and prokaryotes. In humans, serine proteases are involved in coordinating various physiological functions, including digestion, immune response, blood coagulation and reproduction[12]. A cardiac serine protease known as corin, which has substrate specificity similar to trypsin, also helps to regulate blood pressure (via the natriuretic pathway).[13] Knockout mice lacking corin have a hypertensive phenotype.

However, GLE (A-1282567.0) was tested in a biochemical assay for inhibition of a variety of human serine and cysteine proteases, including chymase, elastase, cathepsin B, chymotrypsin types II and VII, kallikrein, and urokinase (see below figure). No inhibition by A-1282567.0 was observed at concentrations up to 200,000 nM, providing a selectivity index of greater than 320,000 for inhibition of HCV GT1a NS3 protease (GT1a NS3 protease IC₅₀ = 0.63 nM, Abbott internal data).

Figure 2 GLE Inhibition of Human Proteases in Biochemical Assays

Inhibition of Human Proteases by A-1282576.0 in Biochemical Assays

Protease	IC ₅₀ , nM	Selectivity, -Fold ^a
Chymase	> 200,000	> 320,000
Elastase	> 200,000	> 320,000
Cathepsin B	> 200,000	> 320,000
Chymotrypsin Type II	> 200,000	> 320,000
Chymotrypsin Type VII	> 200,000	> 320,000
Kallikrein	> 200,000	> 320,000
Urokinase	> 200,000	> 320,000

a. Calculated from the ratio of the IC₅₀ value for the human proteases relative to the HCV GT1a protease IC₅₀ = 0.63 nM.

Reviewer Comment: GLE demonstrated a high level of selectivity for HCV NS3 protease over the human host proteases that were tested. However, it should be noted that protease inhibitors in humans are promiscuous. There are 115 annotated human protease inhibitors responsible for regulating the activity of the 612 known human proteases (ratio of 1:5)[12]. If GLE were to have off target effects, they may be expected to occur in one of the pathways described above. Indeed, a large proportion (27%) of subjects experienced at least one

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

gastrointestinal AE and several individual subjects experienced blood pressure variations, as discussed above. However, given the high background rate of gastrointestinal symptoms and confounding medical histories of subjects with cardiovascular events, it is difficult to credibly establish a causal link. Additionally, and importantly, there were no related signals in pre-clinical studies.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hepatobiliary Events

Prior to NDA submission, FDA asked the Applicant to assemble an independent committee of DILI experts and practicing HCV clinicians, to formally assess the hepatic safety profile of GLE/PIB. The request was based on a small proportion of subjects who experienced on treatment direct and indirect bilirubin elevations in the Phase 2/3 safety database, as presented at the Pre-NDA meeting; and, because of the known safety events observed with earlier generation HCV protease inhibitors which were associated with increases in bilirubin and in some cases, associated with liver decompensation and hepatic death in patients with baseline decompensated cirrhosis. This section presents the results of the Hepatic Panel Evaluation and additional reviewer analyses focusing on assessment of cirrhosis baseline health status of the cirrhotic and non-cirrhotic safety population, liver related safety events and laboratory abnormalities.

Expert Hepatic Panel Evaluation

The Expert Hepatic Panel (EHP) was 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. The panel included:

(b) (6)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

(b) (6)

The panel 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.

The panel structured their review as follows:

Review of Cases of direct or mixed hyperbilirubinemia (total bilirubin increases above baseline of $\geq 2 \times$ ULN with direct/total bilirubin ratio > 0.4), without increases in ALT Grade (**N=4** of 2,369 subjects in the safety database including subjects with severe renal impairment)

Review of Cases of Subjects with Increases in ALT grade to Grade 2+ (ALT $\geq 3 \times$ ULN) and hyperbilirubinemia

(total bilirubin increases above baseline of $\geq 2 \times$ ULN); or Increases in ALT grade to Grade 3+ (ALT $\geq 5 \times$ ULN) (**N=5** of 2,369 subjects in the safety database including subjects with severe renal impairment)

Review of Cases of Hepatic Decompensation Events (Ascites, Hepatic Encephalopathy, Spontaneous Bacterial Peritonitis, Esophageal Variceal Bleeding) (**N=1** of 2,369 subjects in the safety database including subjects with severe renal impairment, as identified by the Applicant)

Review of Cases of cases of post baseline bilirubin elevation $\geq 2X$ ULN, not meeting the above criteria (N=23, of 2,369 subjects in the safety database including subjects with severe renal impairment)

The EHP concluded that none of the cases reviewed were consistent with a "definite," "highly

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

likely" or "probable" event of drug-induced liver injury (DILI), based on the Drug Induced Liver Injury Network [DILIN] likelihood causality scoring.

One case (**Subject 206205**) was considered to be a "possible" event of DILI (likelihood 25% – 49%) but with a most likely alternative etiology ("most likely related to passage of gallstones"). This subject is a 58 year old male with no relevant medical history other than chronic hepatitis C infection without cirrhosis. All liver chemistries were within normal range throughout the study treatment period. On Day 87, at the End of Treatment Visit, the subject's liver chemistries were elevated. The subject had post-baseline increase from nadir of ALT > 5 – 20 × upper limit of normal and an increase in total bilirubin ≥ 2 × upper limit of normal and direct/total bilirubin ratio > 0.4 on Day 87. His alkaline phosphatase, and GGT were also elevated. On Day 106 (Post-Treatment Day 20), after his liver enzymes had normalized, an ultrasound of the liver and biliary system revealed two gallstones without evidence of biliary dilatation. The panel concluded that the concurrent elevations of alkaline phosphatase and GGT were consistent with an obstructive picture likely related to a transient passage of a stone, noting that as an ultrasound was not performed until after the liver chemistries had normalized, thus it would not be surprising that there was no longer any evidence of biliary tree dilatation. See table and graph representations of laboratory values below.

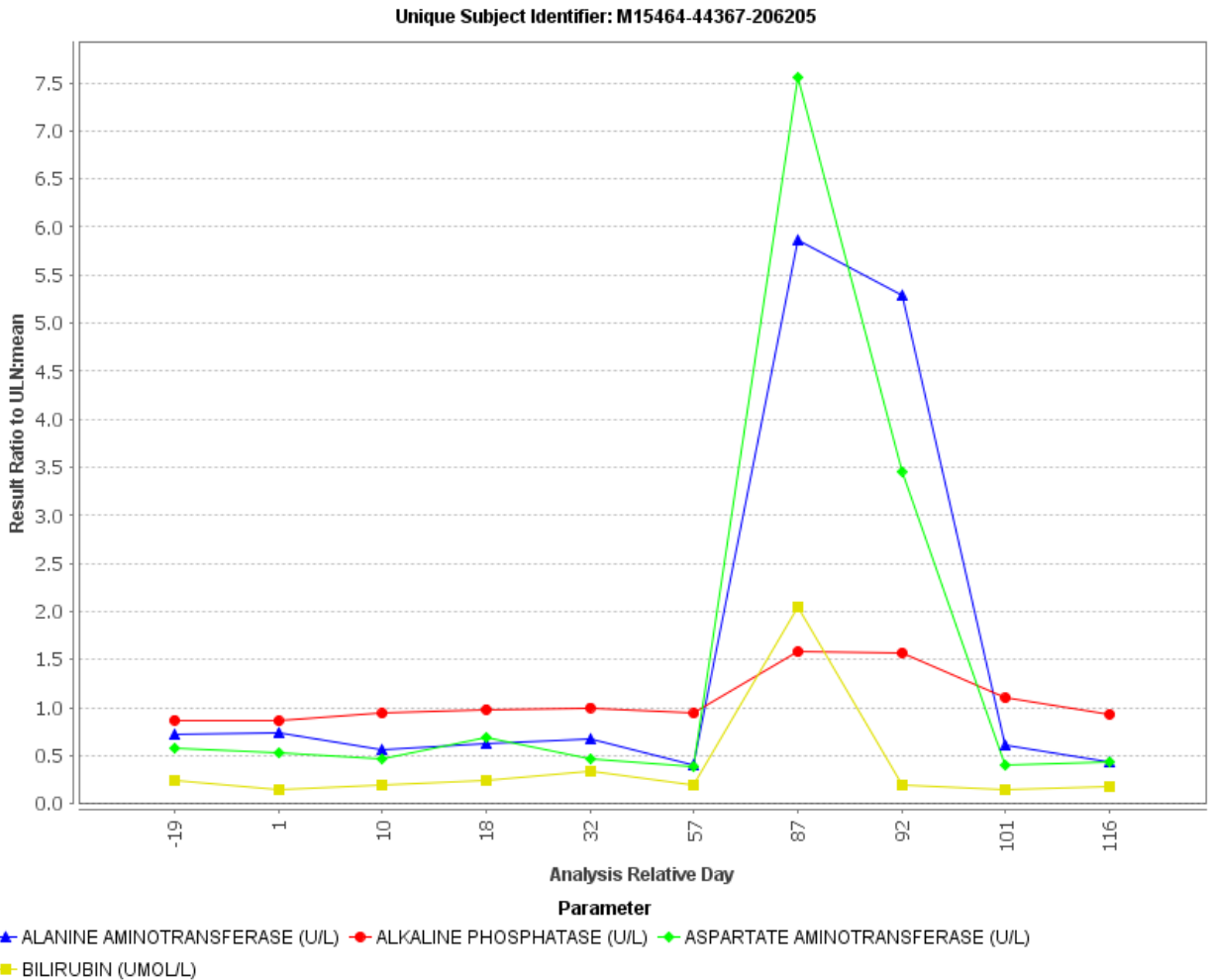
Table 41 Liver Laboratories Subject 206205

Treatment Day	ALT Reference Range: 6 – 43 U/L	AST Reference Range: 11 – 36 U/L	Total Bilirubin Reference Range: 3 – 21 umol/L	Indirect Bilirubin Reference Range: 0 – 21 umol/L	Direct Bilirubin Reference Range: 2 – 7 umol/L	Alkaline Phosphatase Reference Range: 35 – 131 U/L	GGT Reference Range: 10 – 61 U/L	International Normalized Ratio Reference Range: 0.8 – 1.2
Day -19	31	21	5	5.0	2.0	114	25	1.0
Day 1	32	19	3	3.0	2.0	113	29	0.9
Day 10	24	17	4	4.0	2.0	123	27	0.9
Day 18	27	25	5	5.0	2.0	128	28	0.9
Day 32	29	17	7	5.0	2.0	131	32	1.0
Day 57	17	14	4	4.0	2.0	123	21	0.9
Day 87 (Post-Treatment Day 1)	252	272	43	17.0	26.0	207	501	0.9
Day 92 (Post-Treatment Day 6)	219 (local lab; reference ranges: < 41 U/L)	132 (local lab; reference ranges: < 40 U/L)	4 (local lab; reference ranges: not provided)	1.0 (local lab; reference ranges: < 21 umol/L)	3.0 (local lab; reference ranges: not provided)	202 (local lab; reference ranges: < 130 U/L)	654 (local lab; reference ranges: < 60 U/L)	0.85 (local lab; reference range: not provided)
Day 92 (Post-Treatment Day 6)	225	130	4	4.0	2.0	208	595	0.9

Source: EHP Assessment

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Figure 3 Liver Laboratories Results Ratio to ULN Subject 206205



Source ADLBPCS

All remaining cases were considered either "unlikely" events of DILI or events not reflective of liver injury (N/A). The cases were attributed to underlying Gilbert's syndrome and/or transporter effect of the regimen.

Reviewer Comment: Overall the reviewer agrees with the hepatic panel on the assessment of individual cases of bilirubin elevation. None of these subjects reported bilirubin-related adverse events (i.e., jaundice), obvious liver-decompensation related events and none resulted in treatment discontinuations. Most of the reported cases of bilirubin elevation had

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

indirect predominance (23 of the 30 subjects with total bilirubin $\geq 2 \times$ ULN had direct/total bilirubin ratio < 0.4). In addition, most of the 23 of the 30 subjects with bilirubin $\geq 2 \times$ ULN had elevated bilirubin with indirect predominance prior to starting treatment, consistent with an underlying Gilbert's syndrome, which is estimated to affect 3-7% of the US population. (See additional analysis below).

As a part of the same information request, the review team requested that if the findings of the EHP were that direct bilirubin accumulation was benign that the applicant should fully describe the mechanism. Below is an abstraction of this explanation:

Under physiologic conditions, unconjugated (indirect) bilirubin is taken up into hepatocytes by transporters of the organic anion-transporting polypeptide (OATP) family (particularly by human OATP1B1 and OATP1B3), followed by conjugation with glucuronic acid by uridine diphosphate glucose-glucuronosyltransferase [UGT] 1A1), and finally excreted into bile via an ATP-dependent transport (mediated by MRP2). It has been reported that the conjugated (direct) bilirubin can also be transported from hepatocytes back to sinusoidal blood via the efflux transporter MRP3 and excreted in urine as a compensatory pathway to biliary excretion. The conjugated bilirubin can also be taken up again into hepatocytes in the sinusoid by OATP1B1 and OATP1B3. Since GLE/PIB inhibits OATP1B1/3 and is a weak inhibitor of UGT1A1, GLE/PIB has the potential to impact bilirubin transport and metabolism, including conjugated bilirubin.

Reviewer Comment: Overall, the reviewer finds that this is a reasonable explanation.

Baseline Liver Disease in Cirrhotic and Non-Cirrhotic Safety Populations

As presented in Section 8.2.2, 288 of 2,265 subjects (12.7%) in the Phase 2/3 safety dataset (excluding those with renal failure), 288/2,265 were cirrhotic. Overall, over 70% of subjects had a baseline fibrosis Stage of F0-F1. Enrollment criteria limited inclusion of cirrhotic subjects to those with compensated cirrhosis or CTP A, usually considered to have CTP scores of 5 or 6. Appropriately, there was only 1 subject with a CTP score of ≥ 6 in the Phase 2/3 Safety Dataset, excluding subjects in EXPEDITION-4, and one subject in EXPEDITION-4 (M15-462), the trial in subjects with renal failure. For the cirrhotic population the mean baseline CTP score was 5.1 and mean MELD score was 7.3, indicative of mild liver impairment.

Reviewer Comment: Overall the subjects in this study had mild liver disease, only a small proportion with cirrhosis. GLE/PIB will likely be used in broader population of subjects with more advanced fibrosis and compensated CTP A cirrhotic subjects with higher scores (possibly closer to 6). Therefore, the safety findings in the clinical trials may be limited and there remains a risk that liver related events could be observed if this regimen is given to patients with more advanced disease. GLE/PIB is not indicated in patients with decompensated

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

cirrhosis and there are no safety data in this population.

Treatment Emergent Clinical Hepatic Events

Hepatic AEs were identified for the Phase 2/3 Safety Dataset, excluding renal failure using the MedDRA High Level Group Term *Hepatic and Hepatobiliary Disorders*. The overall occurrence of hepatic AEs was low with a total of 3 subjects reporting events of hepatic steatosis, hepatic pain and jaundice. All events were considered grade 1. The event of Jaundice was considered to be reasonably related to study medication by the Investigator. The subjects with these events are described briefly below.

Subject 205104 is a 54 year old Asian male without cirrhosis with a MELD of 6 at baseline. He experienced only the event of hepatic steatosis at TW16, 4 weeks after completing a 12 week course of study drug. On treatment his AST and ALT improved to the normal range, without other laboratory abnormalities except for a mild transient elevation of bilirubin at TW12.

Subject 7010 51 year old white male with cirrhosis and a CTP 5 score experienced hepatic pain shortly after experiencing grade 4 angina pectoris in TW2 (as described in Section 8.4.2). The subject also experienced the AE of nausea starting on TW 1 throughout the study.

Subject 2924 is a 52 year old Asian male without cirrhosis who developed jaundice on study week 12 and subsequently withdrew consent. He also experienced on treatment nausea, lethargy, discolored sputum, asthma and a melanocytic nevus. At Week 4 he had a slight elevation of ALP, which subsequently improved to baseline. AST/ALT were normal at baseline and remained normal over his treatment course. Bilirubin, which was normal at baseline, was slightly elevated after treatment week 1, fluctuated slightly and peaked at treatment week 16 at 2.4 mg/dl. The subject, who's MELD score was 7 at study initiation, had an increase in MELD to 10 at Week 16 (at the time of discontinuation; which was impacted by the elevated bilirubin). This case was not reviewed by the hepatic panel, as his peak bilirubin was just under 2 times the upper limit of normal.

Reviewer Comment: In the case of subject 2924, the reviewer concurs with the Investigator, that the cause of the jaundice and bilirubin elevation could be attributed to the study drug.

In addition, the reviewer examined the one reported case of esophageal varices hemorrhage and the one reported case of hematemesis. These subjects are described briefly below.

Subject 203507 is a 64 year old white male with cirrhosis and a baseline CTP Score of 6, MELD of 17 and a history of varices and portal hypertension developed an esophageal bleed and SAE of anemia on Day 25. Prior to the bleed on TW 1 the subject experienced abdominal distension and decreased appetite. He was also diagnosed with a duodenal ulcer. No worsening of

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

laboratory parameters was observed related to the event of esophageal bleed except for the decrease in hemoglobin. MELD improved on the study drug from 17 at baseline to 11 at the PTW 4 visit. The subject's CTP score improved from a 6 to a 5. The Investigator considered this event not to be causally related to the study drug.

Subject 1502 is a 52 year old white male without cirrhosis at baseline and a MELD score of 6. He also suffered a contusion concurrently and experienced discolored feces approximately 2 weeks after discontinuing treatment. All these events were considered Grade 1.

Reviewer Comment: The review agrees that these events are unlikely related to the study drug. While subject 203507 did experience an initial clinical decompensation event on treatment, other laboratory parameters were not consistent with DILI and both MELD score and CTP improved from baseline.

Hy's Law Cases

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a mortality rate of 10-50%. Hepatocellular injury sufficient to impair bilirubin excretion has been used by the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as an indicator of clinical concern for drug-induced liver injury (DILI) includes: ALT or AST >3x ULN, total bilirubin >2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

Due to a number of confounding factors, the appropriate application and interpretation of Hy's Law in the setting of treatment trials for HCV infection, in general, is unknown. Despite the limitations of Hy's Law in the chronic HCV infected population, the Hy's Law laboratory criteria were used by the reviewer for capturing all potential DILI cases in order to conservatively evaluate the relevant subjects in the clinical safety database (i.e., hepatic safety population).

