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RESEARCH**

APPLICATION NUMBER:

208261Orig1s000

MEDICAL REVIEW(S)

Clinical Review Addendum
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

CLINICAL REVIEW ADDENDUM

Application Type	New Drug Application (NDA)
Application Number(s)	208261
Priority or Standard	Priority
Submit Date(s)	May 28, 2015
Received Date(s)	May 28, 2015
PDUFA Goal Date	January 28, 2016
Division/Office	DAVP/OAP
Reviewer Name(s)	Sarita Boyd, PharmD Prabha Viswanathan, MD
Review Completion Date	October 28, 2015
Addendum Completion Date	January 15, 2016
Established Name (Proposed) Trade Name Applicant	elbasvir and grazoprevir Zepatier™ Merck Sharp & Dohme Corp.
Formulation(s) Dosing Regimen Proposed Indication(s)	Grazoprevir/elbasvir 100mg/50mg fixed-dose combination tablet One tablet orally once daily Treatment of chronic hepatitis C genotypes 1, 4, or 6 infection in adults
Intended Population(s)	Treatment-naïve and treatment-experienced adults with GT 1, 4, or 6 infection, including those with HIV coinfection and/or ESRD receiving or not receiving dialysis
Recommendation on Regulatory Action Recommended Indication(s)	Approval Treatment of chronic hepatitis C genotypes 1 or 4 infection in adults

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During the labeling process, the clinical team's recommendations for GT 1a-infected patients with baseline NS5A polymorphisms evolved. We decided against (b) (4)

(b) (4)

(b) (4) Yet, the label would be incomplete because only data for recommended regimens may be displayed, a policy which would necessitate omission of favorable data for GZR/EBR + RBV for 16 weeks in GT1a-infected patients irrespective of the presence of baseline NS5A polymorphisms.

In order to provide clear guidance for management of GT1a-infected subjects with baseline NS5a polymorphisms, and to address the concerns outlined above, we reconsidered the totality of evidence to determine the optimal regimen for this population. Based on the reasons outlined below, we are recommending GZR/EBR + RBV for 16 weeks for treatment-naïve and PR-experienced GT1a-infected patients with baseline NS5A polymorphisms at amino acid positions 28, 30, 31, and 93. First, although available data in this population are limited to six subjects in C-EDGE TE, all achieved SVR12, and we confirmed with the Applicant that all six subjects also achieved SVR24. The overall results of this treatment arm were promising as well with 97% (103/106) of subjects achieving SVR12 and 0% of subjects experiencing virologic failure at FU12. Additionally, evidence from other HCV DAA development programs support the notion that longer treatment duration and addition of ribavirin generally reduce relapse rates; available data also suggest this general approach may overcome the effect of NS5A baseline polymorphisms. Safety data from C-EDGE TE demonstrate that the addition of RBV and an additional four weeks of treatment maintain a favorable benefit/risk profile. Therefore, the totality of evidence suggests that recommending GZR/EBR + RBV for 16 weeks in GT1a-infected patients with relevant baseline NS5A polymorphisms is more conservative than remaining silent and risking inadvertent or purposeful treatment with a suboptimal regimen. Similarly, the benefit of preventing use of a regimen known to be suboptimal (b) (4)

(b) (4) outweighs the risk that a regimen with limited favorable data (GZR/EBR + RBV for 16 weeks) is also insufficient. We are also issuing a PMR to confirm that GZR/EBR + RBV for at least 16 weeks reduces the rate of virologic failure and rate of treatment-emergent drug resistant viral populations in GT1a-infected patients with baseline NS5A polymorphisms, and the Applicant has agreed.

Section 2.1 of the label was edited to include a recommendation to test patients with HCV GT1a infection for the presence of virus with NS5A resistance-associated polymorphisms prior to initiation of treatment to determine dosage regimen and duration. The following dosage regimens and durations are recommended for GZR/EBR in Section 2.2.

Table 1: Recommended Dosage Regimens and Durations for ZEPATIER for Treatment of HCV Genotype 1 or 4 in Patients with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced [‡] <u>without</u> baseline NS5A polymorphisms*	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced [‡] <u>with</u> baseline NS5A polymorphisms*	ZEPATIER + RBV [¶]	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced	ZEPATIER	12 weeks
Genotype 1a [†] or 1b: PegIFN/RBV/PI-experienced [§]	ZEPATIER + RBV [¶]	12 weeks
Genotype 4: Treatment-Naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced [‡]	ZEPATIER + RBV [¶]	16 weeks

[‡]Patients who have failed treatment with peginterferon alfa (PegIFN) + ribavirin (RBV).

*NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93. See section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV genotype 1a infected patients.

[¶]For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the ribavirin tablet prescribing information for the correct ribavirin dosage.

[†]The optimal ZEPATIER-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at positions 28, 30, 31, and 93 has not been established.

[§]Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

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/s/

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Table of Contents

Glossary..... 9

1 Executive Summary 11

 1.1. Product Introduction..... 11

 1.2. Conclusions on the Substantial Evidence of Effectiveness 11

 1.3. Benefit-Risk Assessment 12

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 23

 3.3. Foreign Regulatory Actions and Marketing History..... 24

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety..... 25

 4.1. Office of Scientific Investigations (OSI) 25

 4.1. Product Quality 25

 4.2. Clinical Microbiology 26

 4.3. Nonclinical Pharmacology/Toxicology 27

 4.4. Clinical Pharmacology 29

 4.4.1. Mechanism of Action 29

 4.4.2. Pharmacodynamics..... 29

 4.4.3. Pharmacokinetics..... 30

 4.5. Devices and Companion Diagnostic Issues 33

 4.6. Consumer Study Reviews..... 33

5 Sources of Clinical Data and Review Strategy 33

 5.1. Table of Clinical Studies..... 33

 5.2. Review Strategy..... 36

6	Review of Relevant Individual Trials Used to Support Efficacy	37
6.1.	C-EDGE TN (P060).....	37
6.1.1.	Study Design.....	37
6.1.2.	Study Results.....	39
6.2.	C-EDGE COINFECTION (P061).....	43
6.2.1.	Study Design.....	43
6.2.2.	Study Results.....	44
6.3.	C-EDGE TE (P068)	47
6.3.1.	Study Design.....	47
6.3.2.	Study Results.....	48
6.4.	C-SALVAGE (P048)	53
6.4.1.	Study Design.....	53
6.4.2.	Study Results.....	54
6.5.	C-SCAPE (P047 Part B)	56
6.5.1.	Study Design.....	56
6.5.2.	Study Results.....	57
6.6.	C-SURFER (P052)	58
6.6.1.	Study Design.....	58
6.6.2.	Study Results.....	60
7	Integrated Review of Effectiveness	65
7.1.	Assessment of Efficacy Across Trials	65
7.1.1.	Primary Endpoints.....	65
7.1.2.	Subpopulations	66
7.1.1.	Onset, Duration, and Durability of Efficacy Effects	72
7.1.2.	Dose and Dose-Response.....	73
7.2.	Additional Efficacy Considerations.....	73
7.2.1.	Considerations on Benefit in the Postmarket Setting	73
7.2.2.	Other Relevant Benefits.....	73
7.3.	Integrated Assessment of Effectiveness	74

8	Review of Safety	75
8.1.	Safety Review Approach	75
8.2.	Review of the Safety Database	76
8.2.1.	Overall Exposure	76
8.2.2.	Relevant characteristics of the safety population:.....	77
8.2.3.	Adequacy of the safety database:	77
8.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	77
8.3.1.	Issues Regarding Data Integrity and Submission Quality	77
8.3.2.	Categorization of Adverse Events.....	78
8.3.3.	Routine Clinical Tests	78
8.4.	Safety Results	79
8.4.1.	Deaths	80
8.4.2.	Serious Adverse Events.....	83
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects	86
8.4.4.	Significant Adverse Events	90
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions.....	91
8.4.6.	Laboratory Findings	94
8.4.7.	Vital Signs	98
8.4.8.	Electrocardiograms (ECGs).....	98
8.4.9.	QT	98
8.4.10.	Immunogenicity.....	99
8.5.	Analysis of Submission-Specific Safety Issues	99
8.5.1.	Hepatobiliary Events.....	99
8.5.2.	Cardiopulmonary Events.....	113
8.5.3.	Psychiatric Events	114
8.5.4.	Musculoskeletal Events	115
8.5.5.	Skin and Soft Tissue Events.....	116
8.5.6.	Renal Events.....	117
8.5.7.	Gastrointestinal Events.....	117
8.5.8.	Neurological Events	117

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

8.6.	Specific Safety Studies/Clinical Trials	117
8.7.	Additional Safety Explorations	129
8.7.1.	Human Carcinogenicity or Tumor Development	129
8.7.2.	Human Reproduction and Pregnancy	130
8.7.3.	Pediatrics and Assessment of Effects on Growth	130
8.7.4.	Overdose, Drug Abuse Potential, Withdrawal, and Rebound	131
8.8.	Safety in the Postmarket Setting.....	131
8.8.1.	Safety Concerns Identified Through Postmarket Experience	131
8.8.2.	Expectations on Safety in the Postmarket Setting	132
8.9.	Additional Safety Issues From Other Disciplines.....	132
8.10.	Integrated Assessment of Safety.....	132
9	Advisory Committee Meeting and Other External Consultations.....	133
10	Labeling Recommendations	133
10.1.	Prescribing Information	133
10.2.	Patient Labeling	135
10.3.	Non-Prescription Labeling	135
11	Risk Evaluation and Mitigation Strategies (REMS)	135
12	Postmarketing Requirements and Commitments.....	135
13	Appendices	136
13.1.	References	136
13.2.	Financial Disclosure	137
13.3.	Pre-Specified Hepatic Safety Events in the Hepatic Safety Population.....	141