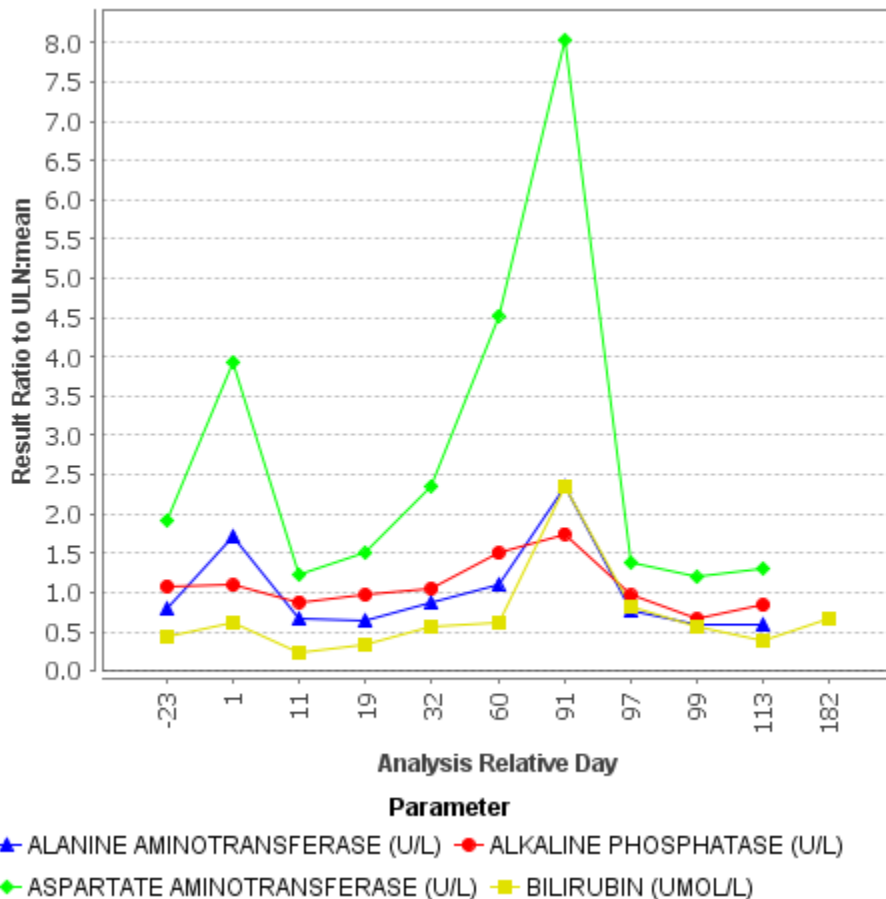
There were 5 subjects in the Phase 2/3 safety dataset, that met post-baseline laboratory criteria of ALT or AST >3x ULN and total bilirubin >2x ULN (subjects **20605**, **30105**, **191101**, **406204**, **501203**). All subjects except **Subject 301501**, were reviewed by the EHP. Subjects 406204 and 501203 had baseline liver laboratory elevations that fluctuated slightly, but trended down and normalized over the course of treatment. Subjects **20605**, **30105** and **191101** are reviewed briefly below.

Subject 20605 was reviewed by the EHP and considered to be the only possible case of DILI (of the cases they reviewed) according to the panel. This case is discussed in detail above.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

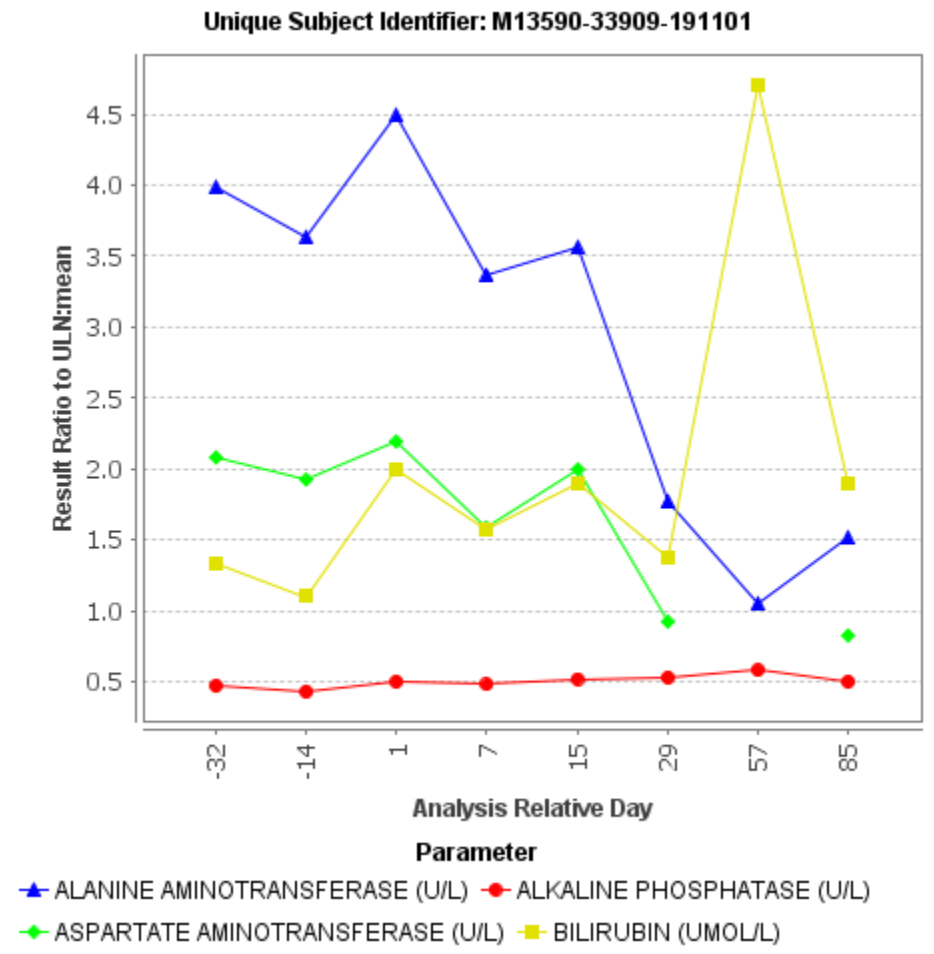
Subject 301501 48 year old white male with cirrhosis experienced a single bilirubin spike on Day 91, shortly after completing a 12 week treatment course of study drug. He also presented with an elevation of AST to 8 times the ULN and mild elevations of ALT and ALP on the same date. All laboratories resolved at the next study visit, Day 97, with the exception of AST which remained slightly elevated. He experienced the AEs of alcohol abuse, weight decrease and anemia (total decrease of 3.2 g/dl from baseline). See Figure below.

Unique Subject Identifier: M14172-53404-301501



Subject 191101 is a 55 year old white male without cirrhosis at baseline, with baseline elevation ALT, AST and bilirubin that trended downward over the course of treatment until Day 29. At Day 57 he experienced a single peak of bilirubin to 4.5 times the ULN with concurrent elevations in AST, ALT or ALP. The EHP stated that the subject had probable Gilbert’s with an unknown cause for the single bilirubin peak which is not characteristic for DILI or transporter effect. See Figure below.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)



Reviewer Comment: As stated above, the reviewer concurs with the assessment of the EHP. In the case of subject 301501, who was not reviewed by the EHP, this subject’s bilirubin and AST elevation occurred off treatment and his history is confounded by alcohol use.

Other Significant Liver Related Laboratory Events

Of 2,369 HCV-infected subjects treated with GLE/PIB in the Phase 2 and Phase 3 safety dataset, and including those with baseline renal failure from EXPEDITION-4, 0.4% (9/2,369) experienced increases in bilirubin to Grade 3 (> 3 × ULN) and 1.3% (30/2,369) experienced bilirubin increases to ≥ 2 × ULN. The majority of subjects with bilirubin ≥ 2 X the upper limit of normal experienced indirect bilirubin elevations. Grade 2 and above ALT, AST and ALP post baseline elevations were rare and overall ALT and AST decreased on treatment. In the Phase 2/3 dataset excluding those with renal failure, mean ALT levels at baseline were 33.6 (U/L) decreasing to 14.6 (U/L) at the final treatment visit; mean AST levels decreased from 27.6 (U/L) to 15.9 U/L at the final treatment visit.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Hepatocellular Carcinoma

There were 6 de-novo cases of hepatocellular carcinoma experienced by subjects in the Phase 2/3 Safety Dataset. Five cases occurred in subjects with cirrhosis and only 2 subjects were (503502 and 603504) were treatment naïve. **Subjects 2703** and **3623** were previously noted to have liver nodules and all except 2 subjects had elevated baseline Alpha-fetoprotein (AFP) levels. All, achieved SVR 12 except for subject **1301** who died, and did not return for his Post Treatment Week 12 Visit; this subject’s SVR 12 status is not known.

Table 42 Cases of Hepatocellular Carcinoma

Unique Subject Identifier	Age	Sex	Race	Day of Onset	BL Fibrosis Stage	Cirrhosis	BL Child Pugh Score	MELD	HCV Genotype	BL AFP	Duration of Treatment (Days)	Achieved SVR 12?
M14172-37834-603504	57	F	WHITE	40	F4	Y	6	11	1	124.9	50	Yes
M14172-40764-503502	52	M	WHITE	92 (8)	F4	Y	5	6	1	3.6	84	Yes
M14868-40622-2703	66	F	ASIAN	85	F4	Y	5	6	3	4.2	113	Yes
M15410-38627-1301	65	M	WHITE	156 (71)	F0-F1	N	NA	6	1	15	85	No
M15410-40724-3921	58	F	WHITE	189 (105)	F4	Y	5	7	1	18	84	Yes
M15410-44318-3623	55	M	WHITE	122 (37)	F4	Y	5	7	1	30.5	85	Yes

Days in parenthesis indicate days since last dose of study drug.

Subject 603504 died 99 days after completing 12 weeks of treatment and did not return for his Post Treatment Week 12 Visit.

Reviewer Comment: Although HCC has been reported among individuals without or with low levels of fibrosis, the risk of HCC increases with fibrosis stage. Most cases of HCV-related HCC occur among patients with advanced fibrosis and cirrhosis. HCC develops at an annual rate of 1%–4% in HCV infected patients with cirrhosis[14]. Although HCC occurs in subjects with all grades of cirrhosis, CPT B and C cirrhosis are independent risk factors for developing HCC in the cirrhotic population[15]. HCC amongst cirrhotic subjects in the Phase 2/3 Safety Dataset (including those with severe renal disease) is 1.3% (5/308), which is consistent with the expected annual incidence of cirrhosis. However, CTP scores were low amongst the overall cirrhotic population and 4/5 cirrhotic subjects with HCC had low CTP scores and MELD scores. In addition, one subject with F0-F1 cirrhosis was diagnosed with HCC on treatment. The effect of DAA treatment on the development of HCC is unknown, but in this case, successful

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

treatment of these subjects did not prevent the development of HCC even in the context of relatively mild cirrhosis or fibrosis.

Safety Update:

Two additional subjects (**Subject 325103** from Study M13-590 and **Subject 3624** from Study M15-410) each experienced a non-treatment emergent event of HCC. Both cases were de novo occurrences of HCC. Neither of these events was considered related to study drug by the Investigator. The Investigator considered the events more likely to be related to longstanding HCV infection for **Subject 325103**, or cirrhosis and benign vascular nodules on the liver for **Subject 3624**.

Subject 325103 is a 55-year-old Asian female, non-user of alcohol, current smoker of cigarettes (0.40 pack/day for 33 years), with relevant history HCV infection without cirrhosis, moderate fatty liver, small liver cyst, liver hemangioma at segment (S)7-S8, liver hemangioma over S8, gallbladder polyp, and palmar erythema, experienced an event of HCC Study Day 180, Post Treatment Day 96.

Subject 3264 is a 58-year-old black female, non-drinker, non-smoker, with relevant medical history of chronic HCV infection with compensated cirrhosis, benign vascular liver nodule, portal hypertension, esophageal varices, and splenomegaly, experienced an event of HCC on Day 242 (Post-Treatment Day 129).

Reviewer Comment: These additional cases do not change the reviewer's assessment as stated above. It is notable, however, that one of these 2 subjects did not have cirrhosis at baseline.

Overall Reviewer Comment (Hepatobiliary): Like other HCV regimens containing protease inhibitors, GLE/PIB will be contraindicated in CTP C cirrhosis based on clinically-significant elevated exposures. It is also not recommended for CTP B cirrhosis because safety and efficacy were not studied in this population. However, the primary review team concludes the available data for hepatobiliary events related events do not support additional liver-related labeling at this time. Liver toxicity and HCC will continue to be monitored in the post-marketing setting.

8.5.2. Rash and Skin Disorders

Rash and pruritus have been noted as significant AEs in earlier generation HCV regimens containing protease inhibitors, and in some cases ribavirin. Treatment Emergent rash and pruritus related AEs were identified for the Phase 2/3 Safety Dataset, excluding renal failure using the MedDRA High Level Group Terms (HLGT) *Epidermal and dermal conditions* and

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Angioedema and urticaria. Epidermal and Dermal Conditions AEs and ADRs occurred in a slightly higher, but similar proportion in the GLE/PIB and placebo arm of ENDURANCE-2 (M15-464), as shown in the below table. Epidermal and dermal conditions occurred in similar proportions in the Phase 2/3 safety dataset, excluding those with severe renal impairment. While there were no events classified under the HLTG Angioedema and urticaria in the placebo controlled trial, there were 6 cases classified as Angioedema and urticaria in the Phase 2/3 dataset excluding renal failure, 3 of these were considered as having events reasonably related to study drug.

Table 43 HLTG Epidermal and Dermal Conditions, Angioedema and Urticaria for Phase 2/3 Safety Dataset

HLTG	ENDURANCE-2 GLE/PIB 12 Weeks N=202	ENDURANCE-2 Placebo 12 weeks N=100	Phase 2/3 Safety Dataset N=2,265
Epidermal and dermal conditions (all causality, all grades)	20 (9.9%)	8 (8.0%)	209 (9.2%)
Epidermal and dermal conditions (related, all grades)	9 (4.5%)	4 (4.0%)	128 (5.6%)
Angioedema and uticaria (all causality, all grades)	No events	No events	3 (0.1%)
Angioedema and uticaria (related, all grades)	No events	No events	6 (0.3%)

Source: Reviewer generated; ADAE.

All Epidermal and dermal conditions AEs had standard toxicity grades of 1 or 2 and no serious events were reported. Of the 6 events classified under the Angioedema and urticarial HLTG, 5 were grade 1 and one was considered grade 2; no events were considered SAEs and study drug was not interrupted or discontinued for any event. All but two subjects had some degree of moderate renal impairment. There was no discernable pattern of laboratory abnormalities and no subject had greater than Grade 2 laboratory abnormalities on treatment. One subject (**3901**) was taking concomitant medications of trazadone, lisinopril (discontinued on treatment), aspirin, ibuprofen and clear eyes. A table describing these events is shown below.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 44 Angioedema and Urticarial Events, Phase 2/3 Safety Dataset

Unique Subject Identifier	Dictionary Derived Term	Reported Term for the Adverse Event	Standard Toxicity Grade	Causality?	Treatment Duration	Analysis Start Relative Day	Analysis End Relative Day	Age	Race	Sex	Other AEs	CREATCL R Group 1 mL min
M13590-40784-160104	Urticaria	PUSTULES AND WHELTS ON THE ARMS AND SHOULDERS	1	y	12 WEEKS	43	112	62	WHITE	M	Back pain Myalgia Rash pustular Musculoskeletal pain Contusion Visual Impairment Hypertension Rotator cuff syndrome	>=60 TO <90
M13594-76269-179303	Urticaria	HIVES	1	N	8 WEEKS	78	NA	59	WHITE	F	Flushing Headache	>=60 TO <90
M14172-40784-304503	Swelling face	SLIGHT SWELLING FACE	1	Y	12 WEEKS	15	20	82	WHITE	F	Back pain Device Breakage Localized Infection	>=30 TO <60
M14867-81200-3901	Swelling face	FACIAL SWELLING	2	N	12 WEEKS	65	66	67	BLACK OR AFRICAN AMERICAN	M	Headache Ocular hyperemia Vision blurred Arthralgia Pain in extremity Pain	>=90

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject Identifier	Dictionary Derived Term	Reported Term for the Adverse Event	Standard Toxicity Grade	Causality?	Treatment Duration	Analysis Start Relative Day	Analysis End Relative Day	Age	Race	Sex	Other AEs	CREATCL R Group 1 mL min
M14868-82703-3713	Swelling face	MILD FACIAL SWELLING	1	Y	8 WEEKS	3	20	38	WHITE	F	Headache Eczema Anxiety Depression Influenza like illness (late)	>=90
M15410-76269-4820	Urticaria	URTICARIA	1	N	16 WEEKS	55	106	70	WHITE	F		>=60 TO <90

Source: reviewer generated; ADAE database

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Reviewer Comment: Overall skin related events while common, were experienced in similar proportion in the placebo arm of ENDURANCE-2. Events of urticaria and facial swelling were overall mild and resolved without the discontinuation of medications. The single event considered Grade 2 (facial swelling) occurred in a subject on lisinopril and lasted one day; lisinopril was discontinued in this subject. The primary review team concludes the available data for skin related events do not support relevant labeling.

8.5.3. Neuropsychiatric Disorders

No neuropsychiatric signals were seen in phase 1 or 2 studies of GLE/PIB, however these events have been evaluated in other DAA regimens, given the history of neuropsychiatric reactions on IFN and RBV containing HCV therapies. To evaluate for a signal in this population, treatment Emergent related AEs were identified for the Phase 2/3 Safety Dataset, excluding renal failure using associated MedDRA High Level Group Terms (HLGT), listed in the below table. Overall neuropsychiatric adverse events were uncommon, and in most cases seen in similar proportions in the placebo arm of ENDURANCE -2 (see table below). There were a total of 2 subjects with SAEs reported in the neuropsychiatric HLGTs evaluated, one subject with suicidal behavior (with a history of depression) and one subject with schizophrenia. These subjects/events are described in the table and text below. All were either grade 1 or 2 events except for the SAE of suicidal behavior.

Table 45 Treatment Emergent Neuropsychiatric Disorders, Phase 2/3 Safety Dataset

HLGT	ENDURANCE-2 GLE/PIB 12 Weeks N=202	ENDURANCE-2 Placebo 12 weeks N=100	Phase 2/3 Safety Dataset N=2,265
Anxiety disorders and symptoms (all causality all grades)	6 (3.0%)	1 (1.0%)	59 (2.6%)
Anxiety disorders and symptoms (related all grades)	3 (1.5%)	0 (0.0%)	22 (1.0%)
Depressed mood disorders and disturbances (all causality all grades)	4 (2.0%)	1 (1.0%)	43 (1.8%)
Depressed mood disorders and disturbances (related all grades)	3 (1.5%)	0 (0.0%)	17 (0.8%)
Deliria (all causality all grades)	1 (0.5%)	0 (0.0%)	1 (0.04%)
Deliria (related all grades)	No events	No events	No events
Disturbances in thinking and perception (all causality all grades)	No events	No events	1 (0.04%)
Disturbances in thinking and perception (related all grades)	No events	No events	1 (0.04%)
Impulse control disorders NEC (all causality all grades)	No events	No events	1 (0.04%)
Impulse control disorders NEC (related all grades)	No events	No events	No events
Manic and bipolar mood disorders and disturbances (all	No events	No events	2 (0.1%)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

causality all grades)			
Manic and bipolar mood disorders and disturbances (related all grades)	No events	No events	No events
Mental impairment disorders (all causality all grades)	1 (0.5%)	1 (1.0%)	32 (1.4%)
Mental impairment disorders (related all grades)	1 (0.5%)	0 (0.0%)	23 (1.0%)
Mood disorders and disturbances NEC (all causality all grades)	1 (0.5%)	1 (1.0%)	49 (2.2%)
Mood disorders and disturbances NEC	1 (0.5%)	1 (1.0%)	29 (1.3%)
Neurological disorders NEC (all causality all grades)	10 (5.0%)	9 (9.0%)	158 (7.0%)
Neurological disorders NEC (Related all grades)	5 (2.5%)	3 (3.0%)	102 (4.5%)
Personality disorders and disturbances in behavior (all causality all grades)	No events	No events	1 (0.04%)
Personality disorders and disturbances in behavior (related all grades)	No events	No events	1 (0.04%)
Psychiatric disorders NEC (all causality all grades)	No events	No events	8 (0.4%)
Psychiatric disorders NEC (related all grades)	No events	No events	1 (0.04%)
Schizophrenia and other psychotic disorders (all causality all grades)	No events	No events	3 (0.1%)
Schizophrenia and other psychotic disorders (related all grades)	No events	No events	2 (0.1%)
Seizures (all causality all grades)	No events	No events	2 (0.1%)
Seizures (related all grades)	No events	No events	No events
Suicidal and self-injurious behaviors NEC (all causality all grades)	No events	No events	1 (0.04%)
Suicidal and self-injurious behaviors NEC (related all grades)	No events	No events	No events

Source: reviewer generated; ADAE database.

Subjects with neuropsychiatric SAEs:

Subject 102103 is a 51-year-old white male with relevant medical history of mild depression (2010), chronic back pain, insomnia, and opiate dependency, experienced arterial injury and suicide attempt. On Day 51, the subject (age 52 at time of event) experienced worsened depression with symptoms of low mood, suicidal ideation, increased sleep, and decreased appetite. On Day 82 (Post-Treatment Day 24), the subject experienced arterial injury and attempted suicide with self-laceration of bilateral antecubital fossa/brachial arteries and ingestion of eight zopiclone 7.5 mg tablets. Following psychiatric evaluation, a primary diagnosis of suicidal intent and other diagnosis of opiate misuse were made on Day 88 (Post-Treatment Day 30). The Investigator and Applicant considered the event of suicide attempt as having no reasonable possibility of being related to study drug and more likely related to temporal implausibility as the onset of the events was more than 3 weeks after the last dose of study drug.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Subject 6810 is a 62-year-old white male with relevant medical history of psychotic episode (possibly drug induced), stress reaction episode, intravenous drug use, drug withdrawal, and current methadone user, experienced an event of schizophrenia. From Day 68 to Day 70, the subject did not attend a scheduled pharmacy appointment for methadone collection. On Day 71, the police were contacted to perform a welfare check. The subject was taken to the hospital and exhibited inability to speak coherently, significant weight loss, and poor self-hygiene, and was admitted for the event of schizophrenia. Urine drug screen was positive for cannabinoids. The Investigator and Applicant considered the event of having no reasonable possibility of being related to study drug. They considered the event as being related to cannabinoids and/or methadone withdrawal.

Reviewer Comment: *Adverse events in this category were relatively uncommon. Anxiety and depressed mood were slightly higher in the GLE/PIB arm of ENDURANCE-2 regardless of causality. Anxiety and depressed mood were coded as ADRs in approximately 1% of the treatment population of the Phase 2/3 dataset. This was not different than the proportional frequency of events in the placebo arm of ENDURANCE-2 when causality was not applied to the placebo study. However these events occur in the Phase 2/3 dataset at a slightly higher frequency than the placebo study when causality was considered in the placebo study. It is therefore difficult to discern if there is a drug effect; if there is a drug effect it would likely only be seen in a larger study population. However of note, there were only 2 serious adverse events in this category, both in subjects with previous histories of mental health disorders and no additional events above Grade 2. Although a larger proportion of subjects experienced neurologic disorders, these events were also common in the placebo arm and there was no discernable pattern of events. Both seizure events occurred in subjects with a history of either underlying seizure disorder (Epilepsy) or previous stroke. In the latter case, treatment course was only notable for discontinuation of lisinopril at the end of treatment visit because of low blood pressure. The primary review team concludes the available data for neuropsychiatric events related events do not support relevant labeling.*

8.5.6 Gastrointestinal Disorders

The Body System or Organ Class (SOC) with the highest proportion of subjects reporting treatment emergent events in the Phase 2/3 dataset was Gastrointestinal disorders, with 605 subjects (approximately 27%) reporting at least one gastrointestinal AE. Of these, 348 (15% overall) were considered ADRs. Similarly, in ENDURANCE-2, subjects in the gastrointestinal disorders SOC experienced the most events. Fifty-five (27%) of subjects in the GLE/PIB arm and 19 (19%) of subjects in the placebo arm reported events in this class; 30 (15%) subjects in the GLE/PIB arm and 16 (16%) subjects in the placebo arm had GI events that were considered related. In the Phase 2/3 safety dataset, the most common events in this SOC by Higher Level

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Group Terms were *Gastrointestinal signs and symptoms* [414 (18%) AEs and 288 (13%) ADRs] and *Gastrointestinal motility and defecation conditions* [226 (10%) AEs and 135(6%) ADRs]. Nausea, diarrhea, dyspepsia, constipation, abdominal pain, abdominal pain upper, abdominal distension and flatulence were all ADRs reported at a frequency of greater than 1%; nausea and diarrhea were reported at the highest frequencies.

Overall there were 5 SAEs and 7 Grade 3 or above events in the Gastrointestinal disorders SOC within Phase 2/3 dataset excluding those with severe renal impairment. No serious events were considered causal; one grade 3 event of Abdominal pain upper (**Subject 2519**). Subjects experiencing gastrointestinal disorders grade 3 or above events and/or SAEs are described in the below table.

Table 46 Treatment Emergent Gastrointestinal Disorders

Unique Study/Subject Identifier	Dictionary Derived Term	Standard Toxicity Grade	Serious Event	Causality?	Total Treatment Duration Weeks	Analysis Start Relative Day	Analysis End Relative Day	Age	Sex	Race
M13590-49103-134106	Constipation	3	N	N	12 WEEKS	56	NA	48	M	WHITE
M14172-48171-203507	Esophageal varices hemorrhage	3	Y	N	12 WEEKS	22	25	64	M	WHITE
M14172-49267-608502	Oral pain	3	N	N	12 WEEKS	21	57	57	M	WHITE
M14868-37759-2519	Abdominal pain upper	3	N	Y	16 WEEKS	39	71	48	M	WHITE
M14868-38646-8007	Umbilical hernia	3	Y	N	16 WEEKS	81	88	53	M	WHITE
M14868-46903-1010	Esophageal spasm	3	N	N	16 WEEKS	54	54	60	F	WHITE
M15464-45465-104203	Hemorrhoids	3	Y	N	12 WEEKS	95	97	56	F	WHITE
M13590-38878-124107	Irritable bowel syndrome	1	Y	N	12 WEEKS	81	106	43	F	WHITE
M14172-37759-612516	Gastric ulcer	2	Y	N	12 WEEKS	14	NA	55	M	WHITE

Reviewer Comment: *Gastrointestinal disorders were the most common AEs reported by SOC and were consistently higher in the GLE/PIB arm of ENDURANCE-2 when compared to placebo. Nausea and diarrhea amongst the most common ADRs with a frequency of 5% or above and this will be reflected in labelling. However, most gastrointestinal events were limited in duration, considered grade 1 or 2 and occurred in a population with a high background rate of gastrointestinal disorders.*

8.6. Safety Analyses by Demographic Subgroups

Differences in adverse events reported by age, sex or gender in the Phase 2/3 Safety Dataset are discussed in this section.

Age

The Phase 2/3 Safety Dataset Set included subjects up to 88 years of age, including 328 (13.8%) who were ≥ 65 years of age. No difference was observed for the percentage of subjects who reported any AE when evaluated by age cohorts. As is clinically expected, numerically greater percentages of subjects who were ≥ 65 years of age experienced any SAE and any AE of Grade ≥ 3 ; very few of these events were considered drug related. See table below.

Table 47 Overview of Adverse Events by Age Phase 2/3 Safety Dataset

	Phase 2 and 3 Analysis Set ^a	
	n (%)	
	Age	
	< 65 Years (N = 2,041)	≥ 65 Years (N = 328)
Any AE	1,392 (68.2)	211 (64.3)
Any DAA-related AE ^{b,c}	857 (42.0)	123 (37.5)
Any AE Grade ≥ 3	66 (3.2)	24 (7.3)
Any DAA-related AE Grade ≥ 3 ^{b,c}	7 (0.3)	2 (0.6)
Any SAE	49 (2.4)	24 (7.3)
Any DAA-related SAE ^{b,c}	1 (< 0.1)	0
Discontinuation of study drug due to:		
Any AE	8 (0.4)	4 (1.2)
Any DAA-related AE ^{b,c}	4 (0.2)	1 (0.3)
Any fatal AE	2 (< 0.1)	1 (0.3)
All deaths ^d	5 (0.2)	2 (0.6)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir;
 SAE = serious adverse event

- a. Including Study M15-462.
- b. DAAs = GLE, PIB, or GLE/PIB.
- c. Investigator assessment.
- d. Includes nontreatment-emergent deaths.

Source: Safety Report and ADAE; data verified

Sex

There were no significant differences in AEs by sex. Adverse events and their incidences reported in male subjects and female subjects were generally similar.

Table 48 Overview of Adverse Events by Sex Phase 2/3 Safety Dataset

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	Phase 2 and 3 Analysis Set ^a	
	n (%)	
	Sex	
	Male (N = 1,318)	Female (N = 1,051)
Any AE	853 (64.7)	750 (71.4)
Any DAA-related AE ^{b,c}	508 (38.5)	472 (44.9)
An AE Grade $\geq$ 3	54 (4.1)	36 (3.4)
Any DAA-related AE Grade $\geq$ 3 ^{b,c}	8 (0.6)	1 (< 0.1)
Any SAE	46 (3.5)	27 (2.6)
Any DAA-related SAE ^{b,c}	1 (< 0.1)	0
Discontinuation of study drug due to:		
Any AE	6 (0.5)	6 (0.6)
Any DAA-related AE ^{b,c}	3 (0.2)	2 (0.2)
Any fatal AE	1 (< 0.1)	2 (0.2)
All deaths ^d	5 (0.4)	2 (0.2)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir;
 SAE = serious adverse event

- a. Including Study M15-462.
- b. DAAs = GLE, PIB, or GLE/PIB.
- c. Investigator assessment.
- d. Includes nontreatment-emergent deaths.

Source : Safety Report and ADAE; data verified

Race

The Phase 2 and 3 Analysis Set included 154 (6.5%) subjects who identified as black. Numerically greater percentages of black subjects experienced any SAE and any AE of Grade $\geq$ 3; however, proportionally EXPEDITION-4 (M15-462) enrolled a larger percentage of subjects identifying as black (25/104). See table.

Table 49 Overview of Adverse Events by Race Phase 2/3 Safety Dataset

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

	Phase 2 and 3 Analysis Set ^a	
	n (%)	
	Race	
	Black (N = 154)	Non-Black (N = 2,212)
Any AE	104 (67.5)	1,496 (67.6)
Any DAA-related AE ^{b,c}	62 (40.3)	916 (41.4)
Any AE Grade ≥ 3	11 (7.1)	79 (3.6)
Any DAA-related AE Grade ≥ 3 ^{b,c}	0	9 (0.4)
Any SAE	11 (7.1)	62 (2.8)
Any DAA-related SAE ^{b,c}	0	1 (< 0.1)
Discontinuation of study drug due to:		
Any AE	2 (1.3)	10 (0.5)
Any DAA-related AE ^{b,c}	0	5 (0.2)
Any fatal AE	1 (0.6)	2 (< 0.1)
All deaths ^d	1 (0.6)	6 (0.3)

AE = adverse event; DAA = direct-acting antiviral agent; GLE = glecaprevir; PIB = pibrentasvir;

SAE = serious adverse event

a. Including Study M15-462.

b. DAAs = GLE, PIB, or GLE/PIB.

c. Investigator assessment.

d. Includes nontreatment-emergent deaths.

Source : Safety Report and ADAE; data verified

Reviewer Comment: *There were no clinically significant or unexpected differences in adverse events reported by age, sex or gender in the Phase 2/3 Safety Dataset. Exploratory analysis confirmed that there were no unexpected or clinically meaningful differences in common adverse events across age, race or sex.*

8.7. Specific Safety Studies/Clinical Trials

Safety in Subjects with Renal Impairment

The safety of GLE-PIB was assessed in the EXPEDITION-4 Trial. As previously described, this trial enrolled subjects with severe renal impairment, including subjects on hemodialysis. All safety analyses were performed on the safety population, N = 104. For the following analyses, only treatment-emergent AEs are presented. Events were considered treatment emergent if they occurred within 30 days of the last study drug dose. The National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4) was used to grade adverse events and laboratory abnormalities.

Treatment-emergent AEs are summarized in the table below. There were 350 treatment-emergent AEs in 74 subjects and 42 SAEs in 25 subjects. Approximately half of the AEs were considered drug-related, but no SAEs were considered drug-related. The rates of AEs and SAEs

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

were higher among cirrhotics than non-cirrhotics.

Table 50 EXPEDITION-4 Safety Summary

	Cirrhotics N = 20	Non-Cirrhotics N = 84	Total N=104
Adverse Events			
Any AEs	20 (100.0)	54 (64.3)	74 (71.2)
Drug-related AEs	12 (60.0)	39 (46.4)	51 (49.0)
Discontinuation due to AEs	2 (10.0)	2 (2.4)	4 (3.8)
Serious Adverse Events			
Any SAEs	11 (55.0)	14 (16.7)	25 (24.0)
Drug-Related SAEs	0 (0)	0 (0)	0 (0)
Discontinuation due to SAEs	0 (0)	2 (2.4)	2 (1.9)
Death	1 (5.0)	0 (0)	1 (1.0)

Source: ADAE dataset
 Reported as n (%)

Deaths

At the time the NDA was filed, there had been 1 death in EXPEDITION-4. This death occurred after the subject completed GLE-PIB therapy and was deemed by the investigator to be unrelated to the study drug. A brief summary of this case is provided below:

- Subject 101602 was a 41 year old man with a medical history that included end-stage renal disease on hemodialysis, cirrhosis, diabetes mellitus, and poorly controlled hypertension. Fourteen days after completing treatment with GLE-PIB, he presented to clinic with impaired speech and difficulty moving his right arm. He was found to have a blood pressure of 249/112 mmHG and a large intraparenchymal hemorrhage. His clinical condition deteriorated rapidly and he expired 17 days after completing GLE-PIB treatment. At last testing (14 days post-treatment), the subject's HCV RNA was undetectable.

Reviewer comment: This subject had multiple risk factors for intracerebral hemorrhage. Most notably, hypertension is one of the most common causes of intracerebral hemorrhage and this subject was reported to have a blood pressure of 249/112 at the time of the intracerebral bleed. Additionally, there is a two week latency period between the end of therapy and the onset of the fatal AE. Based on the timing of the event and the presence of confounding risk factors, this reviewer agrees with the Investigator's assessment that the intracerebral hemorrhage was unlikely to be directly related to the study drug. Further, review of the narrative and CRF shows that the subject's blood pressure was 170/95 mmHg at baseline and

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

180/90 mmHg at the end of treatment. Given the presence of hypertension at baseline and stable, but elevated blood pressure throughout treatment, this reviewer also believes that there is insufficient evidence to implicate the study drug as an indirect cause of the bleed via hypertension.

Serious Adverse Events

Approximately one quarter of subjects in EXPEDITION-4 experienced SAEs. However, none of these SAEs were considered by the Applicant to be treatment related. The reported SAEs are listed by system organ class (SOC) in the table below. Looking at the SOC level, SAEs from the Infections and infestations SOC (7/104, 6.7%) and the Gastrointestinal disorders SOC (6/104, 5.8%) were most common.

Reviewer comment: All SAEs underwent a causality assessment by both the investigator and the Applicant. There was agreement between the investigator and the Applicant in all cases. Based on review of the available data and narratives, this reviewer agrees with the determination that the reported SAEs are not likely to be related to study drug.

Table 51 SAEs occurring in at least 1 Subject, Trial EXPEDITION-4

System Organ Class	N=104 N (%)	Dictionary Derived Term	N=104 N (%)
Infections and infestations	7 (6.7)	Catheter site infection	1 (1.0)
		Erysipelas	1 (1.0)
		Infected fistula	1 (1.0)
		Influenza	1 (1.0)
		Pneumonia	1 (1.0)
		Renal abscess	1 (1.0)
		Wound infection	1 (1.0)
Gastrointestinal disorders	6 (5.8)	Abdominal pain upper	1 (1.0)
		Duodenal ulcer	1 (1.0)
		Gastrointestinal hemorrhage	2 (1.9)
		Nausea	1 (1.0)
		Retroperitoneal hematoma	1 (1.0)
Cardiac disorders	5 (4.8)	Cardiac failure congestive	3 (2.9)
		Hypertensive cardiomyopathy	1 (1.0)
		Mitral valve stenosis	1 (1.0)
Injury, poisoning, and procedural complications	5 (4.8)	Fall	1 (1.0)
		Femur fracture	1 (1.0)
		Limb injury	1 (1.0)
		Patella fracture	1 (1.0)
		Procedural hemorrhage	1 (1.0)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Vascular disorders	5 (4.8)	Hematoma	1 (1.0)
		Hypertension	1 (1.0)
		Hypertensive crisis	2 (1.9)
		Superior vena cava occlusion	1 (1.0)
Renal and urinary disorders	4 (3.8)	Chronic kidney disease	1 (1.0)
		End stage renal disease	1 (1.0)
		Renal hemorrhage	1 (1.0)
		Renal impairment	1 (1.0)
Metabolism and nutritional disorders	2 (1.9)	Fluid overload	1 (1.0)
		Hyperkalemia	1 (1.0)
Nervous system disorders	2 (1.9)	Cerebral hemorrhage	1 (1.0)
		Facial paresis	1 (1.0)
Respiratory, thoracic and mediastinal disorders	2 (1.9)	Pulmonary edema	2 (1.9)
Skin and subcutaneous disorders	1 (1.0)	Hyperhidrosis	1 (1.0)
Musculoskeletal and connective tissue disorders	1 (1.0)	Muscular weakness	1 (1.0)

Source: ADAE

Cardiovascular SAEs:

Upon review of SAEs at the PT level, there were a large number of events from several different SOC categories that could be pooled together as cardiovascular in nature: cardiac failure congestive, hypertensive cardiomyopathy, mitral valve stenosis, fluid overload, pulmonary edema, hypertension, hypertensive crisis, and superior vena cava occlusion. In total, 6 (5.8%) subjects experienced 12 treatment-emergent cardiovascular SAEs. The majority of cardiovascular SAEs can be categorized as either heart failure events or hypertension events.

Cardiac failure congestive was the most commonly reported SAE, occurring in 3 (2.9%) subjects. In addition to the three subjects for whom the PT Cardiac failure congestive was reported, a fourth subject was reported to have experienced on-treatment pulmonary edema and volume overload. A brief summary of each potential heart failure SAE is provided below.

- Subject 908605 is a 63 year-old man with a medical history that includes stage 4 chronic kidney disease, hypercholesterolemia, previous tobacco use, and hypertension. On Day 70 of study treatment he experienced a hypertensive crisis with resultant congestive heart failure and a prolonged hospitalization. On Day 74, the study drug was permanently discontinued due to ongoing heart failure

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

symptoms. On Day 84 the subject was discharged from the hospital and the events were considered resolved.

- Subject 306601 is a 57 year-old man with a history of hypertension, diabetes mellitus, stage 5 chronic kidney disease not on dialysis, previous tobacco use, and cardiomyopathy. On Day 12 of treatment he experienced congestive heart failure and required hospitalization. Study drug was continued and he was discharged 2 days later following diuresis.
- Subject 103604 is a 57 year-old man with a history of chronic kidney disease on dialysis, ischemic cardiomyopathy, congestive heart failure, diabetes mellitus, hypertension, ongoing tobacco use, and hypercholesterolemia. On Day 45 of treatment he developed symptoms of congestive heart failure and was subsequently hospitalized. His HCV treatment was continued and on treatment Day 48 he was discharged and the cardiac event was considered resolved.
- Subject 909605 is a 45 year old woman with a history of hypertension, hyperlipidemia, valvular heart disease, prior tobacco use, and chronic kidney disease on dialysis. She was hospitalized for shortness of breath and pulmonary edema on Day 26 of treatment. This first event resolved with dialysis. Then on Day 63, she presented to the emergency room with shortness of breath and chest pain and was found to have mitral valve stenosis. This was managed medically initially until she ultimately underwent mitral valve replacement on post-treatment Day 47. GLE-PIB was continued throughout these SAEs.

There were 4 serious hypertensive events reported in 2 subjects:

- Subject 908605 is described above.
- Subject 802602 is a 62 year-old man with a history of hypertension, chronic kidney disease on dialysis, and diabetes mellitus. He experienced worsening of his hypertension on Day 80 of his HCV treatment. The study drug was discontinued on Day 83, with just one day of treatment remaining. On post-treatment Day 3, he was reported as having Hypertensive crisis based on a blood pressure of 200/100 mmHg with associated confusion. He was not reported as experiencing any PTs suggestive of heart failure, though according to the narrative provided, his chest x-ray was notable for “cardiac enlargement and minor pulmonary congestion.” The investigator stated the SAE event of hypertensive crisis was not related to treatment.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

In addition to these reported hypertension SAEs, as mentioned previously, subject 101602 who had a history of baseline poorly-controlled hypertension, died of an intracerebral hemorrhage associated with a blood pressure of 249/112 mmHg 14 days after completing his treatment regimen. Please see the discussion above regarding deaths for additional details.