Table of Tables

Table 1. Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection	21
Table 2. GZR and EBR Drug Interaction Potential.....	32
Table 3. Summary of Relevant Clinical Trials.....	34
Table 4. Nomenclature for Description of HCV RNA Levels.....	38
Table 5. C-EDGE TN Subject Demographics and Characteristics	40
Table 6. C-EDGE TN Primary Efficacy Results.....	41
Table 7. C-EDGE TN SVR12 Subgroup Analysis	42
Table 8. C-EDGE TN SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms	43
Table 9. C-EDGE COINFECTION SVR12 Subgroup Analysis	45
Table 10. C-EDGE COINFECTION SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms.....	46
Table 11. C-EDGE TE Patient Disposition	48
Table 12. C-EDGE TE Subject Demographics and Characteristics.....	49
Table 13. C-EDGE TE Primary Efficacy Results	50
Table 14. C-EDGE TE SVR12 Subgroup Analysis.....	51
Table 15. C-EDGE TE SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms	53
Table 16. C-SALVAGE Subject Demographics and Characteristics.....	54
Table 17. C-SURFER Subject Disposition.....	60
Table 18. C-SURFER Demographic and Baseline Disease Characteristics (FAS)	61
Table 19. Proportion of subjects achieving SVR12 in C-SURFER	62
Table 20. C-SURFER SVR12 Subgroup Analysis	64
Table 21. C-EDGE TN, C-EDGE COINFECTION, and C-SCAPE Primary SVR12 Results.....	66
Table 22. SVR12 by Baseline NS5A Polymorphisms in TN and PR-Experienced GT 1 Infected Subjects: Pooled Analysis.....	67
Table 23. C-EDGE TE SVR12 in GT 4 Infected Subjects	70
Table 24. Safety Database: Population and Size.....	77
Table 25. Safety Overview: C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE	79
Table 26. All Reported SAEs in C-EDGE TE	84
Table 27. C-EDGE TE: Treatment-Emergent Adverse Events in Pooled Arms +/- RBV, Regardless of Relatedness and Severity (> 5% difference between arms).....	92
Table 28. Pooled Analysis of Study Treatment-Related AEs by SOC Occurring in at least 5% of Subjects in Any Arm (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)	93
Table 29. Pooled Analysis of Treatment-Related AEs by PT Occurring in at least 5% of Subjects in Any Arm (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE).....	94

Table 30. Pooled Analysis of Treatment-Emergent Chemistry Laboratory Abnormalities (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)	96
Table 31. Pooled Analysis of Treatment-Emergent Hematology Laboratory Abnormalities (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)	97
Table 32. Pooled Hepatic Safety Population: Baseline Characteristics	100
Table 33. Hepatic Laboratory Abnormalities in the Hepatic Safety Population: Worst Post-Baseline Toxicity Grade and Worse than Baseline	101
Table 34. Liver Abnormalities and Events in the Hepatic Safety Population: GZR/EBR vs. Placebo	104
Table 35. Mean Liver Enzyme Results in Subjects with a Pre-specified Late ALT/AST Elevation Event	104
Table 36. Baseline Characteristics in Subjects who Experienced a Hepatic Event	107
Table 37. Cardiac Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE	114
Table 38. Psychiatric Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE.....	115
Table 39. Musculoskeletal Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE.....	116
Table 40. Skin and Subcutaneous Tissue Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE.....	116
Table 41. C-SURFER Safety Summary.....	118
Table 42. SAEs Occurring in at least 1 ITG Subject, Trial C-SURFER.....	121
Table 43. AEs in ≥5% of ITG subjects, all severity and irrespective of causality, C-SURFER.....	123
Table 44. Moderate and severe AEs in ≥2 ITG subjects irrespective of causality, C-SURFER.....	124
Table 45. Related AEs in ≥ 2 ITG subjects, all severity, C-SURFER	125
Table 46. Abnormalities in key chemistry parameters by highest toxicity grade, C-SURFER.....	126
Table 47. Abnormalities in hematology parameters by highest toxicity grade, C-SURFER.....	128
Table 48. Pre-specified Late ALT Elevation, Hepatic ECI, and Hepatic-Related Treatment Discontinuation.....	141

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Table of Figures

Figure 1. C-EDGE TN Trial Design 38
Figure 2. C-EDGE COINFECTION Trial Design 44
Figure 3. C-EDGE TE Trial Design..... 47
Figure 4. C-SALVAGE Trial Design..... 54
Figure 5. C-SURFER Trial Design..... 59
Figure 6. Mean ALT from Baseline through Follow-Up Week 24 in the Hepatic Safety Population
..... 102
Figure 7. Exposure-Safety Evaluation for GZR 109

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Glossary

AE	adverse event
AUC	area under the concentration-time curve
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
CRT	clinical review template
CSR	clinical study report
CYP	cytochrome P450
DAA	direct acting antiviral
DAIDS	Division of AIDS
DMC	data monitoring committee
DDI	drug-drug interaction
DILI	drug-induced liver injury
DTG	deferred treatment group
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EBR	elbasvir
ECI	event of clinical interest
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FU	follow up
GT	genotype
GZR	grazoprevir
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
mFAS	modified full analysis set

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PR	pegylated interferon alfa and ribavirin
PREA	Pediatric Research Equity Act
RBV	ribavirin
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SVR	sustained virologic response
TE	treatment experienced
TEAE	treatment emergent adverse event
TN	treatment naïve
TW	treatment week

1 Executive Summary

1.1. Product Introduction

Grazoprevir (GZR) and elbasvir (EBR) is a fixed-dosed combination (FDC) tablet that contains two new molecular entities (NMEs). GZR is a hepatitis C virus (HCV) NS3/4A protease inhibitor (PI) and EBR 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, 4, or 6 infection in adults. The recommended dosage is one tablet (GZR 100 mg/EBR 50 mg) once daily orally with or without food. The treatment duration and addition of ribavirin (RBV) is dependent upon prior treatment experience, GT, and presence of severe renal impairment or end stage renal disease (ESRD). The proposed dosage regimens and durations for HCV mono-infected and HCV/HIV-1 coinfecting patients with or without cirrhosis are as follows:

- GT 1, 4, (b) (4) Treatment-Naïve (TN) or Treatment-Experienced (TE) Relapsers: GZR/EBR for 12 weeks (b) (4)
- GT 1, 4, (b) (4) Treatment-Experienced On-Treatment Virologic Failures:
 - GT 1b (b) (4) GZR/EBR for 12 weeks
 - GT 1a, 4, (b) (4) GZR/EBR with RBV for 16 weeks
- GT 1, 4, (b) (4) patients with severe renal impairment (b) (4) (b) (4), including patients on dialysis: administer GZR/EBR without RBV according to the treatment duration above. For TE GT 1a, 4, (b) (4) patients with prior on-treatment virologic failure, 12 weeks treatment duration may be considered.

NOTE:

- Treatment-experienced: patients who have failed treatment with peginterferon alfa + RBV (PR) or PR + boceprevir, simeprevir, or telaprevir.
- On-treatment virologic failures: patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.
- In clinical trials, RBV was weight-based (<66 kg = 800 mg/day, 66 to 80 kg = 1000 mg/day, 81 to 105 kg = 1200 mg/day, >105 kg = 1400 mg/day) administered in two divided doses with food.

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 GZR/EBR for treatment of chronic HCV GT 1 or 4 infection in adults. Phase 2 and Phase 3 trials C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE, and C-SURFER evaluated GZR/EBR with and without RBV in various subpopulations, including GT 1, 4, and 6 infected subjects, cirrhotics and non-cirrhotics, HIV coinfecting subjects, and TN

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

and TE subjects. The overall sustained virologic response (SVR12) rates, considered a virologic cure, across trials were 92-97%. The number of GT 1 and 4 infected subjects studied and the effectiveness of GZR/EBR across subpopulations was adequate. (b) (4)



Benefit-Risk Assessment

Clinical Review
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Benefit-Risk Summary and Assessment

Grazoprevir (GZR) is a hepatitis C virus (HCV) NS3/4A protease inhibitor and elbasvir (EBR) is an HCV NS5A inhibitor. GZR/EBR is a fixed-dose combination tablet with a proposed indication for treatment of chronic HCV genotypes (GTs) 1, 4, or 6 infection in adults. Intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients and patients with advanced chronic kidney disease (CKD), including those receiving hemodialysis.

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 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. During this NDA review cycle, the first interferon (IFN) sparing regimen was approved for treatment of GT 4 infection in patients without cirrhosis. However, additional IFN-free treatment options would be beneficial for GT 1 and GT 4 infected patients, particularly for those with cirrhosis, and preferably options that do not require ribavirin (RBV). IFN-free treatment options for GT 6 infection are also necessary. Last, for GT 1, 4, and 6 infection, a major treatment gap remains for CKD patients receiving dialysis as no IFN-sparing regimens are currently available for this patient population.

GZR/EBR demonstrated SVR12 ranging from 92-100% 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. GZR/EBR represents the first IFN-free regimen for treatment of HCV in CKD patients receiving hemodialysis. GZR/EBR is also another highly effective RBV-free single tablet once daily treatment option for TN and PR-experienced GT 1 infection and for TN GT 4 infection. GZR/EBR with RBV is a highly effective option for PI/PR-experienced GT 1 infection and PR-experienced GT 4 infection. (b) (4)

Though SVR12 rates in pivotal trials were high, they included results from GT 1 infected subjects with baseline NS5A polymorphisms. Post-hoc analyses revealed that removal of GT 1a TN and TE subjects who had baseline NS5A polymorphisms decreased the rate of virologic failure by 4-6%. Because these failures resulted in development of additional resistance substitutions and limitation of future treatment options, avoiding

GZR/EBR treatment in these patients is recommended and may further increase overall SVR12 rates. Therefore, baseline NS5A resistance testing is strongly recommended for all TN and TE GT 1a infected patients. Though increased treatment duration from 12 weeks to 16 weeks and the addition of RBV together appears to overcome the effect of baseline NS5A polymorphisms, limited data preclude recommending this option for patients with baseline resistance. Treatment of all GT 1a patients with GZR/EBR with RBV for 16 weeks without screening for baseline NS5A polymorphisms is also not recommended because approximately 90% of these patients would be over-treated and the safety profile is suboptimal compared to 12 weeks of GZR/EBR without RBV. The impact of baseline NS5A polymorphisms in GT 1b infected subjects was lower, yet data suggest that pre-treatment NS5A genotypic screening may be considered for TE GT 1b infected patients to maximize the chance for SVR12 and minimize the risk of developing additional resistance substitutions.

Late ALT elevation was the major safety issue identified in this review. Incidence was relatively low overall (0.8%) but higher (2-3%) in populations shown to have increased exposures, such as females, Asians, and the elderly (> 65 years of age). None were associated with clinical AEs, and all events completely resolved. Late ALT elevation events can be reasonably monitored and managed by hepatic laboratory testing prior to therapy, every four weeks on therapy, and as clinically indicated. No other major safety issues related specifically to GZR/EBR were identified in this review. RBV is associated with common adverse reactions and serious risks, but these safety issues are well known and are not exacerbated by the addition of GZR/EBR based on available data.

Approval of GZR/EBR for treatment of adult patients with HCV GT 1 or 4 infection is fully supported by the available evidence of efficacy and safety. The following regimens, some of which differ from the Applicant's proposal, are recommended based on thorough analysis of efficacy, safety, and virology data overall and in each subpopulation:

- (1) TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration)
- (2) TN and PR-experienced GT 1b infected patients (12 weeks duration)
- (3) PI/PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration with RBV)
- (4) PI/PR-experienced GT 1b infected patients (12 weeks duration with RBV)
- (5) TN GT 4 infected patients (12 weeks duration)
- (6) PR-experienced GT 4 infected patients (16 weeks duration with RBV)
- (7) Advanced CKD patients including those on hemodialysis (same regimens as above, except RBV is not recommended as stated in #3, 4 and 5)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> 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. 	<p>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.</p>
Current Treatment Options	<ul style="list-style-type: none"> The current standard of care treatments for HCV GT 1 infection consist of interferon (IFN) sparing all oral direct-acting antivirals (DAAs), including ledipasvir/sofosbuvir, paritaprevir/ombitasvir/ritonavir + dasabuvir (+/- ribavirin [RBV]), and simeprevir (in combination with sofosbuvir). DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in up to 93-99% of GT 1 infected patients depending on the regimen. During this NDA review cycle, an IFN-free regimen of ombitasvir/paritaprevir/ritonavir with RBV received approval for treatment of HCV GT 4 infection in patients without cirrhosis based on an SVR12 rate of 100%. 	<p>The treatment armamentarium would benefit greatly from new therapeutic options that are well tolerated and equally or more efficacious than current DAA IFN-free options. Avoidance of significant burdens associated with IFN would also be beneficial for subpopulations that do not currently have IFN-free treatment options.</p> <p>There is a specific unmet medical need for</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons																	
	<p>Sofosbuvir with pegylated IFN and RBV (PR) is available for GT 4 infected patients with cirrhosis.</p> <ul style="list-style-type: none"> • Virologic cure rates for GT 4 infected subjects with the above treatment regimens can be up to 96-100%. However, a RBV-free regimen is preferred, and PR-based regimens are highly inconvenient and poorly tolerated. • As of the time of this review, no DAAs or IFN-free regimens are approved for HCV GT 6 infection. • No IFN-free treatment options are available for HCV infected patients receiving hemodialysis. 	<p>IFN-free regimens for patients with CKD undergoing hemodialysis.</p> <p>Additional treatment options would be beneficial for GT 4 infected patients, particularly for those with cirrhosis, and preferably regimens without the need for RBV. IFN-free treatments for GT 6 infection are also needed.</p>																	
<p>Benefit</p>	<ul style="list-style-type: none"> • The efficacy of GZR/EBR was established in five clinical trials (three Phase 3, one Phase 2/3, and one Phase 2), with a total of 1155 HCV patients across all trials. The trials varied in terms of the treatment regimen, treatment duration, HCV GT, and prior treatment experience. • The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 results overall ranged from 92-100% depending on the regimen, HCV GT, and prior treatment history, as well as overall versus subgroup analysis. <table border="1" data-bbox="325 1166 1346 1325"> <thead> <tr> <th data-bbox="325 1166 556 1284" rowspan="2">Treatment-Naive</th> <th colspan="3" data-bbox="556 1166 1045 1203">C-EDGE TN, C-EDGE COINFECTION</th> <th colspan="2" data-bbox="1045 1166 1346 1203">C-SURFER</th> </tr> <tr> <th data-bbox="556 1203 730 1284">GT 1a</th> <th data-bbox="730 1203 892 1284">GT 1b</th> <th data-bbox="892 1203 1045 1284">GT 4</th> <th data-bbox="1045 1203 1186 1284">GT1a CKD/HD</th> <th data-bbox="1186 1203 1346 1284">GT1b CKD/HD</th> </tr> </thead> <tbody> <tr> <td data-bbox="325 1284 556 1325">GZR/EBR, 12w</td> <td data-bbox="556 1284 730 1325">92-94%</td> <td data-bbox="730 1284 892 1325">96-99%</td> <td data-bbox="892 1284 1045 1325">96-100%</td> <td data-bbox="1045 1284 1186 1325">97%</td> <td data-bbox="1186 1284 1346 1325">92%</td> </tr> </tbody> </table>	Treatment-Naive	C-EDGE TN, C-EDGE COINFECTION			C-SURFER		GT 1a	GT 1b	GT 4	GT1a CKD/HD	GT1b CKD/HD	GZR/EBR, 12w	92-94%	96-99%	96-100%	97%	92%	<p>Five clinical trials provide substantial evidence of effectiveness of GZR/EBR in the following populations:</p> <ol style="list-style-type: none"> (1) TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration) (2) TN and PR-experienced GT 1b infected patients (12 weeks duration) (3) PI/PR-experienced GT 1 infected patients (12 weeks duration with RBV) (4) TN GT 4 infected patients (12 weeks duration) (5) PR-experienced GT 4 infected patients (16 weeks duration with RBV) (6) Advanced CKD patients including those on hemodialysis (same regimens as above,
Treatment-Naive	C-EDGE TN, C-EDGE COINFECTION			C-SURFER															
	GT 1a	GT 1b	GT 4	GT1a CKD/HD	GT1b CKD/HD														
GZR/EBR, 12w	92-94%	96-99%	96-100%	97%	92%														