None of the cardiovascular SAEs were assessed by the investigator or the Applicant to be reasonably likely to be related to GLE/PIB. Additionally, although 2 of the subjects (802602 and 908605) discontinued therapy prematurely due to cardiovascular SAEs, all of the subjects described above achieved SVR12.

Reviewer comment: This reviewer agrees with the investigators' assessments that it is unlikely that any of the cardiovascular SAEs were related to GLE/PIB use. All of the cases were confounded by medical conditions that placed the subjects at increased risk for cardiovascular events. Additionally, the lack of a comparator arm limits the ability to assess causality.

Renal SAEs:

Three subjects (2.9%) experienced one or more of the following serious events pertaining to renal function: chronic kidney disease, end stage renal disease, and renal impairment.

- Subject 202601 is a 59 year-old man who was dialysis dependent prior to study enrollment. He was reported as experiencing a serious event of chronic kidney disease on Day 115, at which time, he was hospitalized for an uneventful cadaveric renal transplant.
- Subject 606604 is a 47 year-old man with a history of hypertension, diabetes, and stage 5 chronic kidney disease. On Day 57, he was noted to have worsening renal function. On Day 74, he was hospitalized with asthenia, diarrhea, vomiting, and hypertension and was started on hemodialysis. Study drug was continued without interruption. Dialysis was ongoing at the time of the last report.
- Subject 306601 is a 57 year old man with a history of diabetes, hypertension, cardiomyopathy, and stage 5 chronic kidney disease not on dialysis at the time of enrollment. He experienced congestive heart failure on Day 12 (case described above). On Day 20, he had a second SAE involving hospitalization for worsening renal function and pneumonia. After a prolonged hospitalization, he was discharged

on Day 40, at which time the event of renal impairment was considered resolved. He did not require dialysis and the study drug was not interrupted or discontinued.

Reviewer comments: Overall, the rate of SAEs in this trial was high compared to the rate of SAEs in other trials included in this application (24% vs 1.0-5.8%, respectively). However, this is anticipated, as subjects with advanced renal disease generally have a high degree of comorbidity. This assumption of increased morbidity among subjects with advanced renal disease is supported by the fact that in the C-SURFER trial of elbasvir and grazoprevir in HCV-infected subjects with advanced chronic kidney disease, SAEs were observed in 23% and 20% of the treatment and placebo arms, respectively.

Infections and infestations, Gastrointestinal disorders, Injury, poisoning, and procedural complications, and Cardiac disorders were commonly involved System Organ Classes (SOCs) in both the renal and non-renal populations. Notable differences between the types of SAEs observed in the renal and non-renal populations, include an absence of neoplasms in the renal population and a higher rate of SAEs falling under the Cardiac disorders and Vascular disorders SOCs. As described above, there were many SAEs that could be categorized under the label "cardiovascular disorders." This too is anticipated, as cardiovascular disease is both a risk factor for, and a sequelae of, advanced renal disease. All of the subjects experiencing serious cardiovascular events in this trial had multiple cardiac risk factors and underlying cardiac conditions. Based on the available data from this single trial, it does not appear that the rates or types of SAEs occurring during GLE/PIB treatment differ from the baseline rate of such events among persons with advanced renal disease. Additionally, there were no novel events or any specific pattern of events that suggested a causal association with GLE/PIB treatment in this population.

Discontinuations due to Adverse Events

Four subjects (3.9%) discontinued study drug due to adverse events. Two of these subjects discontinued study drug due to cardiovascular events and are discussed above under serious adverse events (**Subject 802602 and Subject 908605**). None of the cardiovascular events were considered related to study drug. **Subject 303603** discontinued treatment due to diarrhea that was assessed to have a reasonable possibility of being related to the study drug. The subject's first episode of diarrhea occurred on Day 2 and led to interruption of study drug. The second episode of diarrhea occurred on Day 27 and led to treatment discontinuation. On Day 32, the diarrhea was assessed as resolved, suggesting a positive de-challenge. **Subject 504604** discontinued study drug due to pruritus on Day 61 of treatment. This subject had a history of "itching" and the first event of pruritus was reported on Day 1 of study. According to the narrative, at last follow up, the event was ongoing. Nonetheless, the event was considered to have reasonable possibility of being related to study drug.

Non-serious Adverse Events

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

There were 350 treatment-emergent AEs in 74 subjects. AEs occurring in $\geq 5\%$ of subjects, regardless of causality, are reported in table below. Pruritus, fatigue, and nausea were most common, occurring in more than 10% of subjects.

Table 52 Treatment-Emergent AEs in $\geq 5\%$ of subjects, all severity and irrespective of causality, EXPEDITION-4

Dictionary Derived Term	N=104 N (%)
Pruritus	21 (20.2)
Fatigue	15 (14.4)
Nausea	12 (11.5)
Asthenia	10 (9.6)
Diarrhea	10 (9.6)
Decreased appetite	9 (8.7)
Headache	9 (8.7)
Vomiting	7 (6.7)
Dizziness	6 (5.8)
Dyspnea	6 (5.8)

Source: ADAE dataset

Grades 3 and 4 AEs were uncommon in EXPEDITION-4. Grades 3 and 4 AEs that occurred in 2 or more subjects are presented in the table below. There is significant overlap between the SAEs and the Grade 3 and 4 AEs.

Table 53 Treatment-Emergent Grade 3 and 4 AEs in ≥ 2 subjects irrespective of causality, EXPEDITION-4

Dictionary Derived Term	N=104 N (%)		
	Grade 3	Grade 4	Total
Cardiac failure congestive	1 (1.0)	1 (1.0)	2 (1.9)
Diarrhea	2 (1.9)	0	2 (1.9)
Gastrointestinal hemorrhage	2 (1.9)	0	2 (1.9)
Hypertension	0	2 (1.9)	2 (1.9)
Hypertensive crisis	0	2 (1.9)	2 (1.9)
Pruritis	2 (1.9)	0	2 (1.9)
Pulmonary edema	1 (1.0)	1 (1.0)	2 (1.9)

Source: ADAE dataset

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Investigators assessed the causality of each reported AE. Events were classified as having either “reasonable possibility” or “no reasonable possibility” of being related to the study drug. Fifty-one subjects (49%) experienced an AE that was considered reasonably likely to have been related to the study drug. The majority of related AEs were Grade 1 or 2 in severity. There were 5 Grade 3 related AEs reported in 5 subjects (anemia, n = 1; asthenia, n = 1; diarrhea, n = 1; and pruritus, n = 2) and no related Grade 4 AEs were reported. Only two AEs that were assessed to be related to the study drug resulted in treatment discontinuation (diarrhea and pruritus, see above for details). Related AEs that occurred in two or more subjects are presented in Table XX below. Common related AEs reported in this renal population were similar to those reported in other trials of non-renal subjects receiving GLE/PIB. The only notable difference is a higher incidence of pruritus among subjects in EXPEDITION-4 as compared to other GLE/PIB trials (17.3% vs 0.6 - 5.6%, respectively). As shown previously in the table below, none of the SAEs were assessed to be related to study treatment.

Table 54 Related AEs in ≥ 2 subjects, all severity, EXPEDITION-4

Dictionary Derived Term	N=104 N (%)
Pruritus	18 (17.3)
Fatigue	12 (11.5)
Nausea	9 (8.7)
Asthenia	7 (6.7)
Headache	6 (5.8)
Decreased appetite	5 (4.8)
Diarrhea	4 (3.9)
Dizziness	4 (3.9)
Gastroesophageal reflux disease	4 (3.9)
Insomnia	4 (3.9)
Flatulence	3 (2.9)
Vomiting	3 (2.9)
Abdominal distension	2 (1.9)
Anemia	2 (1.9)
Burning sensation	2 (1.9)
Constipation	2 (1.9)
Dyspnea	2 (1.9)
Feeling hot	2 (1.9)
Irritability	2 (1.9)
Muscle spasms	2 (1.9)
Edema peripheral	2 (1.9)
Pruritus generalized	2 (1.9)
Rash pustular	2 (1.9)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Source: ADAE dataset

Laboratory Abnormalities

The tables below display treatment-emergent, graded laboratory abnormalities for chemistry and hematology parameters in EXPEDITION-4. These analyses present the worst change from baseline per subject. Subjects who had abnormal results for the same laboratory test on more than one occasion are counted only once at the highest toxicity grade. The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, was used to assign toxicity grades to all laboratory results reported below.

Table 55 Treatment-emergent abnormalities* in key chemistry parameters by highest toxicity grade, EXPEDITION-4

Laboratory Parameter	N=104 n (%)
Alanine Aminotransferase (IU/L)	
Grade 1 (> ULN to 3.0 x ULN)	1 (1.0)
Alkaline Phosphatase (IU/L)	
Grade 1 (> ULN to 2.5 x ULN)	14 (13.5)
Aspartate Aminotransferase (IU/L)	
Grade 1 (> ULN to 3.0 x ULN)	2 (1.9)
Bilirubin (mg/dL)	
Grade 1 (> ULN to 1.5 x ULN)	6 (5.8)
Grade 2 (> 1.5 to 3.0 x ULN)	1 (1.0)
Grade 3 (> 3.0 to 10 x ULN)	1 (1.0)
Increased Creatinine (mg/dL)	
Grade 1 (> 1 to 1.5 x baseline; or > ULN to 1.5 x ULN)	0
Grade 2 (> 1.5 to 3.0 x baseline; or > 1.5 to 3.0 x ULN)	1 (1.0)
Grade 3 (> 3.0 x baseline; or > 3.0 to 6.0 x ULN)	3 (2.9)
Grade 4 (> 6.0 x ULN)	19 (18.3)
Gamma Glutamyl Transferase (IU/L)	
Grade 1 (> ULN to 2.5 x ULN)	2 (1.9)
International Normalized Ratio (INR)	
Grade 1 (> 1 to 1.5 x ULN)	4 (3.8)
Grade 2 (> 1.5 to 2.5 x ULN)	1 (1.0)
Grade 3 (> 2.5 x ULN)	1 (1.0)
Triglycerides (mmol/L)	
Grade 1** (1.71 mmol/L to 3.42 mmol/L)	23 (22.1)
Grade 2 (> 3.42 mmol/L to 5.7 mmol/L)	8 (7.7)
Grade 3 (> 5.7 mmol/L to 11.4 mmol/L)	1 (1.0)

*The abnormality refers to an elevation *above* the upper limit of normal

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

** The majority of the Grade 1 triglyceride abnormalities were within the normal range

Table 56 Treatment emergent abnormalities* in key hematology parameters by highest toxicity grade, EXPEDITION-4

Laboratory Parameter	N=104 n (%)
Decreased Hemoglobin (g/dL)	
Grade 1 (< LLN to 10.0 g/dL)	23 (22.1)
Grade 2 (< 10 to 8.0 g/dL)	8 (7.7)
Grade 3 (< 8.0 g/dL)	5 (4.8)
Decreased Leukocytes (mm ³)	
Grade 1 (< LLN to 3000/mm ³)	7 (6.7)
Grade 2 (< 3000 to 2000/mm ³)	4 (3.8)
Grade 3 (< 2000 to 1000/mm ³)	1 (1.0)
Decreased Lymphocytes (/mm ³)	
Grade 1 (< LLN to 800/mm ³)	4 (3.8)
Grade 2 (< 800 to 500/mm ³)	9 (8.7)
Grade 3 (< 500 to 200/mm ³)	3 (2.9)
Decreased Neutrophils (mm ³)	
Grade 1 (< LLN to 1500/mm ³)	7 (6.7)
Grade 2 (< 1500 to 1000/mm ³)	1 (1.0)
Grade 3 (< 1000 to 500/mm ³)	1 (1.0)
Decreased Platelet (/mm ³)	
Grade 1 (< LLN to 75,000/mm ³)	12 (11.5)
Grade 2 (< 75,000 to 50,000/mm ³)	2 (1.9)

*The abnormality refers to an elevation *below* the upper limit of normal

As shown above, Grade 3 laboratory abnormalities were uncommon overall but were primarily noted in renal function and white blood cell parameters. There was a single subject who experienced a treatment-emergent grade 3 bilirubin abnormality. There were no treatment-emergent ALT, AST, or ALP abnormalities above Grade 1.

The only Grade 4 laboratory abnormalities involved renal function. Nineteen (18.3%) subjects had Grade 4 elevations in creatinine. Among these subjects, 2 had Grade 2 creatinine elevations at baseline and 17 had Grade 3 elevations at baseline. However, the mean and median creatinine and creatinine clearance were relatively stable throughout treatment (mean creatinine was 6.9 mg/dL and 6.7 mg/dL at baseline and week 84, respectively; and mean creatinine clearance was 0.2 mL/min at both baseline and week 84).

Reviewer comment: Individual subjects are expected to have fluctuations in creatinine and

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

creatinine clearance over time. For those subjects who are dialysis dependent, this may reflect the time from last dialysis session. However, the median and mean creatinine and creatinine clearance values across the study population suggest that renal function was relatively stable throughout treatment. Additionally, as previously mentioned, review of clinical renal events revealed that only a single subject had on-treatment progression of renal dysfunction requiring the initiation of dialysis. Therefore, this reviewer does not believe that GLE/PIB led to any clinically significant effect on renal parameters in this population.

Vital Signs

Analyses of vital signs were conducted for EXPEDITION-4. Significant fluctuations in blood pressure were observed in some individual subjects. The number of subjects experiencing on-treatment extremes in systolic or diastolic blood pressure is presented below:

- Systolic blood pressure $\leq$ 90 mmHg AND a decrease of $\geq$ 20 mmHg from baseline, n=7
- Systolic blood pressure $\geq$ 180 mmHg AND an increase of $\geq$ 20 mmHg from baseline, n=7
- Diastolic blood pressure $\leq$ 50 mmHg AND a decrease of $\geq$ 15 mmHg from baseline, n=4
- Diastolic blood pressure $\geq$ 105 mmHg AND an increase of $\geq$ 15 mmHg from baseline, n=6.

However, the mean systolic and diastolic blood pressure of the safety population overall appeared stable throughout the duration of the study. As noted previously, two subjects experienced treatment-emergent hypertension SAEs and two subjects experienced non-serious treatment-emergent hypertension AEs. Additionally, there were two subjects who experienced non-serious, treatment-emergent hypotension AEs.

Reviewer Comment: The occurrence of blood pressure- related AEs as well as some extreme fluctuations in blood pressure is not unexpected in this study population. Eighty-seven (84%) of subjects in EXPEDITION-4 had reported a medical history of hypertension, hypertensive cardiomyopathy, hypertrophy of LV due to hypertension, arterial hypertension, or severe hypertension at baseline. The variability in blood pressure observed overtime in some subjects may have been influenced by antihypertensive compliance/noncompliance, salt intake, and time from last dialysis session (for those subjects who are dialysis dependent). The occurrence of both extremely high and low blood pressure recordings also argues against GLE/PIB playing a causal role in blood pressure changes, as it is unlikely that both extremes would result from a single mechanism.

There were no clinically meaningful trends observed for the other vital sign parameters.

Electrocardiograms (ECGs)

There were no apparent trends in ECG findings. Two subjects were noted to have QTc prolongation (476 ms and 479 ms) on their week 12 ECGs. Both of these subjects had normal

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

screening ECGs. Neither subject experienced any cardiac AEs.

Adverse Events of Special Interest

- Hepatotoxicity:

The sponsor defined potential cases of hepatotoxicity as 1 of the following:

- ALT value $> 5 \times$ ULN and $\geq 2 \times$ baseline, OR
- Post-nadir increase in ALT grade to Grade 2 (ALT value $> 3 \times$ ULN) and a concurrent total bilirubin $\geq 2 \times$ ULN with direct bilirubin:total bilirubin ratio > 0.4 .

No subjects fulfilled these criteria for hepatotoxicity. Additionally, no subjects met Hy's Law. Of note, DAVP requested that the Sponsor have an Expert Hepatic Panel (EHP) assess all cases involving on-treatment bilirubin elevations $\geq 2 \times$ ULN. Two subjects from EXPEDITION-4 had bilirubin elevations $\geq 2 \times$ ULN and were evaluated by the EHP (subject 501607 and subject 606603). In both cases, the total and direct bilirubin levels increased early in the treatment course, remained elevated throughout treatment, and returned to baseline by post-treatment Day 29. Neither case was associated with any increase in aminotransferase levels or clinical signs of acute hepatitis or hepatic decompensation. Neither case necessitated treatment interruption or discontinuation. The EHP concluded that drug induced liver injury (DILI) was unlikely in both cases. The panel attributed the increases in bilirubin to a transporter effect.

- ***Reviewer comment: The temporal association between the observed bilirubin changes and the starting and stopping of GLE/PIB could be explained by a transporter effect as concluded by the EHP. The absence of aminotransferase elevation and the ability of both of these subjects to complete treatment, suggests that these cases are unlikely to be representative of DILI.***

- Hepatic decompensation/Hepatic Failure:

There were no events clearly suggestive of hepatic decompensation or hepatic failure (i.e. no reports of hepatic encephalopathy, esophageal variceal bleeding, or spontaneous bacterial peritonitis). Deeper investigation revealed non-specific PTs that could be attributable to hepatic decompensation. This reviewer has grouped these events into those with the potential to represent variceal bleeding and those with the potential to represent hepatic encephalopathy. The events are summarized below.

- Three subjects experienced gastrointestinal bleeding during the treatment

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

period (PTs: Gastrointestinal hemorrhage (n = 2) and Hematochezia (n = 1)). Two of these three subjects were cirrhotic. One of the cirrhotic subjects had a concurrent diagnosis of large intestine polyp and the other cirrhotic subject had a vascular jejunal lesion, both of which represent plausible etiologies for gastrointestinal bleeding. None of the three subjects had concurrent laboratory changes (bilirubin, INR, or platelets) suggestive of hepatic decompensation. Two of the gastrointestinal hemorrhage events were serious, none led to treatment discontinuation.

- Six subjects experienced an altered level of consciousness during treatment (PTs: Lethargy (n = 2), Somnolence (n = 1), Confusional state (n = 1), Disorientation (n = 1), and Hallucination (n = 1)). Only one of these subjects was cirrhotic. The cirrhotic subject (101603) was noted to have experienced lethargy at the week 1 visit. This subject had an associated increase in bilirubin from 13.0 umol/L at week -1 to 16 umol/L at week 1. His bilirubin was noted to be trending down at the week 3 visit. No other laboratory findings suggested hepatic decompensation. None of these events were serious and none led to treatment discontinuation.

- Hepatocellular carcinoma:

No subjects developed hepatocellular carcinoma.

Other Safety Events of Interest

Given the imbalance in psychiatric events between the GLE/PIB and placebo arms in ENDURANCE-2, psychiatric AEs were examined in EXPEDITION-4. Five subjects experienced 6 on-treatment AEs related to depression and anxiety (PTs Anxiety, Depressed mood, and Depression). There were no subjects who experienced Suicide or Suicidal ideation; there were no serious psychiatric AEs, and no treatment discontinuations due to psychiatric AEs. Given the absence of a control arm in EXPEDITION-4, it is not possible to determine if the rate of psychiatric events reported in this study is higher than would be anticipated in this patient population.