Dimension	Evidence and Uncertainties	Conclusions and Reasons																																						
	<table border="1" data-bbox="325 414 1207 657"> <thead> <tr> <th rowspan="2"></th> <th colspan="3">C-EDGE TE</th> </tr> <tr> <th>GT 1a</th> <th>GT 1b</th> <th>GT 4</th> </tr> </thead> <tbody> <tr> <td>PR-Experienced</td> <td></td> <td></td> <td></td> </tr> <tr> <td>GZR/EBR, 12w</td> <td>90%</td> <td>100%</td> <td>78%</td> </tr> <tr> <td>GZR/EBR + RBV, 12w</td> <td>93%</td> <td>97%</td> <td>93%</td> </tr> <tr> <td>GZR/EBR, 16w</td> <td>94%</td> <td>96%</td> <td>60%</td> </tr> <tr> <td>GZR/EBR + RBV, 16w</td> <td>95%</td> <td>100%</td> <td>100%</td> </tr> </tbody> </table> <table border="1" data-bbox="325 690 1050 820"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">C-SALVAGE</th> </tr> <tr> <th>GT 1a</th> <th>GT 1b</th> </tr> </thead> <tbody> <tr> <td>PI/PR Experienced*</td> <td></td> <td></td> </tr> <tr> <td>GZR/EBR + RBV, 12w</td> <td>96%</td> <td>98%</td> </tr> </tbody> </table> <p>*PI = boceprevir, simeprevir, or telaprevir</p> <ul style="list-style-type: none"> • SVR12 rates were comparable in subjects with or without cirrhosis, with or without HIV coinfection, and with CKD with or without hemodialysis. • TN and TE clinical trials included GT 6 but contained few (n=15 and n=6, respectively) subjects. • Post-hoc analyses of pooled Phase 2 and Phase 3 trials showed that exclusion of GT 1a infected subjects with baseline NS5A polymorphisms decreased the virologic failure rate from 5% to 1% (TN subjects) and from 8% to 2% (TE subjects). • Overall, 96-97% of GT1a infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistance mutations, and 58% developed resistance to both NS5A inhibitors and NS3/4A PIs, substantially limiting future treatment options. • Though there were fewer GT 1b failures, all six GT 1b infected subjects with 		C-EDGE TE			GT 1a	GT 1b	GT 4	PR-Experienced				GZR/EBR, 12w	90%	100%	78%	GZR/EBR + RBV, 12w	93%	97%	93%	GZR/EBR, 16w	94%	96%	60%	GZR/EBR + RBV, 16w	95%	100%	100%		C-SALVAGE		GT 1a	GT 1b	PI/PR Experienced*			GZR/EBR + RBV, 12w	96%	98%	<p>except RBV is not recommended as stated in #3 and 5)</p> <p>There are no data to evaluate efficacy in PI/PR-experienced GT 4 infected patients.</p> <p style="text-align: right;">(b) (4)</p> <p>Baseline NS5A resistance testing is strongly recommended for all TN and TE GT 1a infected patients to increase the chance for virologic cure and decrease the risk of resistance. In PR-experienced GT 1a infected subjects, screening for baseline NS5A polymorphisms allows for administration of a better tolerated and more convenient regimen, GZR/EBR (without RBV) for 12 weeks.</p> <p>Baseline NS5A resistance testing is not necessary for TN GT 1b infected patients due to high SVR rates and minimal impact of baseline NS5A polymorphisms. Baseline testing may be considered for TE GT 1b infected patients to maximize potential</p>
	C-EDGE TE																																							
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	<p>baseline NS5A polymorphisms who failed treatment developed additional resistance, limiting future treatment options.</p>	<p>efficacy. However, high SVR12 in GT1b subjects support the use of this regimen with or without baseline resistance testing.</p> <p>GZR/EBR fills an important unmet medical need for CKD patients receiving hemodialysis. GZR/EBR is also another highly effective RBV-free single tablet once daily treatment option for TN and PR-experienced GT 1 and TN GT 4 infected subjects, especially with cirrhosis. GZR/EBR with RBV is a highly effective option for PI/PR-experienced GT 1 infection and PR-experienced GT 4 infection.</p>
<p>Risk</p>	<ul style="list-style-type: none"> The safety database for GZR/EBR includes the five aforementioned clinical trials and is considered adequate. C-EDGE TN and C-SURFER included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo. The hepatic safety pool included additional subjects who received GZR 100 mg and EBR 50 mg for at least 12 weeks in other clinical trials. Pre-specified late ALT elevation was the major safety issue identified in this review. This event was previously identified and associated with higher doses. In the hepatic safety pool, 12/1558 (0.8%) subjects experienced this event, which consisted of a swift ALT elevation >5x ULN generally at or after treatment week 8 and usually without symptoms. All subjects had complete resolution, and all 11 GT 1 or 4 infected subjects achieved SVR12. Higher 	<p>Hepatic safety issues with GZR/EBR at the proposed marketed dosages were well characterized during this review. One main event, late ALT elevation, was identified and occurred infrequently. Late ALT elevation was a laboratory event rather than a clinical event.</p> <p>The safety issues with RBV are well known and are not exacerbated by GZR/EBR.</p> <p>GZR/EBR with or without RBV demonstrated an overall favorable safety profile.</p>

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>rates of ALT elevations occurred in the following subpopulations: female sex (2%), Asian race (3%), and age > 65 years (2%). None were associated with clinical AEs.</p> <ul style="list-style-type: none"> • Fatigue, headache, nausea, and asthenia were the most common adverse events (AEs) reported across trials and occurred at a similar rate with placebo. • Subjects treated with GZR/EBR and RBV had notably higher rates of most AEs compared to GZR/EBR without RBV. All were common and well-known RBV-related adverse reactions. Additionally, RBV-treated subjects had a higher rate of discontinuation due to psychiatric AEs. • Drug-drug interactions (DDI) may increase or decrease systemic exposures of GZR and/or EBR, which may increase the risk of adverse reactions or decrease efficacy, respectively. 	
<p>Risk Management</p>	<ul style="list-style-type: none"> • Late ALT elevation is included as a Warning and Precaution in the GZR/EBR product label. Currently approved HCV NS3/4 protease inhibitors (PIs) are associated with similar hepatic events, which are also labeled as a Warning and Precaution. • The Applicant conducted numerous DDI studies to characterize the bidirectional impact of concomitant drugs and GZR/EBR on one another. 	<p>Late ALT elevation is well positioned and characterized in the label. Risk factors and specific guidance for conducting hepatic laboratory testing was added. Instructions for discontinuation of GZR/EBR are adequate and consistent with other NS3/4 PIs. Labeling adequately addresses DDIs by designation of drugs as contraindicated or not recommended, when necessary.</p>

2 Therapeutic Context

2.1. Analysis of Condition

Globally it is estimated that over 100 million people are infected with chronic HCV, including approximately 3 million people in the United States (U.S.). At least six different HCV GTs have been identified, numbered 1 to 6, with further breakdown into subtypes for several of the known GTs (e.g., GT 1 subtypes 1a and 1b). In the U.S., GT 1 is the most common (72%; 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 U.S. but may predominate in other parts of the world.¹

The natural history of chronic HCV typically involves an asymptomatic period in early stages with progression to cirrhosis, hepatocellular carcinoma, liver failure, or death, if left untreated. HCV is a leading cause of chronic liver disease and is currently the most common reason for liver transplantation in the U.S. 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 cessation of treatment (i.e., 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 hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality.²⁻⁴

HCV infection is an independent predictor of mortality among patients with Stage 4 or 5 CKD, and the interplay of CKD and chronic HCV confers a high burden of morbidity for this medically fragile population. Left untreated, HCV infection can lead to progressive hepatic dysfunction while also accelerating the deterioration of renal function. Furthermore, chronic HCV infection can limit eligibility for kidney transplant and compromise graft survival in those who do undergo renal transplant.

The prevalence rate of HCV among patients undergoing hemodialysis within a U.S. hemodialysis network has been reported as 7.8% (range: 5.5 – 9.8%), and it is estimated that over 60,000 HCV-infected patients will require hemodialysis by 2020.⁵⁻⁶ Compared to non-HCV-infected CKD Stage 4 or 5 patients (eGFR < 30 mL/min/1.7 m²), HCV-infected CKD Stage 4 or 5 patients have poor graft survival and higher overall mortality outcomes following renal transplantation.⁷⁻⁸ Treatment of HCV infection prior to transplantation, compared to untreated HCV controls, has been shown to decrease the risk of *de novo* glomerulonephritis, post-transplant diabetes mellitus, and chronic allograft nephropathy.⁹

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

2.2. Analysis of Current Treatment Options

Genotype 1

Approved, standard of care treatments for chronic HCV GT 1 infection consist of IFN-sparing all oral DAAs, which are displayed in Table 1. The table is current as of the time this review was completed. IFN-free treatment options for GT 1 infection all result in very high SVR12 rates and most have favorable safety profiles. Still, the treatment armamentarium would benefit greatly from new therapeutic options that are well tolerated and equally or more efficacious than current IFN-free DAA options.

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
Ledipasvir/sofosbuvir FDC (Harvoni®)	NS5A inhibitor/NS5B inhibitor (nucleotide)	GT 1	2014	1 tablet orally once daily for 8, 12, or 24 weeks	SVR 95-99%	Serious symptomatic bradycardia when coadministered with amiodarone
Paritaprevir/ombitasvir/ritonavir FDC + dasabuvir (Viekira Pak®)	NS3/4A PI/NS5A inhibitor/NS5B inhibitor (non-nucleoside)	GT 1	2014	2 FDC tablets once daily + 1 dasabuvir tablet twice daily (+/- ribavirin) for 12 or 24 weeks	SVR 95-99%	Increased risk of ALT elevations
Simeprevir (Olysio®)	NS3/4 PI	GT 1	2013	1 capsule orally once daily (with sofosbuvir) for 12 or 24 weeks	SVR 93-97%	Hepatic decompensation and hepatic failure; photosensitivity; rash

Genotype 4

Until recently, treatment of HCV GT 4 infection consisted of PR for up to 48 weeks. In 2013, sofosbuvir in combination with PR was approved for treatment of GT 4 infection based on data in 28 subjects. Despite a high response rate (27/28, 96%), the sofosbuvir combination regimen requires co-administration of IFN.

PegIFN is administered as a weekly injection and is poorly tolerated in many patients. It is associated with numerous serious and life-threatening toxicities including neuropsychiatric, autoimmune, ischemic and infectious disorders, and bone marrow suppression. Importantly, a significant proportion of HCV infected patients are intolerant to IFN or ineligible (based on co-morbidities or age) to use IFN-based therapies.

Because of the limitations of IFN-based therapies, there has been great interest in recent years

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

in developing IFN-free regimens consisting of combinations of multiple classes of HCV oral agents with improved tolerance, shortened duration of treatment, and broader eligibility for treatment across patient populations. For example, during the NDA review cycle for GZR/EBR, an IFN-free regimen consisting of ombitasvir, paritaprevir, and ritonavir (Technivie®) with RBV was approved for treatment of HCV GT 4 in TN and TE patients without cirrhosis. Ombitasvir, paritaprevir, and ritonavir without RBV may also be considered for TN patients who cannot take or tolerate RBV. Still, GT 4 infected patients, particularly with cirrhosis, would benefit from additional IFN-free treatment options.