Conclusions:

Among 104 subjects treated in EXPEDITION-4, 102 (98%) achieved SVR12 and there were no virologic failures. This high SVR12 rate and absence of virologic failures suggests that the presence of renal failure does not impact the efficacy of GLE/PIB. The adverse events observed in this trial were increased in prevalence and severity compared to the adverse events observed

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

in other trials in this application. This is likely due to the high baseline rate of morbidity associated with advanced renal disease. Notably, the rate of serious adverse events in EXPEDITION-4 was comparable to that observed in previous HCV trials in subjects with advanced renal disease (i.e. the GZR/EBR trial, C-SURFER). In conclusion, this reviewer believes that GLE/PIB is a safe and effective HCV regimen for subjects with severe chronic renal impairment. It is an important addition to the HCV armamentarium for HCV genotype 2, 3, 5, and 6 infected subjects with severe renal impairment for whom there are currently no other treatment options available.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The relatively short duration of GLE/PIB treatment (8-16 weeks) and planned follow-up (generally 24 weeks) in clinical trials limits the assessment for oncologic events in clinical trials. Twenty-six subjects (1%) in the Phase 2/3 safety population, had an event in the Neoplasms Benign, Malignant, and Unspecified SOC, 20 of who experienced treatment emergent events in this SOC. Preferred Terms associated with this SOC are shown below. Overall, there were 8 cases of de-novo HCC, including those in the safety update (see Section 8.5.1).

Table 57 Subjects with Neoplasms Benign, Malignant, and Unspecified Phase 2/3 Dataset, excluding those with renal failure

Unique Subject Identifier	Age	Sex	Cirrhosis	Dictionary Derived Term	Treatment Emergent	Serious Event
M13590-38898-230105	67	M	N	Lung neoplasm malignant		Y
M13590-39408-170110	44	F	N	Breast cancer		Y
M13590-45362-243105	41	F	N	Uterine leiomyoma	Y	Y
M13590-45610-312103	52	M	N	Acanthoma	Y	N
M13590-45610-312103	52	M	N	Melanocytic nevus	Y	N
M13590-45746-122109	45	M	N	Lipoma	Y	N
M13594-32999-129308	49	F	N	Benign hydatidiform mole		Y
M13594-44319-120301	59	F	N	Paranasal sinus and nasal cavity malignant neoplasm recurrent	Y	Y
M14172-37834-603504	57	F	Y	Hepatocellular carcinoma	Y	Y

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject Identifier	Age	Sex	Cirrhosis	Dictionary Derived Term	Treatment Emergent	Serious Event
M14172-40603-204507	64	M	Y	Skin cancer	Y	N
M14172-40764-503502	52	M	Y	Hepatocellular carcinoma	Y	Y
M14172-48586-605501	64	F	Y	Basal cell carcinoma	Y	N
M14867-42730-3408	67	F	N	Adenocarcinoma	Y	Y
M14868-32999-7015	58	F	N	Seborrheic keratosis	Y	N
M14868-37759-2520	64	M	N	Benign neoplasm of skin	Y	N
M14868-40622-2703	66	F	Y	Hepatic neoplasm	Y	Y
M14868-45216-4011	52	M	Y	Colon cancer	Y	Y
M14868-51321-7408	66	M	N	Squamous cell carcinoma	Y	N
M14868-53553-5004	70	F	N	Squamous cell carcinoma of skin	Y	N
M14868-53724-3002	66	F	Y	Squamous cell carcinoma of skin	Y	Y
M14868-91926-4606	54	M	N	Prostate cancer	Y	N
M15410-38627-1301	65	M	N	Hepatic cancer metastatic		Y
M15410-40621-3022	57	M	N	Melanocytic nevus	Y	N
M15410-40724-3921	58	F	Y	Hepatic cancer		Y
M15410-44318-3623	55	M	Y	Hepatocellular carcinoma		Y
M15410-53286-2924	52	M	N	Melanocytic nevus	Y	N
M15464-53362-702203	62	F	N	Skin papilloma	Y	N

Reviewer Comment: Based on the available data from the Phase 2 and 3 trials in the Safety Dataset, there is not sufficient clinical information to assess the carcinogenicity for the GLE/PIB combination regimen. Although a few subjects who experienced HCC and other malignancies did not meet the typical risk profile for cancer, there does not appear to be a clear signal. Some human serine protease inhibitors including human Secretory leukocyte protease inhibitor (SLPI) may have a role in human carcinogenesis[16-18]. However, there was no signal found in animal/toxicology studies for GLE, a serine protease inhibitor that has high specificity for HCV. Surveillance for malignancies, in particular HCC, will continue postmarketing in collaboration with DPV II.

8.8.2. Human Reproduction and Pregnancy

For both GLE and PIB, there were no clinically relevant adverse effects on male or female fertility in mice, embryofetal development in mice or rabbits, or pre/post-natal development in mice. Pregnant and lactating women were excluded from participation for all Phase 2 and Phase 3 trials. However, six pregnancies were reported in the Phase 2 and 3 studies, including

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

in subjects in arms not included in the Phase 2 and 3 dataset. These included 2 spontaneous abortions, 2 elective abortions, and 2 subjects who are due to deliver in (b) (6)

Subject 131102 (GLE/PIB 300 mg/120 mg QD for 8 weeks) completed 8 weeks of treatment and had a positive pregnancy test result 28 days after the last dose of study drug. The estimated date of delivery was (b) (6). The safety update report provided follow-up on this subject, who gave birth to a healthy baby on (b) (6)

Subject 129308 (GLE/PIB 300 mg/120 mg QD for 8 weeks) had a positive urine pregnancy test on Day 29 and discontinued study drug. On Day 70, an abdominal ultrasound showed molar pregnancy and the subject underwent an elective abortion.

Subject 167303 (GLE/PIB 300 mg/120 mg QD for 12 weeks) had a spontaneous abortion (treatment-emergent SAE of abortion missed) on Day 72 (15 days after last dose of study drug).

Subject 104205 (GLE/PIB 300 mg/120 mg QD for 12 weeks) became pregnant during the study. The site was informed of the subject's pregnancy on (b) (6) (b) (6) days after the last dose of study drug). The estimated date of delivery is (b) (6).

Subject 2101 (GLE 200 mg QD + PIB 120 mg QD + RBV × 12 weeks) in Part 1 of the study had positive urine pregnancy tests on Days 85, 113, and 141. The pregnancy resulted in a spontaneous abortion (nontreatment-emergent SAE of abortion spontaneous, considered to be related to RBV).

Subject 6903 (GLE 300 mg QD + PIB 120 mg QD × 8 weeks) in Part 2 of the study had a positive urine pregnancy test 72 and 101 days after the last dose of study drugs. The subject underwent an elective abortion (nontreatment-emergent SAE of abortion induced, considered not related to study drug).

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric data are available for review with this application. However, the Applicant has discussed the size and scope of future pediatric trials with DAVP. In conformance with current regulatory requirements, on July 15, 2016, FDA confirmed agreement with AbbVie Inc.'s Agreed Initial Pediatric Study Plan via IND 127416.

AbbVie, requested deferral of pediatric studies for the proposed indication in pediatric patients ≥ 3 to < 18 years because it is anticipated that the DAA regimen will be ready for approval for use in adults before pediatric studies are complete. A partial waiver was also requested for pediatric patients < 3 years of age on the basis that clinical trials in this age group are impossible or highly impractical because the number of patients requiring treatments is very small.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

There is no anticipated potential for abuse of GLE or PIB given their poor brain penetration and the fact that their pharmacological targets are not associated with pathways known to be related to reward. The highest doses administered to healthy volunteers is 1200mg once daily for 7 days for GLE and 600 mg once daily for 10 days for PIB. The highest doses administered to healthy volunteers is 1200mg once daily for 7 days for GLE and 600 mg once daily for 10 days for PIB. In Phase 1 studies, among healthy subjects given multiple doses of GLE 700 mg QD or higher, 2 subjects had asymptomatic Grade 3 ALT and 3 subjects had Grade 3 total bilirubin elevations. Other than these rare, asymptomatic ALT and bilirubin elevations, the highest single and multiple doses were generally well-tolerated.

In cases of overdose, patients should be monitored for clinical or laboratory signs of toxicity and appropriate symptomatic treatment should be administered. GLE and PIB are not significantly removed by hemodialysis.

8.9. **Safety in the Postmarket Setting**

8.9.1. **Safety Concerns Identified Through Postmarket Experience**

There is no postmarket experience with either GLE or PIB as neither is available on the U.S market or any foreign market.

Effective February 2017, all DAA labels include a Boxed Warning and a Warning and Precaution regarding the risk of hepatitis B virus (HBV) reactivation, resulting in fulminant hepatitis, hepatic failure and death in HCV/HBV coinfecting patients who received treatment with DAA drugs for chronic HCV infection. This safety information was identified from adverse event reports from the FDA Adverse Event Reporting System (FAERS) and medical literature.

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

Reviewer Comment: Although no cases were reported in the safety database for GLE/PIB, the same Boxed Warning and Warnings and Precautions language will be included in the label regarding the risk for HBV reactivation in HCV/HBV coinfecting patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting can be managed by routine pharmacovigilance activities. While there were few hepatic events, there were also few subjects with cirrhosis (288/2,265) in the Phase 2/3 safety dataset. More serious hepatic events, such as hepatic decompensation or hepatic failure, may occur in the postmarket setting, as has occurred with other approved DAA combinations. Furthermore, when a larger number of patients are exposed to GLE/PIB in the postmarket setting, some are likely to experience higher exposures, and additional safety signals may be identified.

8.10. Integrated Assessment of Safety

The safety database for GLE/PIB includes 2,265 subjects without severe renal impairment and 104 subjects with severe renal impairment who received at least one dose of GLE/PIB at the indicated dose and duration and is considered adequate. The trials included small but adequate numbers of subjects with compensated CTP A cirrhosis and subjects with severe renal disease to assess safety in these subpopulations, respectively.

Headache (9%), fatigue (8%), nausea (6%), and diarrhea (5%) were the most common ADRs and occurred at greater than or equal to 5% in ENDURANCE-2, the 12 week placebo controlled study of subjects without severe renal impairment. All these ADRs except fatigue occurred at higher rates in the GLE/PIB arm of the placebo controlled trial. They were also reported in fairly similar proportion 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 major clinical trials in which subjects without severe renal impairment. In subjects without severe renal impairment there only one serious adverse event, transient ischemic attack, considered by the Investigator as reasonably related to the study drug. The proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.3% (7/2,265).

In subjects with severe renal impairment in EXPEDITION=4, ADRs observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with GLE/PIB were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with GLE/PIB who reported an adverse reaction, 55% had adverse reactions of mild severity (Grade 1). No subjects experienced a serious adverse reaction. The proportion of subjects who permanently

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

discontinued treatment due to adverse reactions was 2%.

Given that a small proportion of subjects had post-baseline bilirubin elevations (30/2,369 or 1.3%), an expert hepatic panel was convened, and liver safety was thoroughly examined for this review. Most of the reported cases of bilirubin elevation had indirect predominance (23 of the 30 subjects with total bilirubin $\geq 2 \times$ ULN had direct/total bilirubin ratio < 0.4). In addition, most of the 23 of the 30 subjects with bilirubin $\geq 2 \times$ ULN had elevated bilirubin with indirect predominance prior to starting treatment, consistent with an underlying Gilbert's syndrome, which is estimated to affect 3-7% of the US population. None of these subjects reported bilirubin-related adverse events (i.e., jaundice), obvious liver-decompensation related events and none resulted in treatment discontinuations. Bilirubin elevations were consistent with known inhibition of OATP1B1/3 and UGT1A1. Overall, ALT and AST trended down rapidly in the active treatment groups as HCV viral load decreased.

The EHP panel identified only one possible case of DILI (likelihood 25% – 49%) but with a most likely alternative etiology ("most likely related to passage of gallstones"). Overall the liver safety evaluation was reassuring, but it should be noted that there were only a small proportion of subjects (approximately 13%) with compensated cirrhosis (CTA) and a relatively low mean CTP score of 5.1. In previous HCV PI containing regimens, patients with decompensated (CTP B and C) liver disease had a higher frequency of liver related events. Based on clinically-significant elevated exposures, GLE/PIB will be contraindicated for patients with CTP C liver disease. Because of a lack of efficacy and safety data, GLE/PIB is not recommended for patients with CTP B liver disease.

The MedDRA SOC with the highest proportion of subjects reporting treatment emergent events in the Phase 2/3 dataset was Gastrointestinal disorders, with 605 subjects (approximately 27%) reporting at least one gastrointestinal AE of any severity; with similar proportions seen in the GLE/PIB arm of the placebo controlled study. Of these, 348 (15% overall) were considered ADRs. Nausea, diarrhea, dyspepsia, constipation, abdominal pain, abdominal pain upper, abdominal distension and flatulence were all ADRs seen at a frequency of greater than 1%; nausea and diarrhea were seen at the highest frequencies. Overall there were 5 SAEs and 7 Grade 3 or above events in the Gastrointestinal disorders SOC within Phase 2/3 dataset excluding those with severe renal impairment. No serious events were considered causal; one grade 3 event of "Abdominal pain upper" was considered causal. However, most gastrointestinal were mild or moderate events (grade 1 or 2), and were seen in the context of a high background rate of gastrointestinal symptoms in the study population. These ADRs appear uncomfortable but overall manageable for the durations of treatment indicated, and generally, did not impact the ability to complete the duration of treatment.

Overall approximately 84 (3.7%) of subjects experienced either an increased systolic or diastolic

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

blood pressure readings and/or experienced an adverse event of hypertension. In addition, 57 (2.5%) subjects experienced either decreased systolic or diastolic blood pressure readings and/or experienced an adverse event of hypotension or orthostatic hypotension. This could suggest a possible blood pressure signal in both directions. However, the majority of the cases, especially amongst those with increased blood pressure had confounding medical histories and trends were difficult to follow given appropriate medical interventions (i.e. titrating or initiating antihypertensives) for blood pressure control. It is also possible that these values reflect natural variation and/or an unmasking of a chronic disease (particularly hypertension) in the context of the additional clinical scrutiny subjects receive in a clinical trial.

Given that several cases of hypotension occurred in subjects with baseline hypertension on anti-hypertensives with no other explanation for low blood pressure, some of the hypotension may be explained by drug-drug interactions, although a specific interaction has not been identified by the review team to date. Similarly, for those with increased blood pressure, the majority of subjects were on concomitant medications at baseline, either for hypertension or other chronic diseases. Drug-drug interactions, hepatic metabolism or hepatic transporters could also play a role in treatment emergent hypertension, in this context. There were no preclinical cardiac or hypertensive signals. At the time of this review the review team is still examining this issue and it is not being considered for labelling. However, given the relatively short indicated duration of treatment, if a signal was detected, monitoring and treating on-treatment blood pressure elevations, would be sufficient practical intervention and something that would be expected to occur even in the absence of specific labelling.

Given the frequency of AEs in these categories, Rash and Skin Conditions and Neuropsychiatric Disorders were also closely evaluated in this review. However, no additional major safety issues or concerns specifically related to GLE or PIB were identified in these reviews.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held and no external consultations were place by DAVP.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are the current general clinical recommendations for

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

proposed labeling. There were substantial labeling changes to Sections to 1, 2, 6 and 14 which are provided below.

1. Indications and Usage

For consistency with labeling of other DAAs, the phrase “infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)” was added to the indication sentence.

TRADENAME is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) [see *Dosage and Administration (2.2)* and *Clinical Studies (14)*].

2. Dosage and Administration

2.1 *Testing Prior to the Initiation of Therapy*

For consistency with labelling of other DAAs, the following is added:

“Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with TRADENAME [see Warnings and Precautions (5.1)].”

2.2 *Recommended Dosage in Adults*

The following section has had major revisions and is updated based on FDA review of efficacy data for each subpopulation as discussed throughout the efficacy review:

TRADENAME is a fixed-dose combination product containing glecaprevir 100 mg and pibrentasvir 40 mg in each tablet

The recommended oral dosage of TRADENAME is three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) taken once daily with food [see *Clinical Pharmacology (12.3)*].

(b) (4)

(b) (4)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

(b) (4)

4. Contraindications

TRADENAME is contraindicated in patients with severe hepatic impairment (Child-Pugh C) [see *Dosage and Administration* (2.4), *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)].

TRADENAME is contraindicated (b) (4) [see *Drug Interaction* (7.3) and *Clinical Pharmacology* (12.3)]:

- Atazanavir

(b) (4) rifampin, (b) (4)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

5. Warnings and Precautions

For consistency with labelling of other DAAs, the same language as other DAA labels regarding the Risk of HBV reactivation was added to this section.

6. Adverse Reactions: Clinical Trials Experience

Section 6 had significant changes and additions of data from the controlled trials ENDURANCE-2 and ENDURANCE-3. The following is the currently proposed FDA wording for Section 6:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of TRADENAME cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overall Adverse Reactions in HCV-Infected Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

The adverse reactions data for TRADENAME in subjects without cirrhosis or with compensated cirrhosis (Child-Pugh A) were derived from Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV who received TRADENAME for 8, 12 or 16 weeks [see *Clinical Studies (14)*].

The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received TRADENAME for 8, 12 or 16 weeks.

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 TRADENAME were headache (13%), fatigue (11%), and nausea (8%). In subjects receiving TRADENAME who experienced adverse reactions, 80% had an adverse reaction of mild severity (Grade 1). One subject experienced a serious adverse reaction.

Adverse reactions (type and severity) were similar for subjects receiving TRADENAME for 8, 12 or 16 weeks. The type and severity of adverse reactions in subjects with compensated cirrhosis (Child-Pugh A) were comparable to those seen in subjects without cirrhosis.

Adverse Reactions in HCV-Infected Adults treated with TRADENAME in Controlled Trials

ENDURANCE-2

(b) (4)



Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 3. Adverse Reactions Reported in ≥5% of Treatment-Naïve and PRS-Experienced Adults Without Cirrhosis Receiving TRADENAME for 12 Weeks in ENDURANCE-2

Adverse Reaction	TRADENAME 12 Weeks (N = 202) %	Placebo 12 Weeks (N = 100) %
Headache	9	6
Nausea	6	2
Diarrhea	5	2

ENDURANCE-3



Table 4. Adverse Reactions Reported in ≥5% of Treatment-Naïve [REDACTED] Without Cirrhosis Receiving TRADENAME for 8 Weeks or 12 Weeks in ENDURANCE-3 (b) (4)

ADVERSE REACTION	TRADENAME 8 Weeks (N=157) %	TRADENAME 12 Weeks (N=233) %	DCV + SOF 12 Weeks (N=115) %
Headache	16	17	15
Fatigue	11	14	12
Nausea	19	12	12
Diarrhea	7	3	3

DCV=daclatasvir, SOF=sofosbuvir

Adverse Reactions in HCV-Infected Adults With Severe Renal Impairment Including Subjects on Dialysis

The safety of TRADENAME in subjects with chronic kidney disease (Stage 4 or Stage 5 including subjects on dialysis) with genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis was assessed in 104 subjects (EXPEDITION-4) who received [TRADENAME] for 12 weeks. The most common adverse reactions observed in greater than or equal to 5% of subjects receiving 12 weeks of treatment with TRADENAME

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

were pruritus (17%), fatigue (12%), nausea (9%), asthenia (7%), and headache (6%). In subjects treated with TRADENAME who reported an adverse reaction, 90% had adverse reactions of mild or moderate severity (Grade 1 or 2). The proportion of subjects who permanently discontinued treatment due to adverse reactions was 2%.

14. Clinical Studies

Section 14 had a large amount of editing and changes based on review of the efficacy data and changes made to the various treatment durations by genotype and subpopulation. Therefore, this section provides the currently proposed labeling. As labeling negotiations are ongoing, it is expected that some of these presentations may change.

Table 12 summarizes the clinical trials conducted to support the effectiveness of TRADENAME in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 infection according to treatment history and cirrhosis status.

Table 12. Clinical Trials Conducted with TRADENAME in Adults With HCV Genotype 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical Trial	(b) (4) *
TN and PRS-TE Subjects Without Cirrhosis		
GT1	ENDURANCE-1	Tradename for 8 (n=351) or 12 weeks (n=352)
GT2	SURVEYOR-2	Tradename for 8 weeks (n=197)
GT3	ENDURANCE-3	Tradename for 8 (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2	Tradename for 16 (PRS-TE only) weeks (n=22)
GT4, 5, 6	ENDURANCE-4	Tradename for 12 weeks (n=26, GT5; n=19, GT6)
	SURVEYOR-1	Tradename for 12 weeks (n=1, GT5; n=11, GT6)
	SURVEYOR-2	Tradename for 8 weeks (n=46, GT4)
TN and PRS-TE Subjects With Compensated Cirrhosis (b) (4)		
GT1, 2, 4, 5, 6	EXPEDITION-1	Tradename for 12 weeks (n=146)
GT3	SURVEYOR-2	Tradename for 12 weeks (TN only) (n=40) or 16 weeks (PRS-TE only) (n=47)
Subjects With CKD Stage 4 and 5 Without Cirrhosis or With Compensated Cirrhosis (b) (4)		
GT1-6	EXPEDITION-4	Tradename for 12 weeks (n=104)

NS5A Inhibitor or PI-Experienced Subjects Without Cirrhosis or With Compensated Cirrhosis

GT1	MAGELLAN-1	Tradename for 12 (n=25) or 16 weeks (n=17)

TN=treatment naïve

PRS-TE= 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 protease inhibitor or NS5A inhibitor.

PI=protease inhibitor

CKD=chronic kidney disease

* Treatment durations for some trial arms shown in this table do not reflect recommended dosing for the respective genotypes, prior treatment history, and/or cirrhosis status. For recommended dosing in adults, see *Dosage and Administration (2.2)*

Serum HCV RNA values were measured during the clinical trials using the Roche COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with a lower limit of quantification (LLOQ) of 15 IU/mL (except for SURVEYOR-1 and SURVEYOR-2 which used the Roche COBAS TaqMan real-time reverse transcriptase-PCR (RT-PCR) assay v. 2.0 with an LLOQ of 25 IU/mL). The primary endpoint across all clinical trials was sustained virologic response (SVR12), defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment. Relapse was defined as HCV RNA $\geq$ LLOQ after end-of-treatment response among subjects who completed treatment. Subjects who discontinued due to an adverse event, subject withdrawal or were lost to follow-up were counted as SVR12 failures.

Demographics and Baseline Characteristics of Clinical Trials in Treatment-Naïve or PRS Treatment-Experienced Adults Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Of the (b) (4) treated subjects without cirrhosis or with compensated cirrhosis who were treatment-naïve or treatment-experienced to a combination of interferon, peginterferon, ribavirin and/or sofosbuvir (PRS), the median age was 54 years (range: 19 to 88); 73% were treatment-naïve, 27% were PRS treatment-experienced; 39% were HCV genotype 1; 21% were HCV genotype 2; 29% were HCV genotype 3; (b) (4)% were HCV genotype 4; 4% were HCV genotype 5-6; (b) (4)% were $\geq$ 65 years; (b) (4)% were male; 5% were Black; (b) (4)% had cirrhosis; 5% had severe renal impairment or end stage renal disease; 20% had a body mass index of at least 30 kg per m²; and median baseline HCV RNA level was 6.2 log₁₀ IU/mL.

14.2 Treatment Naïve or PRS Treatment Experienced Adults With HCV Genotype 1, 2, 4, 5, or 6 Infection Without Cirrhosis

The efficacy of TRADENAME in subjects who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5 or 6 chronic HCV infection without cirrhosis was studied in four trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

ENDURANCE-1 was a randomized (1:1), open-label, multi-national trial comparing the efficacy of 8 weeks of treatment with TRADENAME versus 12 weeks of treatment in subjects without cirrhosis with genotype 1 infection with or without HIV-1 co-infection (n=33 co-infected). Table 13 presents SVR12 in TRADENAME-treated genotype 1 infected subjects for the 8 week treatment arm. (b) (4)

[Redacted text block]

[Large redacted text block]

14.3 Treatment-Naïve or PRS Treatment-Experienced Adults with HCV Genotype 1, 2, 4, 5, or 6 Infection With Compensated Cirrhosis (b) (4)

The efficacy of TRADENAME in subjects who were treatment-naïve or treatment-experienced to combinations of peginterferon, ribavirin and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5 or 6 chronic hepatitis C virus infection with compensated cirrhosis was studied in the single-arm, open-label EXPEDITION-1 trial, which included 146 subjects treated with TRADENAME for 12 weeks.

Table 14. EXPEDITION-1: (b) (4)

	TRADENAME 12 Weeks (N=146)					
	Total (all GTs) (N=146)	GT-1 (N=90)	GT-2 (N=31)	GT-4 (N=16)	GT-5 (N=2)	GT-6 (N=7)
SVR12	99% (145/146)	99% (89/90)	100% (31/31)	100% (16/16)	100% (2/2)	100% (7/7)
Outcome for Subjects Without SVR12						
On-treatment VF	0/146	0/90	0/31	0/16	0/2	0/7
Relapse	<1% (1/144)	1% (1/88)	0/31	0/16	0/2	0/7
GT = genotype VF = virologic failure						

14.4 Treatment-Naïve or PRS Treatment-Experienced Adults With HCV Genotype 3 Infection Without Cirrhosis or With Compensated Cirrhosis (b) (4)

(b) (4)

ENDURANCE-3 was a partially-randomized, open-label, active-controlled trial in treatment-naïve subjects. Subjects were randomized (2:1) to either TRADENAME for 12 weeks or the combination of sofosbuvir and daclatasvir for 12 weeks; subsequently the trial included a third non-randomized arm with TRADENAME for 8 weeks. The SVR12 data are summarized in Table 15. (b) (4)

Table 15. ENDURANCE-3: (b) (4)

	TRADENAME¹ 8 weeks (N=157)	TRADENAME 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 TRADENAME 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 TRADENAME 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 TRADENAME 12 weeks and DCV + SOF 12 weeks. (b) (4)			

SURVEYOR-2 Part 3 was a part of an open-label trial randomizing PRS treatment-experienced subjects with genotype 3 infection and without cirrhosis to 12- or 16-weeks of treatment. In addition, the trial evaluated the efficacy of TRADENAME in genotype 3 infected subjects with compensated cirrhosis in two dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (b) (4) durations. Among PRS treatment-experienced subjects treated with TRADENAME for 16 weeks, 49% (34/69) had failed a previous regimen containing sofosbuvir.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Table 16. SURVEYOR-2 Part 3: SVR12 and Other Outcomes in Treatment-Naïve or PRS Treatment-Experienced, HCV Genotype 3-Infected Adults Without Cirrhosis or With Compensated Cirrhosis (b) (4)

	Treatment-Naïve With Compensated Cirrhosis (Child-Pugh A)	PRS Treatment-Experienced Without Cirrhosis or With Compensated Cirrhosis (b) (4)
	TRADENAME 12 weeks (N=40)	TRADENAME 16 weeks (N=69)
SVR12	98% (39/40)	96% (66/69)
Outcome for Subjects Without SVR12		
On-treatment VF	0/40	1% (1/69)
Relapse	0/40	3% (2/68)
Other*	3% (1/40)	0/69
SVR12 by (b) (4) Cirrhosis Status (b) (4)		
Without Cirrhosis	NA	(b) (4) % (21/22)
With Compensated Cirrhosis (b) (4)	98% (39/40)	96% (45/47)
VF=virologic failure		
* Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.		

14.5 Treatment-Naïve and PRS Treatment-Experienced Adults With CKD Stage 4 and 5 and Chronic HCV Infection Without Cirrhosis or With Compensated Cirrhosis (b) (4)

EXPEDITION-4 was an open-label, single-arm, multicenter trial to evaluate safety and efficacy in subjects with severe renal impairment (CKD Stages 4 and 5) (b) (4). There were 104 subjects enrolled, 82% were on hemodialysis, and 53%, 15%, 11%, 19%, 1% and 1% were infected with HCV genotypes 1, 2, 3, 4, 5 and 6; respectively. Overall, 19% of subjects had compensated cirrhosis and 81% of subjects were non-cirrhotic; 58% and 42% of subjects were treatment-naïve and PRS treatment-experienced, respectively. The overall SVR12 was 98% and no subjects experienced virologic failure. The presence of renal impairment did not affect efficacy; no dose-adjustments were required during the trial.

14.6 Adults Who are NS5A Inhibitor or NS3/4A-Protease Inhibitor-Experienced, Without Cirrhosis or With Compensated Cirrhosis (b) (4)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

MAGELLAN-1 was a randomized, multipart, open-label trial in 141 genotype 1- or 4-infected subjects who failed a previous regimen containing NS5A and/or NS3/4A protease inhibitors (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 these analyses). Part 2 (n=91) randomized genotype 1- or 4-infected subjects without cirrhosis or with compensated cirrhosis to 12- or 16-weeks of treatment with TRADENAME.

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 protease inhibitor experienced only; 19% were ≥65 years, 69% were male; 26% were Black; 43% had a body mass index ≥ 30 kg/m²; 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.

Due to higher rates of virologic failure and treatment-emergent drug resistance, the data do not support labeling for treatment of HCV genotype 1 infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced.

Table 17. MAGELLAN-1

	(b) (4)	
	(b) (4)	
	TRADENAME 12 weeks (N=25)	TRADENAME 16 weeks (N=17)
SVR12	92% (23/25)	94% (16/17)
Outcome for Subjects Without SVR		
On-treatment Virologic Failure	0/25	6% (1/17)
Relapse	0/25	0/16
Other ³	8% (2/25)	0/17
PI= protease inhibitor ¹ Includes subjects who are treatment-experienced with an NS3/4A PI (boceprevir, simeprevir, or telaprevir) and who are NS5A inhibitor-naive. ² Includes subjects who are treatment-experienced with an NS5A inhibitor (daclatasvir or ledipasvir in combination with sofosbuvir) and who are NS3/4A PI naive. ³ Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.		

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Not Applicable.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were still under discussion at the time this review was completed. This section includes PMRs and PMCs that will be proposed by the clinical review team.

- A PMR will be issued for pediatric trials to assess safety and efficacy of GLE/PIB in pediatric subjects ages 3 to < 18 years of age with chronic HCV (b) (4) infection, as required under the Pediatric Research Equity Act (PREA)

Clinical Review
Larissa Stabinski, MD
Aimee Hodowanec, MD
NDA 209394
Mavyret® (glecaprevir and pibrentasvir)

- Formal submission of data from M16-126: [REDACTED] (b) (4)
[REDACTED] Hepatitis C Virus (HCV) Genotype 5 or 6 Infection
- Formal submission of data from HCV/HIV coinfecting trial

13 Appendices

13.1. Appendix A: References

1. Gower, E., et al., *Global epidemiology and genotype distribution of the hepatitis C virus infection*. J Hepatol, 2014. **61**(1 Suppl): p. S45-57.
2. Dibonaventura, M.D., et al., *Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey*. PLoS One, 2014. **9**(1): p. e86070.
3. Smith, D.B., et al., *Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource*. Hepatology, 2014. **59**(1): p. 318-27.
4. Fattovich, G., et al., *Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients*. Gastroenterology, 1997. **112**(2): p. 463-72.
5. Planas, R., et al., *Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients*. J Hepatol, 2004. **40**(5): p. 823-30.
6. van der Meer, A.J., et al., *Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis*. JAMA, 2012. **308**(24): p. 2584-93.
7. Backus, L.I., et al., *A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C*. Clin Gastroenterol Hepatol, 2011. **9**(6): p. 509-516 e1.
8. Singal, A.G., et al., *A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus*. Clin Gastroenterol Hepatol, 2010. **8**(3): p. 280-8, 288 e1.
9. Chen, J., et al., *Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies*. Gastroenterology, 2013. **144**(7): p. 1450-1455 e2.
10. *Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment* 2016.
11. Chobanian, A.V., et al., *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report*. JAMA, 2003. **289**(19): p. 2560-72.

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

12. Farady, C.J. and C.S. Craik, *Mechanisms of macromolecular protease inhibitors*. *Chembiochem*, 2010. **11**(17): p. 2341-6.
13. Turner, N.C.A., *Blood Pressure, Proteases and Inhibitors* in *Encyclopedia of Cell Biology*. 2016, Elsevier.
14. El-Serag, H.B., *Hepatocellular carcinoma and hepatitis C in the United States*. *Hepatology*, 2002. **36**(5 Suppl 1): p. S74-83.
15. Bolondi, L., et al., *Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis*. *Gut*, 2001. **48**(2): p. 251-9.
16. Devoogdt, N., et al., *Secretory leukocyte protease inhibitor promotes the tumorigenic and metastatic potential of cancer cells*. *Proc Natl Acad Sci U S A*, 2003. **100**(10): p. 5778-82.
17. Zheng, D., et al., *Secretory leukocyte protease inhibitor is a survival and proliferation factor for castration-resistant prostate cancer*. *Oncogene*, 2016. **35**(36): p. 4807-15.
18. Stepien, T., et al., *Elevated Concentrations of SERPINE2/Protease Nexin-1 and Secretory Leukocyte Protease Inhibitor in the Serum of Patients with Papillary Thyroid Cancer*. *Dis Markers*, 2017. **2017**: p. 4962137.

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

13.2. Appendix B: Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of GLE/PIB.

Covered Clinical Study (Name and/or Number): 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), MAGELLAN-1 (M15-410) and EXPEDITION-4 (M15-462)

Was a list of clinical Investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of Investigators identified: <u>2494</u>		
Number of Investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of Investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>55</u>		
If there are Investigators with disclosable financial interests/arrangements, identify the number of Investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the Investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>55</u> Proprietary interest in the product tested held by Investigator: <u>0</u> Significant equity interest held by Investigator in S		

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of Investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

13.3. Appendix C: Reported Hypertension Adverse Reactions Phase 2/3 Dataset, excluding those with renal impairment (considered causal by Investigator)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M13583-47009-804404	43	F	Black or African American	N	Hypertension (8 - ongoing)	1	N	N	21	9	Nausea (1 - 10) Constipation (1 - 6) Palpitations (4 - 20) Gastroesophageal reflux disease (9 - 30) Constipation (10 - 32) Palpitations (22 - 59) Influenza like illness (31 - 71) Cough (54 - ongoing) Influenza like illness (111 - ongoing)	Low Ferritin (N) Neutropenia (N) Chronic upper right quadrant pain due to gallstones (N) Interstitial cystitis (N) Left kidney angioliopoma (N) Fever (N)	Paracetamol (111 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M13590-38627-343106	55	F	White	N	Hypertension (25 to ongoing)	1	N	N	28	14	Middle insomnia (1 - ongoing) Thirst (1 - ongoing)	Octopic pregnancy surgery that resulted in blood transfusion (Y) Post menopausal (Y) Octopic pregnancy syndrome (N) Headaches (Y) Cough (Y)	Acetylsalicylic acid (prescreening - ongoing) Ibuprofen (prescreening - ongoing) Multivitamin/05516001 (prescreening - ongoing) Glucosamine & chondroitin/07759401 (prescreening - ongoing) Biotin (prescreening - -32) Silybum marianum (prescreening - -32) Acetylsalicylic acid (prescreening - ongoing) Calcium carbonate (prescreening - ongoing) Medinite (-27 - -24) Lisinopril (25 - 79) Losartan (80 - ongoing)
M13590-39545-110104	54	F	White	N	Hypertension (15 - ongoing)	2	N	N	-11	7	Fatigue (7 - ongoing) Disturbance in attention (7 - ongoing)	Post menopausal (N)	Amlodipine (15 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M13590-40784-160102	63	F	White	Y	Hypertension (29 - 92)	2	N	N	5	5	Diarrhea (4 - 9) Fatigue (67 - 92) Palpitations (83 - ongoing)	Common cold (N) Chronic hepatitis B (N) Stomach pain (N) Post menopausal (N) Fracture of the lower left leg (N) Headache (non-migraine) (Y) Drug abuse (N) Tiredness (N)	Ibuprofen (prescreening - ongoing) Acetylcysteine (1 - 14) Zinc (1 - 14) Ramipril (15 - 29) Ramipril (30 - 57) Ramipril (52 - 57) Ramipril (58 - ongoing) Lercanidipine (68 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M13590-40784-160104	62	M	White	Y	Hypertension (56 - ongoing)	1	N	N	34	22	Back pain (17 - ongoing) Myalgia (35 - 35) Rash pustular (43 - 112) Urticaria (43 - 112) Musculoskeletal pain (53 - ongoing) Contusion (54 - 99) Visual impairment (56 - 99) Rotator cuff syndrome (63 - ongoing)	Chronic myelogenous leukemia (N) Cardiac arrhythmia - sinus bradycardia (Y) Stem cell transplantation (N)	Acetylsalicylic acid (prescreening - ongoing) Ramipril (prescreening - ongoing) Dexamethasone (35 - 35) Piroxicam (35 - 35) Ibuprofen (53 - 56) Ramipril (56 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M13590-45599-296105	59	F	White	N	Hypertension (15 - ongoing)	2	N	Y	55	23	Urinary tract infection (1 - 21)	Cholelithiasis (N) Nephrolithiasis (N) Post menopausal (N) Hyperlipidemia - hypercholesterolemia (N) Tendinitis (N) Occasional bilateral side pain (N) Environmental allergies - seasonal allergy (N)	Ciprofloxacin (15 - 21) Captopril (15 - 66) Bisoprolol (67 - ongoing) Losartan (73 - ongoing)
M13594-43110-147308	43	M	White	N	Hypertension (29 -141)	1	N	N	-16	6	Fatigue (22 - 43) Rash (25 - 36)	Liver biopsy (N) Adult polycystic kidney disease (Y)	Aciclovir (25 - 28)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M14172-40724-502501	75	F	White	Y	Hypertension (2 - 142)	2	N	N	59	20	Pruritis (1 - 10) Dyspepsia (1 - 2) Skin candida (23 - 35) Dizziness (31 - 31) Back pain (61 - ongoing) Dyspnoea (100 - 100)	Chronic hepatitis C (Y) Hyperglycemia (intolerance to glucose) (N) Asthma (Y) Allergy to acarid (N)	Salbutamol (prescreening - ongoing) Enalapril (prescreening - 1) Enalapril (prescreening - prescreening) Ebastine (1 - 3) Ebastine (8 - 10) Enalapril (8 - 28) Hydrochlorothiazide (26 - 30) Clotrimazole (28 - 35) Enalapril (30 - 142)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M14868-48171-9401	57	F	White	N	Hypertension (29 - 141)	1	N	N	7	11	Energy increased (3 - ongoing) Abdominal distension (5 - 11) Flatulence (5 - 11) Pruritus generalized (9 - 59) Edema peripheral (57 - ongoing) Back pain (81 - 134) Arthralgia (81 - 134)	Conjunctivitis (N) Migraine headache (Y) Depression (N) Fatigue (Y) Osteoarthritis (fingers) (Y) Cervical facet syndrome (Y) Gastroesophageal reflux disease (Y) Nonalcoholic steatohepatitic (N) Constipation (N) Post menopausal (N) D&C (2) - (N) Pylonephritis (N) Kidney infection (N) Endometriosis (N) Post partum hemorrhage (N) Right renal cyst (N) Penicilin and sulfa allergy (N) Blood transfusion (N) Hepatitis C (Y)	Pantoprazole (8 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M14868-50890-2605	57	M	White	Y	Hypertension (8 - ongoing)	2	N	N	-9	19	Headache (1 - 139) Rash (1 - 15) Fatigue (1 - 139) Diarrhea (2 - 4) Gastroesophageal reflux disease (9 - 32) Memory impairment (9 - 93) Influenza like illness (109 - 139)	Anxiety (Y) Chronic back pain (Y) Insomnia (Y)	Karvea HCT (prescreening - 64) Diazepam (prescreening - ongoing) Tramadol (prescreening - ongoing) Temazepam (prescreening - 34) Tapentadol (-79 - -77) Pregablin (-32 - -1) Paracetamol (1 - 139) Loperamide (3 - 4) Karvea HCT (35 - ongoing) Paracetamol (109 - 139) Paracetamol (prescreening - 34)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M15410-38645-2501	59	M	Black or African American	Y	Hypertension (72 - 86)	2	N	Y	14	17	Headache (2 - 2) Wound (49 - 60)	Neuropathy (Y) Back pain (Y) Leg pain (Y) Erectile dysfunction (Y) Hepatitis C (Y)	Gabapentin (prescreening - ongoing) Sildenafil (prescreening - ongoing) Vicodin (prescreening - ongoing) Panadeine Co (prescreening - ongoing) Tramadol (prescreening - ongoing) Lisinopril (prescreening - 26) Zestoretic (27 - 77) Cefalexin (50 - 60) Lisinopril (78 - ongoing)
M15410-40621-3034	59	M	White	Y	Hypertension (66 - ongoing)	1	N	N	25	15	Lethargy (36 - 103)	Gastroesophageal reflux disease (N) Cirrhosis of the liver (N) Cholecystitis (N) Cholecystectomy (N) Small oesophageal varices (N) Gastritis (N) Intravenous drug use (N) Hepatitis C (N)	Coveram (prescreening - ongoing) Hydrochlorothiazide (66 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M15410-44372-4021	47	F	White	N	Hyper-tensive crisis (39 - 57)	1	N	N	11	14	N/A	Groin herniorrhaphy (N) Inguinal hernia (N) Uterine fibroid embolisation (N) Uterine fibroids (N) Hepatitis C (Y)	Amlodipine (42 - ongoing) Enaphl (43 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M15464-44366-201203	78	M	White	N	Hypertension (15 - ongoing)	2	N	N	13	15	Headache (-12 - 88) Abdominal distension (3 - 4) Asthenia (10 - 65) Gastroesophageal reflux disease (10 - ongoing) Vertigo (24 - 45) Diarrhea (25 - 45) Abdominal distension (25 - 88) Asthenia (65 - 133)	Chronic sinusitis (Y) Obesity (Y) Fracture of left ankle (N) Pollen allergy (Y)	Paracetamol (prescreening - ongoing) Prednisolone (1 - 4) Pristinamycin (1 - 4) Gaviscon (10 - 36) Lercanidipine (15 - ongoing) Candesartan (23 - ongoing) Poly-karaya (29 - 34) Desloratadine (96 - 139)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Pre-existing Hypertension Diagnosis (Y/N)	Hypertension Adverse Event MedDRA 19.0 Preferred Term (Day Onset - Day End)	Grade	Criterion 2 Flag Systolic (Y/N)	Criterion 2 Flag Diastolic (Y/N)	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset - Day End)	Other Past Medical History (currently ongoing, symptomatic or requiring treatment Y/N)	Concomitant Medications
M15464-45746-103201	73	F	White	Y	Hypertension (29 - ongoing)	1	N	N	-2	-8	Diarrhea (8 to 85)	Transfusion (N) Monoclonal gammopathy (N) Rest angina (Y) Hypertensive cardiopathy (Y) Peripheral vascular disease-venous (legs) (N) Biliary cyst (N) Hepatic ganglion (N) Lithiasis intavesicularly (N) Nephrolithiasis (N) Post menopausal (N) Right hand osteoarthritis (N)	Hyzaar (prescreening - -12) Nebivolol (prescreening - ongoing) Hyzaar (-11 - 29) Hyzaar (30 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