Genotype 6

As of the time of completion of this review, no DAA or IFN-free regimens are approved for treatment of HCV GT 6 infection. As previously mentioned, IFN-based regimens are highly inconvenient and poorly tolerated.

Chronic Kidney Disease (CKD) Stage 4 or 5

Currently, there are no IFN-free treatment options for HCV GT 1, 4, or 6 in patients receiving hemodialysis. Approved treatments for HCV GT 1 infection require no dosage adjustments in patients with estimated creatinine clearance > 30 mL/min. However, for sofosbuvir-containing regimens no dosage recommendation can be given for patients with CKD Stage 4 (eGFR 15-29 mL/min/1.73 m²) or Stage 5 (eGFR < 15 mL/min/1.73 m²) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. Although Viekira Pak does not require a dosage adjustment in patients with any stage of CKD, no studies in patients receiving hemodialysis have been completed and the appropriate dosage for this patient population is unknown; ribavirin is also required as part of the regimen in many patients and may exacerbate CKD-related anemia.

PegIFN with or without RBV has been evaluated in advanced CKD patients, and dosing recommendations are available for patients receiving dialysis. However, SVR rates are poor (56%), tolerability is low, and IFN-containing regimens are no longer recommended for treatment of HCV GT 1 infection. Hence, there is a significant unmet medical need for IFN-free treatment for CKD patients receiving hemodialysis.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

GZR/EBR contains two NMEs and neither component is currently marketed in the U.S.

CDER Clinical Review Template 2015 Edition

Version date: April 9, 2015 for initial rollout (NME/original BLA reviews)

22

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

3.2. Summary of Presubmission/Submission Regulatory Activity

Merck submitted an initial IND application for GZR (IND 110261) and for EBR (IND 114298) for treatment of chronic HCV infection on November 22, 2010, and March 22, 2012, respectively, after conducting preliminary Phase 1 studies for each in Belgium. Development of the combination of GZR and EBR occurred under IND 110261. This section describes key events or activities that occurred under IND 110261 during the GZR and EBR clinical development program.

Partial Clinical Hold

On February 22, 2012, Merck informed FDA of the preliminary results of the second interim analysis of Protocol 003, in which TN, non-cirrhotic subjects were randomized (1:1:1:1) to receive either GZR at one of four dose levels (100, 200, 400, or 800 mg once daily) or boceprevir (800 mg three times daily), in combination with PR. The safety results showed dose-related increases in liver transaminases in subjects receiving GZR, which led FDA to place the IND on Partial Clinical Hold on March 20, 2012. FDA informed Merck that human subjects would be exposed to an unreasonable and significant risk of illness or injury and there was insufficient information to assess risks to human subjects based on the observed dose-related increases in transaminase levels. Subjects already assigned to the 100 or 200 mg dose groups were allowed to continue receiving GZR doses per protocol, but no new subjects could be enrolled into P003 at any dose and no new enrollment into any clinical trials using any dose of GZR in any patient population was allowed.

Merck subsequently provided a safety update for subjects previously enrolled in two cohorts of P003, all of whom completed treatment or discontinued study, and at which point no subjects remained on GZR. Late ALT/AST elevations >2-fold the ULN occurred in 4%, 3%, 21%, and 24% of subjects in the 100, 200, 400, and 800 mg dose groups, respectively, and were generally of larger magnitudes in the 400 and 800 mg dose groups. In many subjects, ALT/AST elevations improved with continued GZR treatment, and no subjects discontinued GZR due to ALT/AST elevations.

FDA concluded there were no changes in the pattern, frequency, or severity of ALT/AST elevations since initial reporting of abnormalities. In addition, early elevation of total bilirubin was observed but also resolved with continued treatment. There was one clear case of liver injury in a patient who received 800 mg of GZR, but symptoms and laboratory abnormalities resolved after stopping the drug and did not recur after a brief rechallenge. Furthermore, Merck adequately demonstrated an exposure-response relationship, and efficacy of GZR 100 mg appeared promising with substantial benefits over existing treatment options at the time. On August 24, 2012, FDA removed the Partial Clinical Hold for GZR and allowed Merck to

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

proceed with proposed studies of GZR \leq 100 mg. Please refer to Dr. Mary Singer's Review of Complete Response to Partial Clinical Hold for more details.

Breakthrough Therapy Designation

On August 26, 2013, FDA granted Merck's request for Breakthrough Therapy designation for treatment of chronic HCV infection and subsequently amended it to specify HCV GT 1. On January 30, 2015, FDA informed Merck of the Agency's Intent to Rescind Breakthrough Therapy designation based on recent approval of treatment regimens (i.e., Harvoni and Viekira Pak) demonstrating SVR12 rates of 94-100% with overall favorable safety profiles in patients with GT 1 infection. Merck subsequently requested Breakthrough Therapy designation for treatment of HCV GT 4 infection and of HCV GT 1, 4, or 6 infection in patients with advanced CKD, including ESRD on hemodialysis. On April 1, 2015, FDA granted both requests, except narrowed the second designation to include only GT 1 infection in patients with ESRD on hemodialysis.

End-of-Phase 2 Meeting

FDA and the Applicant agreed upon the patient population, dose selection, trial design, endpoints, and statistical analysis approach for Phase 3 trials C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE. Preliminary comments provided to the Applicant were sufficient, and the Applicant cancelled the meeting.

Pre-NDA Meeting

During the pre-NDA meeting, FDA recommended the Applicant have an independent expert committee perform a formal written assessment of the hepatic safety profile of GZR/EBR including an assessment of the adequacy of the proposed labeling to address this issue. FDA recommended that the committee be comprised of drug-induced liver injury (DILI) experts as well as practicing HCV clinicians, including members not affiliated with Merck or Merck's HCV clinical trials. Additionally, FDA requested the Applicant provide both the committee's consensus opinion and the individual opinions of each committee member. The Applicant agreed to these recommendations.

3.3. Foreign Regulatory Actions and Marketing History

GZR/EBR is not currently marketed in any country.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

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

4.1. Office of Scientific Investigations (OSI)

Inspection sites were selected from two pivotal Phase 3 trials, C-EDGE TN and C-EDGE TE, which involved the majority of the patient population reflected in the proposed indication. Six total sites were selected from the large number of sites per study based on relatively high enrollment and number of protocol deviations. One U.S. site was specifically chosen due to high enrollment as well as a being named in a complaint according to a document of complaints provided by OSI. The anonymous complainant made the following concerning allegations: (1) SAEs are altered to appear as if no SAE occurred, (2) subjects are not allowed sufficient time to read the informed consent form, (3) there is a lack of clinical investigator oversight, and (4) there are issues with drug storage temperatures.

Both domestic and foreign sites were selected because this would be the first approval of this new drug, and clinical trial protocols C-EDGE TN and C-EDGE TE were conducted as global trials. Because a substantial amount of the clinical trial experience with this drug has been at foreign sites, particularly in Europe, it is desirable to include foreign sites in the DSI inspections to verify the quality of conduct of the study.

The final reports from the clinical site inspections were pending at the time of this review.

4.1. Product Quality

GZR/EBR is supplied as an FDC, film-coated tablet that contains 100 mg of GZR drug substance and 50 mg of EBR drug substance. The FDC tablet was the product used during Phase 3 clinical trials. GZR exists as a (b) (4) and EBR used in the FDC tablet is the (b) (4) free base form. Both GZR and EBR (b) (4) have a (b) (4) solubility profile. GZR is (b) (4) while EBR is hygroscopic (b) (4). GZR is (b) (4) EBR is also (b) (4)

The GZR/EBR FDC tablet is composed of the following inactive ingredients: sodium lauryl sulfate, copovidone, (b) (4) mannitol, croscarmellose sodium, sodium chloride, colloidal silicon dioxide, magnesium stearate, hypromellose (b) (4) vitamin E polyethylene glycol succinate, microcrystalline cellulose, lactose monohydrate, (b) (4) Beige (b) (4) and carnuba wax. The film-coating excipients for (b) (4) Beige (b) (4)

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

include lactose monohydrate, hypromellose (b) (4) titanium dioxide, triacetin, iron oxide yellow, iron oxide red, and ferrous ferric oxide.

Please refer to the CMC Review by Dr. George Lunn 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 GZR/EBR. The final report from the inspection of the production facilities was not available at the time of this review.

4.2. **Clinical Microbiology**

This section includes a brief summary of key GZR and EBR nonclinical virology characteristics to support clinical trials evaluating this combination regimen. Please refer to the Clinical Virology Review by Dr. Takashi Komatsu for additional details. Discussion of clinical virology assessments, including baseline polymorphisms and outcome, development of resistance, and consequences of virologic failure is provided in Sections 6 and 7 (clinical efficacy).

Mechanism of Action

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

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

Antiviral Activity in Cell Culture

In HCV replicon assays, GZR inhibited HCV replication with EC₅₀ values of approximately (b) (4) (b) (4), respectively, against HCV replicons derived from GT 1a, 1b, and 4 laboratory strains and clinical isolates. The median EC₅₀ values against replicons derived from GTs 2, 3, 5, and 6 were (b) (4), respectively.

In HCV replicon assays, EBR inhibited HCV replication with EC₅₀ values of approximately (b) (4) (b) (4) for GT 1a, 1b, and 4 laboratory strains and clinical isolates. The median EC₅₀ values against replicons derived from GTs 2, 3, 5, and 6 were (b) (4) respectively.

GZR combined with EBR or RBV showed no antagonistic effect.

Effect of Individual Amino Acid Substitutions on Anti-HCV Activity

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

In HCV GT 1a replicons, single NS3 substitutions D168A/E/G/S/V reduced cell culture antiviral activity of GZR by 2- to 81-fold. In HCV GT 1b replicons, single NS3 substitutions F43S, A156S/T/V, and D168A/G/V reduced antiviral activity of GZR by ^(b)₍₄₎ to 375-fold. In HCV GT 4 replicons, single NS3 substitutions D168A/V reduced antiviral activity by 110- to 320-fold.

In HCV GT 1a replicons, single NS5A substitutions Q30D/E/H/R, L31M/V, and Y93C/H/N reduced cell culture antiviral activity of EBR by ^(b)₍₄₎ to 2000-fold. In HCV GT 1b replicons, single NS5A substitutions L31F and Y93H reduced antiviral activity of EBR by ^(b)₍₄₎. In HCV GT 4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced antiviral activity by 3- to 23-fold.

4.3. Nonclinical Pharmacology/Toxicology

For both EBR and GZR, no clear target organs of toxicity were identified with exposures up to 5 times the clinical exposure from EBR 50 mg and GZR 100 mg. No specific overlapping toxicity of potential significant clinical concern was identified in animals administered EBR or GZR alone. This section provides a brief overview of the cardinal findings from nonclinical toxicology studies conducted in support of this application. Please refer to the Pharmacology/Toxicology Review by Dr. Christopher Ellis for additional details.

Safety Pharmacology and Repeat-Dose Toxicology

Safety pharmacology studies were performed in rats and dogs, and repeat-dose toxicology studies were performed in mice, rats, and dogs for up to 3, 6, and 9 months duration, respectively.

For EBR, no target organs of toxicity were identified in toxicology studies in mice, rats and dogs after oral administration of up to 1000 mg/kg/day of EBR for up to 1, 6 and 9 months at area under the curve (AUC) exposures \geq 55, 9 and 8 times higher, respectively, than clinical exposure at the recommended dose.

GZR studies revealed toxicity involving multiple organ systems at high exposure. Elevated heart rate was observed in dogs at an exposure 195 times higher than clinical exposure, with no effects observed at an exposure 52 times higher than clinical exposure. Hepatobiliary toxicity was observed in mice and dogs at AUC exposure \geq 74 times higher than the clinical dose, manifested as elevated bilirubin and liver enzymes and histologic changes to liver and gallbladder tissue. Hematologic, renal, and gastrointestinal toxicity were observed at AUC exposures 282-747 times the clinical exposure.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Phototoxicity

Phototoxicity studies were conducted in pigmented rats. No dermal or ocular phototoxicity was observed at EBR AUC exposure 9 times the clinical exposure. There were no phototoxicity concerns for GZR.

Fertility and Early Embryonic Development

Male fertility:

In the male fertility study for EBR, no effects on sperm count were seen in rats at an exposure 5 times higher than clinical exposure. An approximately 15% decrease in sperm count was observed at AUC exposure 9 times higher than clinical exposure at the recommended dose, but there were no effects on testicular weight, sperm motility and morphology or male fertility parameters. No testicular toxicity was observed in rats administered EBR for up to 6 months at AUC exposure 11 times higher than clinical exposure at the recommended dose.

In the male fertility study for GZR, no effect on male fertility was observed in rats at AUC exposure 144 times higher than clinical exposure. Testicular toxicity consisting of seminiferous tubule degeneration, decreased testes weight and sperm count in the epididymis was observed at AUC exposures 1,376 and ≥ 163 times higher than clinical exposure in the 1 and 9 month repeat-dose toxicology studies, respectively, in dogs, while no testicular effects were seen at AUC exposures 231 and 37 times higher than clinical exposure in the 1 and 9 month studies, respectively. Testicular toxicity was not observed in mice and rats at up to 3 and 6 months at AUC exposures 747 and 282 times higher, respectively, than the clinical exposure at the recommended dose.

Female Fertility:

No drug-related effects were observed on female fertility at EBR AUC exposure 7 times higher than clinical exposure and GZR exposure 84 times the clinical exposure.

Embryo-Fetal Development (EFD) and Pre- and Post-Natal Development (PPND):

EFD studies were conducted in rats and rabbits, while PPND studies were conducted in rats.

No EBR-related developmental effects were observed in rats or rabbits at AUC exposures 10 and 18 times higher, respectively, than clinical exposure. Fetal plasma levels were only 0.6-2% that of maternal plasma concentrations achieved under the conditions studied, whereas significant concentrations were detected in milk two hours post-dose: milk to maternal plasma ratio of approximately 4.2 on lactation day 14.

No GZR-related developmental effects were observed in rats or rabbits at AUC exposures ≥ 78 and 41 times the clinical exposure, respectively. GZR and related metabolites can cross the placenta, resulting in fetal plasma concentrations of up to 7% (rabbits) and 89% (rats) that of

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

maternal concentrations achieved under the conditions studied. Significant concentrations were present in milk two and eight hours post-dose: milk concentrations from 54 to 87% that in maternal plasma on lactation day 14.

Genetic Toxicology

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

4.4. **Clinical Pharmacology**

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK), pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Drs. Su-Young Choi and Luning (Ada) Zhuang for full details.

4.4.1. **Mechanism of Action**

GZR is an NS3/4A PI, and EBR is an NS5A replication inhibitor.

4.4.2. **Pharmacodynamics**

Dose-Response

Phase 1b study 5172-P004 showed GZR monotherapy at doses of 50 mg and higher are on the plateau of the dose-response curve for HCV GT 1. Phase 2 trial 003 showed similar efficacy of GZR 100-800 mg when coadministered with PR. In P003, ALT/AST elevations with at least four weeks of treatment occurred disproportionately among subjects receiving higher doses. Exposure-related increases in ALT/AST elevations led to a dosage cap of 100 mg daily in subsequent trials. See Section 3.2 (Partial Clinical Hold) for more details. Phase 2 trial 038 subsequently demonstrated similar SVR12 results with GZR 50 mg (84%) and GZR 100 mg (89%) but lower SVR12 with GZR 25 mg (54%), each in combination with PR. Safety results were similar with all three doses. Based on efficacy and safety results in these Phase 2 dose-ranging trials, GZR 100 mg was selected for further evaluation.

Phase 1b monotherapy study 8742-P002 showed EBR 10 mg and 50 mg have similar efficacy but 50 mg may provide more sustained suppression of GT 1a. Phase 2 trial C-WORTHY (P035/Part A) demonstrated similar SVR12 results with EBR 20 mg (100%) and 50 mg (96%), each in combination with GZR 100 mg. Because no dose-related toxicities occurred, EBR 50 mg was selected for further evaluation.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

See Sections 7.1.2 and 8.5.1 for additional exposure-response efficacy and safety analyses, respectively.

4.4.3. **Pharmacokinetics**

Absorption, Distribution, Metabolism, and Elimination

GZR and EBR reached maximum plasma concentrations (C_{max}) at 2 hours and 3 hours after oral administration, respectively.

GZR/EBR may be administered without regard to food because changes in plasma concentrations with a high-calorie, high-fat meal in healthy subjects were not clinically meaningful.

GZR and EBR are highly protein bound ($\geq 99\%$) to both serum albumin and alpha-1-acid glycoprotein. GZR is a substrate of OATP1B, which is expected to result in significant distribution in the liver.

GZR and EBR are metabolized by cytochrome P450 (CYP) 3A4 *in vitro*. The primary route of elimination of both drugs is feces, with $< 1\%$ elimination in the urine. GZR and EBR have mean elimination half-lives of 31 hours and 24 hours, respectively, in HCV infected patients. GZR PK is non-linear with apparent dose and time dependencies, while EBR PK appears to be linear and time dependent. Steady-state levels of GZR 100 mg and EBR 50 mg are reached within six days of administration.

Hepatic Impairment

Increased GZR exposures (area under the curve over a 24 hour dosing interval [AUC_{24hr}]) in patients with mild hepatic impairment are not clinically relevant. GZR exposures were 65% higher in HCV infected patients with mild hepatic impairment compared to HCV infected non-cirrhotic patients based on population PK analysis. Similarly, in HCV uninfected subjects with mild hepatic impairment, GZR exposures were 66% higher than matched healthy volunteers. EBR exposures were not significantly different between subjects with mild hepatic impairment and with normal hepatic function in population pharmacokinetic analysis. The Applicant proposes that GZR/EBR may be administered to patients with mild hepatic impairment.

Increased GZR exposures in patients with moderate or severe hepatic impairment are considered clinically relevant due to possible increased risk of ALT elevation, the exposure-dependent safety event of interest for GZR. GZR exposures were increased by 4.8-fold and 11.7-fold in HCV uninfected subjects with moderate and severe hepatic impairment,

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

respectively, as compared to matched healthy volunteers. The Applicant proposes (b) (4) GZR/EBR in patients with moderate hepatic impairment and to contraindicate GZR/EBR in patients with severe hepatic impairment.