13.4. Appendix D: Subjects with Potential Cardiovascular Events or Selected Symptoms and Systolic Blood Pressure Changes of ≥ 20 mmHg, Phase 2/3 safety dataset, excluding subjects with severe renal impairment

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-40724-502501	75	F	White	Hypertension (Y)	Dyspnea (100 - 100)	1	No reasonable possibility	59	20	52	13	Pruritus (1 - 10) Dyspepsia (1 - 2) Hypertension (2 - 142) Skin candida (23 - 35) Dizziness (31 - 31) Back pain (61-ongoing)	Salbutamol (prescreening - ongoing) Enalapril (prescreening - -1) Ebastine (1 - 3) Enalapril (8 - 28) Hydrochlorothiazide (26 - 30) Clotrimazole (28 - 35) Enalapril (30 - 142) Ebastine (8 - 10)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-37741-4305	69	M	White	Hypertension (Y) CABG- Angioplasty (N) Cardioversion (N) Atrial fibrillation (Y) Coronary arteriosclerosis (Y)	Edema peripheral (51 - 83)	1	Reasonable possibility	55	26	32.9	20.4	Nasopharyngitis (1 - 14) Ligament sprain (80 - 98) Sunburn (80 - 87)	Acetylsalicylic acid (-55 - ongoing) Atenolol (-55 - ongoing) Colecalciferol (-55 - ongoing) Glimepiride (-55 - ongoing) Hydrochlorothiazide w/ losartan (-55 - ongoing) Multivitamin (-55 - ongoing) Tamsulosin (-55 - ongoing) Ubidecarenone (-55 - ongoing) Simvastatin (-55 - -16) Warfarin (-55 - 83) Nitrofurantoin (-55 - 92) Sotalol (-55 - 222) Pravastatin (-15 - 104) Paracetamol (-4 - ongoing) Vicodin (-4 - 3) Warfarin (84 - ongoing) Simvastatin (105 - ongoing)
M14172-33226-609505	61	M	White	Peripheral vascular disease-atrial; indicative of old infarct (N)	Atrial flutter (85 - 99)	1	No reasonable possibility	45	28	39	19.4	N/A	Morphine (prescreening - 56) Tradazone (-4 - 87) Fentanyl (51 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-44408-4208	56	F	White	N/A	Chest pain (69 - 71)	1	No reasonable possibility	42	4	19.6	-0.6	Oropharyngeal pain (1 - 2) Fatigue (15 - ongoing) Back pain (23 - 24) Neck pain (29 - ongoing) Flank pain (84 - ongoing) Arthralgia (113 - ongoing)	Plantago ovata (prescreening - ongoing) Paracetamol (prescreening - ongoing) Ibuprofen (prescreening - 1) Omeprazole (prescreening - 8) Amitriptyline (prescreening - 29) Nicotine (prescreening - 1) Esomeprazole (8 - ongoing) Amitriptyline (29 - ongoing)
M14868-46903-1016	65	M	White	Hypertension (Y) Dyslipidemia (Y) Diastolic dysfunction (N)	Oedema periphera (39 - 57)	1	Reasonable possibility	40	15	10.7	4.3	Fatigue (2 - 62) Pruritis (25 - 35) Dry eye (26 - 39) Blood alkaline phosphatase increased (29 - 85) Pruritis (35 - 54) Dry eyes (39 - 55)	Vitamin B complex (prescreening - ongoing) Ergocalciferol (prescreening - ongoing) Ascorbic acid (prescreening - 62) Tri-buffered bufferin (prescreening - ongoing) Escitalopram (prescreening - ongoing) Gabapentin (prescreening - ongoing) Coloxyl with senna (prescreening - ongoing) Magnesium

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
													(prescreening - 62) Pantoprazole (prescreening - 15) Diazepam (prescreening - 62) Salbutamol (prescreening - ongoing) Baclofen (prescreening - ongoing) Terazosin (prescreening - ongoing) Clonidine (prescreening - 62) Losartan (prescreening - 62) Ondansetron (prescreening - 62) Melatonin (prescreening - ongoing) Quetiapine (prescreening - 62) Verapamil (prescreening - 62) Midrid (prescreening - 62) Ketorolac (prescreening - 62) Opti free estuche (26 - 55) Diphenhydramine (39 - 54)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
													Benadryl itch stopping gel maximum strength (44 - 54) Hydrochlorothiazide (6 - 62) Quetiapine (62 - ongoing)
M14868-53724-3002	66	F	White	Hypertension (Y) Atrial fibrillation (Y) Septal infarct (N)	Chest discomfort (22 - 86)	1	No reasonable possibility	40	25	6.7	19.5	Contusion (7 - 14) Dizziness (29 - 30) Squamous cell carcinoma of skin (37 - 91) Fatigue (43 - 45) Fatigue (65 - ongoing) Wound infection (99 - 101)	Valsartan (prescreening - ongoing) Levothyroxine (prescreening - -36) Colecalciferol (prescreening - ongoing) Diltiazem (prescreening - ongoing) Apixaban (prescreening - ongoing) Ubidecarenone (-67 - ongoing) Xylocaine - epinephrine (91 - 91) Mupirocin (99 - 101)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-47008-148307	37	M	Asian	N/A	Headache (1 - ongoing) Dyspnoea (3 - ongoing)	1 1	Reasonable possibility No reasonable possibility	28	19	21.6	13.4	Gingival pain (1 - 26) Fatigue (2 - ongoing) Skin burning sensation (2 - ongoing) Dyspepsia (52 - ongoing) Nasopharyngitis (86 - 113)	Beclometasone (prescreening - ongoing) Hyoscine (prescreening - ongoing) Lansoprazole (prescreening - 52) Ranitidine (52 - ongoing) Night nurse/00447601 (92 - 99)
M13594-49354-111305	35	M	White	N/A	Headache (65 - 83) Chest pain (72 - 76)	1 1	No reasonable possibility No reasonable possibility	27	-1	-3.8	-6.2	N/A	Ibuprofen (65 - 83)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-38645-6204	66	M	White	Hypertension (Y)	Atrial fibrillation (58 - 59) Defect conduction intraventricular (58 - 59)	1 1	No reasonable possibility No reasonable possibility	27	14	-0.3	5	N/A	Multivitamin (prescreening - ongoing) Glibenclamide (prescreening - ongoing) Amlodipine (prescreening - ongoing) Acetylsalicylic acid (prescreening - ongoing) Zestoretic (prescreening - ongoing) Metformin (prescreening - ongoing) Pioglitazone (prescreening - ongoing) Atorvastatin (prescreening - -7) Gemfibrozil (72 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-34085-176304	56	M	White	Hypertension (Y) Coronary heart disease (Y)	Oedema peripheral (85 - ongoing)	1	Reasonable possibility	25	10	18	-2	Dyspepsia (1 - 10) Dizziness (1 - 135) Dyspepsia (15 - ongoing) Sinusitis (106 - 119)	Insulin (prescreening - ongoing) Pregabalin (prescreening - ongoing) Amlodipine (prescreening - ongoing) Hydrochlorothiazide (prescreening - ongoing) Ramipril (prescreening - ongoing) Tamsulosin (prescreening - ongoing) Atorvastatin (prescreening - -15) Pantoprazole (prescreening - -14) Acetylsalicylic acid (prescreening - ongoing) Pravastatin (-14 - ongoing) Pantoprazole (8 - 10) Pantoprazole (15 - 57) Ranitidine (57 - ongoing) Amoxicillin (113 - 119)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-45227-103505	40	M	White	Cerebral hemorrhage (N)	Cerebral haemorrhage (143 - 144)	5	No reasonable possibility	25	26	0.8	6.4	Influenza like illness (7 - 10) Petechiae (8 - 10) Oedema peripheral (8 - 10) Epistaxis (9 - 14) Fatigue (18 - 68)	Tranexamic acid (prescreening - 143) Paracetamol (prescreening - 143) Wilate (prescreening - - 16) Wilate (prescreening - 15) Etoricoxib (prescreening - 143) Levetiracetam (prescreening - 143) Wilate (-10 - 15) Wilate (9 - 9) Arnica Montana (9 - 10) Cefuroxime (9 - 15) Vitapantol (14 - 79) Sterimar CU (14 - 139) Wilate (16 - 78) Betamethosone (28 - 36) Thiamphenicol (28 - 36) Wilate (79 - 143)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-14966-206501	53	M	White	N/A	Chest pain (103 - 103)	1	No reasonable possibility	22	7	12.6	1	Fatigue (2 - ongoing) Dry mouth (2 - ongoing) Contusion (52 - 85) Fall (52 - 85) Laceration	Rabeprazole (prescreening - ongoing) Furosemide (prescreening - 2) Gabapentin (prescreening - 2) Spironolactone (prescreening - 2) Ipratropium w/salbutamol (prescreening - ongoing) Celecoxib (-97 - ongoing) Gabapentin (2 - ongoing) Furosemide (3 - ongoing) Spironolactone (3 - ongoing) Acetylsalicylic acid (113 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14867-91926-3109	54	F	White	N/A	Dyspnoea (72 - ongoing)	1	No reasonable possibility	22	5	-1.8	-3.7	Hyperhidrosis (2 - 6) Chills (2 - 6) Nausea (4 - ongoing) Insomnia (4 - 47) Restlessness (4 - 47) Irritability (4 - 48) Fatigue (16 - ongoing) Night sweats (22 - 48) Pain (34 - ongoing) Cough (47 - 73) Hyperhidrosis (59 - ongoing) Decreased appetite (78 - ongoing)	Cholesterol (prescreening - ongoing) Magnesium (prescreening - -17) Paracetamol (prescreening - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13583-47009-804404	43	F	Black or African American	N/A	Palpitations (4 - 20) Hypertension (9 - ongoing) Palpitations (22 - 59)	1 1 1	Reasonable possibility Reasonable possibility Reasonable possibility	21	9	11.4	1.2	Nausea (1 - 10) Constipation (1 - 6) Gastroesophageal reflux disease (9 - 30) Constipation (10 - 32) Influenza like illness (31 - 71) Cough (54 - ongoing) Influenza like illness (111 - ongoing)	Paracetamol (111 - ongoing)
M14868-46903-1010	60	F	White	Hyperlipidemia (n)	Chest pain (54 - 54)	3	No reasonable possibility	21	16	10.7	7.2	Headache (2 - 84) Clostridium difficile colitis (3 - 84) Disturbance in attention (5 - 169) Fatigue (5 - 123) Urinary tract infection (26	Vitamins, other combinations (prescreening - ongoing) Collagen (prescreening - ongoing) Calcium w/magnesium/vitamin D NOS (prescreening - ongoing) Other combinations of nutrients (prescreening - ongoing) Juice plus (prescreening -

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
												- 42) Onychoclasia (26 - 123) Epistaxis (26 - 123) Oesophageal spasm (54 - 54)	ongoing) Spironolactone (prescreening - ongoing) Furosemide (prescreening - ongoing) Hydrocodone (9 - ongoing) Ibuprofen (9 - ongoing) Epinephrine (9 - 9) Lidocaine (9 - 9) Nitrofurantoin (28 - 42) Phenazopyridine (28 - 42) Acetylsalicylic acid (54 - 54) Antacids, other combinations (54 - 54) Vicodin (54 - 54) Ranitidine (54 - 67)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

13.5. Appendix E: Subjects with Potential Cardiovascular Events or Selected Symptoms and Diastolic Blood Pressure Changes of ≥ 10 mmHg, Phase 2/3 safety dataset excluding subjects with severe renal impairment

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-33226-609505	61	M	White	Peripheral vascular disease-atrial; indicative of old infarct (N)	Atrial flutter (85 - 99)	1	No reasonable possibility	45	28	39	19.4	N/A	Morphine (prescreening - 56) Tradzadone (-4 - 87) Fentanyl (51 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-37741-4305	69	M	White	Hypertension (Y) CABG-Angioplasty (N) Cardioversion (N) Atrial fibrillation (Y) Coronary arteriosclerosis (Y)	Oedema peripheral (51 - 83)	1	Reasonable possibility	55	26	32.9	20.4	Nasopharyngitis (1 - 14) Ligament sprain (80 - 98) Sunburn (80 - 87)	Acetylsalicylic acid (-55 - ongoing) Atenolol (-55 - ongoing) Colecalciferol (-55 - ongoing) Glimepiride (-55 - ongoing) Hydrochlorothiazide w/ losartan (-55 - ongoing) Multivitamin (-55 - ongoing) Tamsulosin (-55 - ongoing) Ubidecarenone (-55 - ongoing) Simvastatin (-55 - -16) Warfarin (-55 - 83) Nitrofurantoin (-55 - 92) Sotalol (-55 - 222) Pravastatin (-15 - 104) Paracetamol (-4 - ongoing) Vicodin (-4 - 3) Warfarin (84 - ongoing) Simvastatin (105 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-45227-103505	40	M	White	Cerebral hemorrhage (N)	Cerebral haemorrhage (143 - 144)	5	No reasonable possibility	25	26	0.8	6.4	Influenza like illness (7 - 10) Petechiae (8 - 10) Oedema peripheral (8 - 10) Epistaxis (9 - 14) Fatigue (18 - 68)	Tranexamic acid (prescreening - 143) Paracetamol (prescreening - 143) Wilate (prescreening - -16) Wilate (prescreening - 15) Etoricoxib (prescreening - 143) Levetiracetam (prescreening - 143) Wilate (-10 - 15) Wilate (9 - 9) Arnica Montana (9 - 10) Cefuroxime (9 - 15) Vitapantol (14 - 79) Sterimar CU (14 - 139) Wilate (16 - 78) Betamethosone (28 - 36) Thiamphenicol (28 - 36) Wilate (79 - 143)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13583-50985-803403	80	F	White	Hypertension (Y)	Chest pain (14 - 14) Chest pain (28 - 28)	1 1	No reasonable possibility No reasonable possibility	3	26	-8	6.2	Pruritis (2 - 4) Flushing (2 - 4) Balance disorder (3 - 3) Fatigue (3 - 141) Pruritis (4 - 99) Inflammation (4 - ongoing) Nausea (6 - 6) Abdominal discomfort (9 - 57) Peripheral coldness (11 - ongoing) Night sweats (13 - 57) Vision blurred (13 - 13) Nightmare (13 - 13) Insomnia (24 - 107) Lethargy (29 - 141) Paraesthesia (56 - 56) Arthritis (56 - 56) Gout (72 - ongoing) Diarrhoea (84 - 84) Otitis externa (96 - 141)	Losartan (prescreening - 1) Bendroflumethiazide (prescreening - ongoing) Paracetamol (prescreening - ongoing) Diclofenac (prescreening - ongoing) Lansoprazole (prescreening - ongoing) Hydrocortisone (prescreening - ongoing) Acetylsalicylic acid (prescreening - ongoing) Losartan (1 - 169) Cetirizine (6 - 99) Flucloxacillin (74 - 82) Paracetamol (99 - ongoing) Otomize (101 - 114)

CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout NME/original BLA reviews)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-53724-3002	66	F	White	Hypertension (Y) Atrial fibrillation (Y) Septal infarct (N)	Chest discomfort (22 - 86)	1	No reasonable possibility	40	25	6.7	19.5	Contusion (7 - 14) Dizziness (29 - 30) Squamous cell carcinoma of skin (37 - 91) Fatigue (43 - 45) Fatigue (65 - ongoing) Wound infection (99 - 101)	Valsartan (prescreening - ongoing) Levothyroxine (prescreening - -36) Colecalciferol (prescreening - ongoing) Diltiazem (prescreening - ongoing) Apixaban (prescreening - ongoing) Ubidecarenone (-67 - ongoing) Xylocaine - epinephrine (91 - 91) Mupirocin (99 - 101)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M15410-50807-2803	51	M	Black	Headache (N) Angina (Y) Hypertension (Y)	Dyspnoea exertional (3 - ongoing) Angina pectoris (14 - 122)	1 1	No reasonable possibility No reasonable possibility	19	25	2.6	4.9	Back pain (25 - 42)	Ascorbic acid (prescreening - ongoing) Thomapyrin N (prescreening - ongoing) Glycerol trinitrate (prescreening - ongoing) Calcium carbonate (prescreening - ongoing) Sertraline (prescreening - ongoing) Acetylsalicylic acid (prescreening - ongoing) Buspirone (prescreening - ongoing) Atenolol (prescreening - ongoing) Mirtazapine (prescreening - ongoing) Cyclobenzaprine (prescreening - ongoing) Omeprazole (prescreening - ongoing) Sucralfate (prescreening - ongoing) Oxycodone (27 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-48171-9407	60	F	White	Ankle swelling, peripheral vascular disease venous (Y) Bicuspid valve regurgitation (N) Varicose veins, legs (N) Benign PACs and PCVs (N)	Palpitations (2 - 4)	1	Reasonable possibility	16	25	0	15.7	Fatigue (2 - 60) Pruritus generalised (87 - 190)	Zopiclone (prescreening - ongoing) Ergocalciferol (prescreening - ongoing) Estradiol (prescreening - ongoing) Paracetamol (-18 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-45400-139302	45	F	White	N/A	Chest discomfort (5 - ongoing)	2	No reasonable possibility	9	24	-3.4	10.2	Salivary hypersecretion (3 - 98) Insomnia (3 - 37) Gastroesophageal reflux disease (7 - 85) Neck Pain (53 - 93) Genital abscess (53 - 93) Oropharyngeal pain (95 - 102)	Levonorgestrel (prescreening - ongoing) Ibuprofen (prescreening - ongoing) Yeast dried (-35 - -35) Ibuprofen (4 - 4) Pantoprazole (8 - ongoing) Acemetacin (84 - 85) Spektramox (84 - 90) Fucicort (84 - 93) Paracetamol (95 - 102) Ibuprofen (95 - 102)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-40724-502501	75	F	White	Hypertension (Y)	Dyspnoea (100 - 100)	1	No reasonable possibility	59	20	52	13	Pruritus (1 - 10) Dyspepsia (1 - 2) Hypertension (2 - 142) Skin candida (23 - 35) Dizziness (31 - 31) Back pain (61-ongoing)	Salbutamol (prescreening - ongoing) Enalapril (prescreening - 1) Ebastine (1 - 3) Enalapril (8 - 28) Hydrochlorothiazide (26 - 30) Clotrimazole (28 - 35) Enalapril (30 - 142) Ebastine (8 - 10)
M13590-50897-196101	53	F	White	N/A	Dyspnoea (17 - ongoing)	1	No reasonable possibility	10	20	-6	11	Memory impairment (17 - ongoing) Oral herpes (55 - 62)	Levothyroxine (prescreening - ongoing) Penciclovir (55 - 56) Aciclovir (57 - 61)
M15410-44318-3622	45	M	Black	Hypertension (Y)	Cardiac hypertrophy (39 - ongoing) Hypertensive heart disease (39 - ongoing)	1 1	No reasonable possibility No reasonable possibility	0	20	-9.7	10.7	Nausea (1 - 1) Vertigo (1 - 1) Muscle spasms (2 - 2) Rash papular (109 - ongoing)	Exenatide (prescreening - ongoing) Insulin detemir (prescreening - ongoing) Novomix (prescreening - ongoing) Perindopril Arg/amlodipine Fisher (prescreening - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-47008-148307	37	M	Asian	N/A	Headache (1 - ongoing) Dyspnoea (3 - ongoing)	1 1	Reasonable possibility No reasonable possibility	28	19	21.6	13.4	Gingival pain (1 - 26) Fatigue (2 - ongoing) Skin burning sensation (2 - ongoing) Dyspepsia (52 - ongoing) Nasopharyngitis (86 - 113)	Beclometasone (prescreening - ongoing) Hyoscine (prescreening - ongoing) Lansoprazole (prescreening - 52) Ranitidine (52 - ongoing) Night nurse/00447601 (92 - 99)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M15464-15314-811201	48	F	White	Hypertension (Y) Hyperlipidemia (Y)	Dyspnoea (85 - 113) Musculoskeletal chest pain (85 - 169)	1 1	No reasonable possibility No reasonable possibility	7	19	2.8	11.4	Flank pain (43 - 64) Fatigue (56 - 169) Pruritus (85 - 113)	Iron (prescreening - ongoing) Glibenclamide (prescreening - ongoing) Metformin (prescreening - ongoing) Atorvastatin (prescreening - -19) Lisinopril (prescreening - ongoing) Liraglutide (prescreening - ongoing) Metoclopramide (prescreening - ongoing) Pantoprazole (prescreening - ongoing) Rosuvastatin (-18 - ongoing) Ibuprofen (43 - 64) Narine/01202601 (99 - 113)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-46903-1010	60	F	White	Hyperlipidemia (n)	Chest pain (54 - 54)	3	No reasonable possibility	21	16	10.7	7.2	Headache (2 - 84) Clostridium difficile colitis (3 - 84) Disturbance in attention (5 - 169) Fatigue (5 - 123) Urinary tract infection (26 - 42) Onychoclasia (26 - 123) Epistaxis (26 - 123) Oesophageal spasm (54 - 54)	Vitamins, other combinations (prescreening - ongoing) Collagen (prescreening - ongoing) Calcium w/magnesium/vitamin D NOS (prescreening - ongoing) Other combinations of nutrients (prescreening - ongoing) Juice plus (prescreening - ongoing) Spironolactone (prescreening - ongoing) Furosemide (prescreening - ongoing) Hydrocodone (9 - ongoing) Ibuprofen (9 - ongoing) Epinephrine (9 - 9) Lidocaine (9 - 9) Nitrofurantoin (28 - 42) Phenazopyridine (28 - 42) Acetylsalicylic acid (54 - 54) Antacids, other combinations (54 - 54) Vicodin (54 - 54) Ranitidine (54 - 67)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-46903-1016	65	M	White	Hypertension (Y) Dyslipidemia (Y) Diastolic dysfunction (N)	Oedema periphera (39 - 57)	1	Reasonable possibility	40	15	10.7	4.3	Fatigue (2 - 62) Pruritis (25 - 35) Dry eye (26 - 39) Blood alkaline phosphatase increased (29 - 85) Pruritis (35 - 54) Dry eyes (39 - 55)	Vitamin B complex (prescreening - ongoing) Ergocalciferol (prescreening - ongoing) Ascorbic acid (prescreening - 62) Tri-buffered bufferin (prescreening - ongoing) Escitalopram (prescreening - ongoing) Gabapentin (prescreening - ongoing) Coloxyl with senna (prescreening - ongoing) Magnesium (prescreening - 62) Pantoprazole (prescreening - 15) Diazepam (prescreening - 62) Salbutamol (prescreening - ongoing) Baclofen (prescreening - ongoing) Terazosin (prescreening - ongoing) Clonidine (prescreening - 62) Losartan (prescreening - 62) Ondansetron (prescreening - 62) Melatonin (prescreening - ongoing) Quetiapine (prescreening - 62) Verapamil (prescreening - 62)

CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout NME/original BLA reviews)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13590-34085-161104	52	M	White	N/A	Oedema peripheral (8 - ongoing)	2	No reasonable possibility	10	15	-7.5	5	Somnolence (1 - 3) Memory impairment (9 - ongoing)	Diamorphine (prescreening - ongoing) Amisulpride (prescreening - ongoing) Torsemide (27 - ongoing)
M14172-40724-502506	71	M	White	Hypertension (N) Left anterior fascicular block (N)	Chest pain (22 - 141)	2	No reasonable possibility	10	15	3	2	Abdominal pain upper (22 - ongoing) Back pain (30 - ongoing) Animal bite (106 - 106)	Mirabegron (-81 - ongoing) Dexetoprofen (57 - 57) Augmentin/00756801 (106 - 110)
M15464-46971-605202	44	M	White	Hypertension (Y)	Oedema (35 - 38)	1	No reasonable possibility	7	15	-1	5.6	Nausea (3 - 3)	Budesonide w/formoterol fumarate (prescreening - ongoing) Indapamide (prescreening - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-38645-6204	66	M	White	Hypertension (Y)	Atrial fibrillation (58 - 59) Defect conduction intraventricular (58 - 59)	1 1	No reasonable possibility No reasonable possibility	27	14	-0.3	5	N/A	Multivitamin (prescreening - ongoing) Glibenclamide (prescreening - ongoing) Amlodipine (prescreening - ongoing) Acetylsalicylic acid (prescreening - ongoing) Zestoretic (prescreening - ongoing) Metformin (prescreening - ongoing) Pioglitazone (prescreening - ongoing) Atorvastatin (prescreening - -7) Gemfibrozil (72 - ongoing)
M15410-38853-2225	63	M	Black	N/A	Chest Discomfort (54 - 55)	1	No reasonable possibility	18	14	7.9	5.5	Fatigue (16 - 69) Flank pain (20 - 23)	Multivitamin (prescreening - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-48582-2113	58	M	White	N/A	Dyspnoea (5 - ongoing)	1	No reasonable possibility	17	13	-1.8	3.5	Dizziness (1 - 2) Head discomfort (6 - 37) Fatigue (9 - 62) Presyncope (71 - 73)	Mirtazapine (prescreening - ongoing) Tamsulosin (prescreening - ongoing) Finasteride (11 - ongoing) Vitamins, other combinations (69 - 71)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14172-40784-304502	76	M	White	Myocardial infarction Coronary two-artery disease (Y) Arterial hypertension AV-junctional escape rhythm (Y) Valvular aortic stenosis (N)	Dyspnea (91 - 91) Chest Pain (99 - ongoing) Dyspnoea (106 - ongoing) Acute myocardial infarction (120 - 122)	1 2 3	No reasonable possibility No reasonable possibility No reasonable possibility No reasonable possibility	10	13	-5.6	1.4	Nasal dryness (2 - 9) Hyperuricaemia (8 - 15) Hyperuricemia (29 - 57) Hyperuricemia (39 - ongoing) Constipation (64 - ongoing) Dyrruria (64 - ongoing) Cough (7 - 92)	Movicol/08437601 (prescreening-ongoing) Levothyroxine (prescreening - ongoing) Smivastatin (prescreening - -15) Ramipril (prescreening - 121) Pantoprazole (prescreening - 162) Torsemide (prescreening - 162) Insulin glargine (prescreening - ongoing) Insulin aspart (prescreening - ongoing) Acetylsalicylic acid (prescreening - ongoing) Bisacodyl (prescreening - ongoing) Pravastin (-14 - 85) Pravastin (86 - 162) Iodine (114 - 121) Heprain (120 - 120) Nitrendipine (120 - 120) Amlodipine (120 - 162) Amphotericin B (122 - 162) Ramipril (122 - 162) Metamizole (163 - ongoing) Linum usitatissimum (163 - 163) Cernevit/06027301 (163 - 164) Enoxaparin (163 - 164) Propofol (163 - 164) Ranididine (163 - 164)

CDER Clinical Review Template 2015 Edition
 Version date: November 5, 2015 for initial rollout NME/original BLA reviews)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13583-21909-200402	43	F	Asian	N/A	Tachycardia (12 - 62)	1	No reasonable possibility	5	12	4.5	7.5	Fatigue (1 - ongoing) Nausea (1 - 62) Myalgia (9 - ongoing) Anxiety (10 - 62) Polydipsia (12 - 62) Feeling hot (12 - 62) Memory impairment (12 - 62) Increased appetite (12 - 62) Viral upper respiratory tract infection (24 - 62)	Centrum /02217401 (prescreening - ongoing) Fish oil (prescreening - ongoing) Ergocalciferol (prescreening - ongoing) Duloxetine (63 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13590-50852-326104	62	F	Asian	Right carotid transient ischemic attack (N)	Transient ischaemic attack (4 - 10)	3	No reasonable possibility	2	12	-2.5	3.8	Dry eye (5 - 10) Dizziness (10 - 14) Cough (10 - 35) Oropharyngeal pain (10 - 35) Cough (69 - 84) Pruritus (76 - 112)	Etoricoxib (-34 - -20) Levocetirizine (1 - 8) Acetylsalicylic acid (5 - ongoing) Other ophthalmologicals (5 - 10) Paracetamol (10 - ongoing) Piracetam (10 - ongoing) Mecobalamin (10 - ongoing) Ambroxol (10 - 76) Medicon A (15 - 76) Fluocinonide (85 - ongoing)
M14868-53359-6909	49	F	Asian	N/A	Palpitations (78 - 83)	1	No reasonable possibility	12	11	-3.4	4.6	Fatigue (2 - ongoing) Nasopharyngitis (2 - 5) Thirst (7 - 10) Feeling hot (7 - 10) Nasopharyngitis (103 - 108) Ligament sprain (120 - 141)	Paracetamol (103 - 105) Paracetamol (120 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-52481-5704	35	F	Asian	N/A	Headache (1 - 22) Dyspnoea (67 - 96)	1 1	Reasonable possibility No reasonable possibility	9	11	-2.8	-1.1	Nausea (2 - 11) Abdominal pain (2 - 11) Constipation (3 - 16) Eczema (8 - ongoing) Iron deficiency (36 - ongoing) Anxiety (81 - 96)	Avena sativa oil (prescreening - 75) Avena sativa cream (prescreening - 75) Betamethasone (18 - ongoing) Dermol (18 - ongoing) Paraffin (18 - ongoing) Paraffin liquid (18 - ongoing) Iron (43 - ongoing)
M14868-48171-9401	57	F	White	N/A	Oedema peripheral (57 - ongoing) Hypertension (29 to 141)	1 1	Reasonable possibility Reasonable possibility	7	11	-4	2.8	Energy increased (3 - ongoing) Abdominal distension (5 - 11) Flatulence (5 - 11) Pruritis generalised (9 - 59) Back pain (81 - 134) Arthralgia (81 - 134)	Pantoprazole (8 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-53762-140308	65	M	White	Polycythemia (N) Varicosis (N)	Headache (5 - 15) Dyspnoea (22 - 26)	1 1	Reasonable possibility No reasonable possibility	-6	11	-15.3	3.8	Nausea (2 - 60) Fatigue (5 - 58) Diarrhoea (13 - 58) Eyelid oedema (25 - 50) Pain (26 - 100) Thrombophlebitis (50 - 88)	Paracetamol (prescreening - ongoing) Seretide (prescreening - ongoing) Tiotropium (prescreening - ongoing) Hypericum perforatum (prescreening - -22) Lorazepam (prescreening - ongoing) Colecalciferol (prescreening - ongoing) Carmellose (prescreening - ongoing) Metoclopramide (8 - ongoing) Heparin (50 - 56) Enoxaparin (59 - ongoing)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-34085-176304	56	M	White	Hypertension (Y) Coronary heart disease (Y)	Oedema peripheral (85 - ongoing)	1	Reasonable possibility	25	10	18	-2	Dyspepsia (1 - 10) Dizziness (1 - 135) Dyspepsia (15 - ongoing) Sinusitis (106 - 119)	Insulin (prescreening - ongoing) Pregabalin (prescreening - ongoing) Amlodipine (prescreening - ongoing) Hydrochlorothiazide (prescreening - ongoing) Ramipril (prescreening - ongoing) Tamsulosin (prescreening - ongoing) Atorvastatin (prescreening - -15) Pantoprazole (prescreening - -14) Acetylsalicylic acid (prescreening - ongoing) Pravastatin (-14 - ongoing) Pantoprazole (8 - 10) Pantoprazole (15 - 57) Ranitidine (57 - ongoing) Amoxicillin (113 - 119)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13583-44318-301404	41	M	White	N/A	Chest pain (17 - ongoing)	1	Reasonable possibility	10	10	0.3	-4.5	Pharyngitis (16 - 25) Cough (17 - ongoing) Asthenia (18 - ongoing) Insomnia (18 - ongoing) Gastroesophageal reflux disease (19 - ongoing) Sinusitis (92 - ongoing) Left ear pain (105 - ongoing)	Amoxicillin (16 - 25) Cetirizine (17 - ongoing) Omeprazole (57 - ongoing) Amoxicillin (92 - ongoing) Beclometasone (92 - ongoing)
M13590-44436-290102	75	F	White	N/A	Atrial fibrillation (16 - ongoing) Headache (54 - 55)	1 1	No reasonable possibility No reasonable possibility	10	10	2.5	0	Hypertension (70 - ongoing)	Acetylsalicylic acid (16 - ongoing) Paracetamol (54 - 55) Bisoprolol (70 - ongoing)
M15410-40621-3025	58	M	White	N/A	Chest Discomfort (39 - 39)	1	No reasonable possibility	10	10	1.9	3.8	Fatigue (1 - 103) Dyspepsia (39 - 103)	Salbutamol (prescreening - ongoing) Paracetamol (7 - 7) Mylanta (79 - 103)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M15464-50807-805209	58	F	White	Headaches (N)	Oedema (85 - ongoing)	1	No reasonable possibility	6	10	-9.4	-0.4	Myalgia (26 - 43) Breast haematoma (26 - 43) Contusion (26 - 43) Diverticulitis (84 - 94)	Omeprazole (prescreening - 41) Asenapine (prescreening - ongoing) Fluoxetine (prescreening - ongoing) Tramadol (prescreening - 5) Glimepiride (prescreening - ongoing) Simvastatin (prescreening - -30) Diphenhydramine (prescreening - -29) Cetirizine (-86 - -29) Metformin (-50 - ongoing) Pravastatin (-30 - 9) Diphenhydramine (4 - -28) Pravastatin (9 - ongoing) Bupropion (15 - ongoing) Ibuprofen (26 - 36) Iopamidol (27 - 27) Vicodin (27 - 34) Amoxicillin w/ clavulanate potassium (84 - 94) Vicodin (84 - 94) Ibuprofen (84 - 94)

Clinical Review
 Larissa Stabinski, MD
 Aimee Hodowanec, MD
 NDA 209394
 Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M14868-47500-2804	33	M	White	N/A	Dyspnoea exertional (3 - 79)	1	No reasonable possibility	4	10	-3	-4.5	N/A	Mirtazapine (-80 - -25) Amoxicillin (-39 - -35) Mirtazapine (-24 - ongoing)
M14868-82703-3703	49	F	White	N/A	Palpitations (36 - 40)	1	No reasonable possibility	2	10	-4.7	4.8	Abdominal discomfort (7 - 36) Diarrhoea (7 - 10) Nausea (7 - 7) Fatigue (14 - 37) Back pain (39 - 55) Nausea (44 - 57) Upper respiratory tract infection (61 - 87) Diarrhoea (44 to 57)	Salbutamol (prescreening - ongoing) Lithium (prescreening - ongoing) Lorazepam (0.5 mg) (prescreening - ongoing) Lorazepam (1.0 mg) (prescreening - ongoing) Olanzapine (prescreening - ongoing) Lamotrigine (prescreening - ongoing) Seretide (prescreening - ongoing) Norethisterone (prescreening - ongoing) Estradiol (prescreening - ongoing) Herbal cough and cold remedies, other (62 - 62) Panadeine Co (75 - 81) Amoxicillin (80 - 87) Bifidobacterium bifidum w/bifidobac (81 - 91)

Clinical Review

Larissa Stabinski, MD

Aimee Hodowanec, MD

NDA 209394

Mavyret® (glecaprevir and pibrentasvir)

Unique Subject ID	Age	Gender	Race	Previous History of Cardiovascular Disease ((ongoing, currently symptomatic or requiring treatment Y/N)	Adverse Event MedDRA 19.0 Preferred Term for Events of Interest (Day Onset- Day End)	Grade	Causality	Maximum Change from Baseline Systolic Blood Pressure mmHg (Day)	Maximum Change from Baseline Diastolic Blood Pressure mmHg (Day)	Mean Change from Baseline Systolic Blood Pressure mmHg	Mean Change from Baseline Diastolic Blood Pressure mmHg	Other Adverse Events MedDRA 19.0 Preferred Term (Day Onset- Day End)	Concomitant Medications (Start date - End date)
M13594-45473-135301	25	M	White	N/A	Chest pain (54 - ongoing)	1	No reasonable possibility	0	10	0	4	Nausea (4 - 120) Abdominal pain upper (4 - ongoing)	Bekform (prescreening - ongoing) Salbutamol (prescreening - ongoing) Omeprazole (95 - 95)

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

/s/

LARISSA L STABINSKI
06/12/2017
reformatted version

AIMEE C HODOWANEC
06/12/2017

WENDY W CARTER
06/12/2017