Reviewer Comment: The proposed recommendations for patients with mild or with severe hepatic impairment are reasonable. In patients with moderate hepatic impairment, an approximate 5-fold increase in GZR exposures is concerning given a known exposure-related safety concern with GZR. It is unknown whether late ALT elevation events in patients with moderate hepatic impairment would mimic events that occurred in Phase 2 and Phase 3 trials, which included subjects with no or mild hepatic impairment. Additionally, one Child-Pugh B subject died during a clinical trial evaluating a dose of GZR 50 mg (rather than 100 mg) with EBR 50 mg (see Section 8.4.1); the Applicant is no longer pursuing this patient population. Given the proposed FDC product contains 100 mg of GZR and given the exposure-related hepatic concerns, a contraindication in patients with moderate hepatic impairment may be warranted.

Renal Impairment

PK evaluations in HCV uninfected and HCV infected patients with severe renal impairment, including those receiving hemodialysis, showed no significant differences in GZR or EBR exposures compared to matched healthy volunteers. Furthermore, GZR and EBR were minimally eliminated by a 4-hour hemodialysis session.

Gender, Age, and Race

Based on population PK analyses, GZR exposures are estimated to be 30% higher in females compared to males, 50% higher in Asians compared to Whites, and 20% higher in elderly (≥ 65 years of age) compared to younger (< 65 years of age) patients. See Section 8.5.1 for implications of the incidence of late ALT elevations, the safety event of concern with GZR.

Based on population PK analyses, EBR exposures are estimated to be 50% higher in females compared to males, 15% higher in Asians compared to Whites, and 16% higher in elderly (≥ 65 years of age) compared to younger (< 65 years of age) patients. These differences are not clinically relevant.

HCV Infected and HCV Uninfected Subjects

GZR (100 mg) exposure is approximately 2-fold higher in HCV infected patients compared to healthy subjects, while EBR (50 mg) exposures are comparable between the two groups. Thus, GZR 200 mg and EBR 50 mg were generally used for drug interaction studies in healthy subjects.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Drug Interactions

Drug interactions with GZR/EBR as the perpetrator or victim are possible as described in Table 2.

Table 2. GZR and EBR Drug Interaction Potential

Potential for Drug Interactions (select enzymes and transporters based on <i>in vitro</i> study results)					
	P-gp	CYP2C8	CYP3A4	OATP1B1	OATP1B3
GZR	substrate	inhibitor	substrate inhibitor	substrate inhibitor	substrate inhibitor
EBR	substrate inhibitor		substrate	inhibitor	inhibitor

Source: Based on the Clinical Pharmacology review by Dr. Su-Young Choi

No clinically relevant drug interactions were observed with dolutegravir, raltegravir, rilpivirine, mycophenolate mofetil, prednisone, pantoprazole, phosphate binders (sevelamer, calcium carbonate), oral contraceptives, pitavastatin, pravastatin, methadone, or buprenorphine.

FDA’s Clinical Pharmacology team made the following clinical recommendations with respect to drug interactions:

- 1. Co-administration is contraindicated due to significant increases in GZR exposure, which may increase the risk of late ALT elevation:** atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r), cyclosporine (CsA), or other OATP1B inhibitors that may significantly increase GZR exposure. GZR exposures are increased 10.6-fold, 12.9-fold, and 15.2-fold with ATV/r, LPV/r, and CsA, respectively.
- 2. Co-administration is not recommended due to significant increases in GZR exposure:** ketoconazole or darunavir/ritonavir (DRV/r). GZR exposures are increased 3-fold and 7.5-fold with ketoconazole and DRV/r, respectively.
- 3. Co-administration is contraindicated due to significant decreases in GZR or EBR exposures:** efavirenz, rifampin and other strong CYP3A4 inducers. GZR C₂₄ is decreased 90% with rifampin. GZR and EBR exposures are decreased 83% and 54%, respectively, with efavirenz.
- 4. Dose adjustment of co-administrated drugs or close clinical monitoring is recommended:** atorvastatin, rosuvastatin and tacrolimus. The clinical pharmacology team was awaiting

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

consult recommendations for specific dosing recommendations at the time this review was completed.

4.5. Devices and Companion Diagnostic Issues

Not applicable

4.6. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below contains a summary of all Phase 2 and Phase 3 trials in the Applicant's clinical safety database for GZR and EBR that were submitted with this NDA.

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ORIGINAL

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 3. Summary of Relevant Clinical Trials

Trial Identity	Phase	Trial Design	GT	Regimen	Study Population	No. of patients enrolled	Data at NDA Submission	No. of Centers and Countries
Studies to Support Efficacy and Safety								
060 C-EDGE TN	3	Randomized, parallel-group, double-blind trial	1, 4, 6	12 weeks, no RBV (ITG vs. DTG)	TN \pm cirrhosis	421 (316 ITG; 105 DTG)	Safety and SVR ₁₂ for ITG. Safety and EOT data for DTG.	60 centers 10 countries
061 C-EDGE CO-INFECTION	3	Single-arm, open-label trial	1, 4, 6	12 weeks, no RBV	HIV coinfecting TN \pm cirrhosis	218	Safety and SVR ₁₂	37 centers 9 countries
068 C-EDGE TE	3	Randomized, parallel-group, open-label trial	1, 4, 6	12 or 16 weeks \pm RBV	PR PTF \pm cirrhosis + HIV coinfection	420	Safety and SVR ₁₂	65 centers 15 countries
052 C-SURFER	2/3	Randomized, parallel-group, double-blind trial	1	12 weeks, no RBV (ITG vs. DTG)	CKD Stages 4-5 including dialysis	235 (111 ITG, 113 DTG, 11 intensive PK)	Safety and SVR ₁₂ of ITG + intensive PK group. Safety and EOT data on DTG.	79 centers 12 countries
047 C-SCAPE Part B	2	Randomized, open-label trial	4, 5, 6	12 weeks \pm RBV	TN, non-cirrhotic	41	Safety and SVR ₂₄	30 centers 7 countries
048 C-SALVAGE	2	Open-label trial	1	12 weeks + RBV	DAA/PR PTF \pm cirrhosis	79	Safety and SVR ₁₂	14 centers 4 countries
Other Studies Pertinent to the Review of Efficacy or Safety								
003	2	Randomized, active-controlled, dose-ranging trial with RGT	1	12 weeks GZR 100, 200, 400, or 800 mg + 24-48 weeks PR vs. BOC	TN \pm cirrhosis	302 on GZR/PR; 66 on BOC/PR	SVR ₂₄	70 centers 7 countries

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Trial Identity	Phase	Trial Design	GT	Regimen	Study Population	No. of patients enrolled	Data at NDA Submission	No. of Centers and Countries
				+ PR				
035/ Part A C-WORTHY	2	Randomized, double-blind trial	1	12 weeks GZR (100 mg)/EBR (20 or 50 mg) ± RBV	TN or PR null-responders ± cirrhosis; HIV+ TN non-cirrhotic	65	SVR ₂₄	76 centers 12 countries
035/ Part B C-WORTHY	2	Randomized, double-blind trial	1	8, 12, or 18 weeks ± RBV	TN, non-cirrhotic	406	Safety and SVR ₂₄	
035/Part C C-WORTHY	2	Randomized, double-blind trial	1b	8 weeks ± RBV	TN, non-cirrhotic	61	Safety and SVR ₁₂	
038	2	Randomized, dose-ranging, double-blind trial	1	12 weeks GZR 25, 50, or 100 mg + PR	TN, non-cirrhotic	87	SVR ₂₄	19 centers 5 countries
039	2	Randomized, open-label trial	1	12 or 24 weeks GZR 100 mg + RBV	TN, non-cirrhotic	26	SVR ₂₄	6 centers 3 countries
058 Part A	2	Randomized, open-label trial	1	12 weeks, no RBV	Japanese TN or PR PTF, non-cirrhotic	62	Safety and SVR ₄	19 centers 1 country (Japan)
059 Part A	2	Randomized, open-label trial	1	12 weeks, no RBV	Child-Pugh B ± cirrhosis	40	Safety and SVR ₄	9 centers 1 country (U.S.)

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

5.2. Review Strategy

Dr. Sarita Boyd is the primary clinical reviewer for clinical trials associated with this NDA except C-SURFER. Dr. Prabha Viswanathan is the primary clinical reviewer for C-SURFER. Both 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 reviewer, Dr. LaRee Tracy, and the virology reviewer, Dr. Takashi Komatsu. 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.

We used the JumpStart service provided by the Computational Science Center (CSC) at Center for Drug Evaluation and Research (CDER). The JumpStart team assessed data fitness and provided exploratory safety analyses for C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SURFER.

The clinical review for GZR/EBR is based primarily on the pivotal Phase 3 trials C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE, Phase 2 trial C-SALVAGE, and Phase 2/3 trial C-SURFER. C-SALVAGE provides the only data for subjects who failed prior PI/PR treatment, a patient population for which the Applicant is seeking an indication. C-SURFER is critical for the subpopulation of patients with CKD Stage 4 or 5, including those receiving hemodialysis.

In addition to the five aforementioned trials, data from other Phase 2 trials highlighted in the summary table above were reviewed for key safety analyses, as described in Section 8. These supportive Phase 2 trials include subjects in the safety analyses who were exposed to GZR and EBR at the proposed dose and duration for marketing. Other Phase 2 subjects from these trials, while contributing to the overall safety database presented by the Applicant, were not included in specific data analyses because of different doses (i.e., GZR >100 mg or EBR <50 mg), different regimens (e.g., GZR + PR or GZR + EBR + SOF), or shorter durations (i.e., <12 weeks) that these subjects received in particular arms. However, Phase 2 subjects infected with HCV GTs other than those in the proposed indication, if included in particular arms, were not excluded from key safety analyses, as the safety profile is not expected to differ based on HCV GT.

While Phase 2 trial C-SCAPE is not critical for most safety analyses, this trial provides additional efficacy data for GT 4 and GT 6 infected patients, which represent a relatively small portion of Phase 3 trials. Additional Phase 2 trials, particularly C-WORTHY, also support efficacy analyses; however, the clinical efficacy review focuses on data from C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SCAPE, C-SALVAGE, and C-SURFER. Please see the statistical review by Dr. LaRee Tracy for discussion of the key efficacy findings from additional Phase 2 trials.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

6 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant states that clinical trials were conducted following Good Clinical Practice standards and considerations for the ethical treatment of human subjects. The Applicant specifies that clinical trials not conducted under U.S. IND were conducted in compliance with ICH E6 and 21CFR 312.20.

6.1. C-EDGE TN (P060)

6.1.1. Study Design

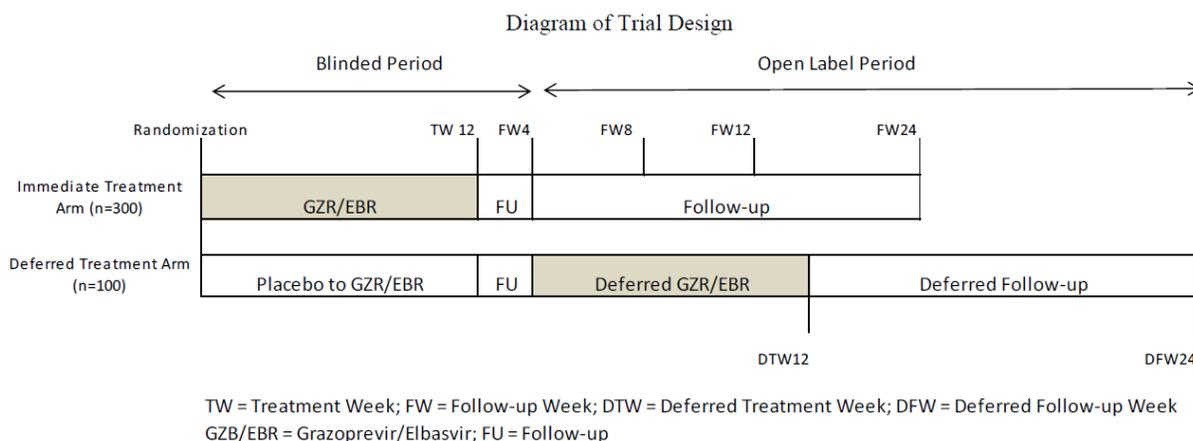
Overview

C-EDGE TN (P060) was a Phase 3 randomized (3:1), parallel-group, placebo-controlled, double-blind trial. The patient population consisted of TN cirrhotic and non-cirrhotic subjects with chronic HCV GT 1, 4, or 6 infection. HIV coinfecting subjects were excluded. The regimen was GZR/EBR for 12 weeks (immediate treatment group [ITG]) vs. placebo (deferred treatment group [DTG]). The DTG received GZR/EBR for 12 weeks following unblinding. Randomization was stratified by fibrosis stage (cirrhotic vs. non-cirrhotic) and HCV subtype (GT 1a vs. GT 1 non-A vs. GT 4/6).

The presence of cirrhosis was determined by (1) liver biopsy, or (2) Fibroscan result >12.5 kPa within 12 months, or (3) FibroSure® (FibroTest®) score of >0.75 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) of >2 during screening. The absence of cirrhosis was determined by (1) liver biopsy within 24 months, or (2) Fibroscan result ≤12.5 kPa, or (3) FibroSure® (FibroTest®) score ≤0.48 and APRI ≤1. Liver biopsy was required in the absence of a definitive diagnosis of presence or absence of cirrhosis using the above criteria.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Figure 1. C-EDGE TN Trial Design



Source: P060v01 CSR

The trial began on June 11, 2014, and is ongoing. The NDA submission contains primary efficacy and safety results for the ITG and placebo/DTG. The trial is being conducted at 60 centers across Australia (4), Czech Republic (4), France (5), Germany (5), Israel (5), Puerto Rico (3), South Korea (3), Sweden (4), Taiwan (3), and the U.S. (24).

Study Endpoints

The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ (TD[u] or TND) 12 weeks after the end of study treatment. HCV RNA levels in plasma were measured using the Roche COBAS™ AmpliPrep/COBAS Taqman® HCV Test, v2.0, with a lower limit of quantification (LLOQ) of 15 IU/mL and a lower limit of detection of 15 IU/mL. Nomenclature for describing HCV RNA levels is as follows.

Table 4. Nomenclature for Description of HCV RNA Levels

Abbreviation	Definition	HCV RNA Level
TND	Target not detected	HCV RNA not detected
TD(u)	Target detected but unquantifiable	HCV RNA < LLOQ
TD(q)	Target Detected, quantifiable	HCV RNA ≥ LLOQ

The primary safety endpoint was clinical evaluation of AEs, including events of clinical interest (ECIs), and inspection of other safety parameters collected in the study. Protocol-defined hepatic ECIs were as follows provided none were associated with virologic failure:

1. ALT or AST >500 IU/L regardless of baseline ALT/AST

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

2. ALT or AST >3x baseline AND >100 IU/L
3. Alkaline phosphatase >3x ULN

Lack of efficacy was categorized as follows:

Non-response: HCV RNA detected at end of treatment (EOT) without <LLOQ on treatment

Rebound: Confirmed >1 log₁₀ IU/mL increase in HCV RNA from nadir while on treatment

Virologic breakthrough: Confirmed HCV RNA ≥LLOQ after being <LLOQ while on treatment

Relapse: Confirmed HCV RNA ≥LLOQ following EOT, after becoming TND at EOT

Statistical Analysis Plan

The primary hypothesis was that subjects in the ITG would achieve an SVR12 rate superior to the reference rate of 73% (derived from Phase 3 trials of simeprevir/PR in TN, HCV mono-infected subjects after adjusting for the expected proportion of subjects with cirrhosis in this study and an expected improved safety profile related to an IFN-free regimen), with testing at 1-sided significance level (type-I error) of 0.025. A two-sided 95% confidence interval (CI) was also planned for the SVR12 rate. The analysis population is the full analysis set (FAS), and the missing data approach is missing=failure.

The All-Subjects-As-Treated population was pre-specified for safety analyses. AEs or elevated laboratory values reported as hepatic ECIs were identified *a priori* as safety parameters of interest; p-values and 95% CI for between-treatment differences (ITG vs. DTG) were calculated.

6.1.2. Study Results

Patient Disposition

Of the 469 subjects screened, 421 were randomized to treatment, and all subjects received at least one dose of therapy. In the ITG (n=316), 311 subjects completed treatment, while five subjects prematurely discontinued treatment due to an AE (n=3), lost to FU (n=1), and death (n=1). In the placebo/DTG (n=105), 104 completed treatment with placebo, while one subject discontinued treatment prematurely due to an AE.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table of Demographic Characteristics

The table below describes the baseline demographics and characteristics for subjects in the FAS.

Table 5. C-EDGE TN Subject Demographics and Characteristics

Characteristic (%)	ITG (n=316)	DTG (n=105)
Gender (Male)	171 (54.1)	56 (53.3)
Age (years)		
Mean (+/-se)	52.2 (0.6)	53.8 (1.1)
Range	20-78	22-76
% ≥ 65 years	9.2	17.1
Race		
White	191 (60.4)	73 (69.5)
Black/African American	59 (18.7)	18 (17.1)
Asian	54 (17.1)	13 (12.4)
Other	12 (3.8)	1 (0.01)
IL28B Genotype		
CC	106 (33.5)	37 (35.2)
Non-CC	208 (65.8)	67 (63.8)
Missing	2 (0.6)	1 (1.0)
Baseline HCV RNA Log10 (IU/mL)		
Mean (+/-SD)	6.1 (0.7)	6.1 (0.6)
Median	6.2	6.1
Range	1.8-7.3	4.4-7.2
HCV Genotype		
1a	157 (49.7)	54 (51.4)
1b	131 (41.4)	40 (38.1)
4	18 (5.7)	8 (7.6)
6	10 (3.2)	3 (2.9)
Hepatic Stage		
Non-Cirrhotic	246 (77.8)	83 (79.0)
Cirrhotic	70 (22.1)	22 (21.0)
Fibrosis Stage[^]		
F0-F2	210 (66.5)	69 (65.7)
F3	36 (11.4)	14 (13.3)
F4	70 (22.2)	22 (20.1)
Region		
US	147 (46.5)	57 (54.3)
Non-US	169 (53.5)	48 (45.7)

[^]Score F0=no fibrosis, F1=mild fibrosis, F2=moderate fibrosis, F3=severe fibrosis, F4=cirrhosis

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Reviewer Comment: Baseline characteristics were similar between groups, except almost twice as many elderly subjects (>65 years of age) were enrolled in the DTG. This age group has been shown to have higher GZR exposures, which may impact safety but is not likely to impact efficacy.

Efficacy Results – Primary Endpoint

For the ITG, SVR12 results overall and by subgroup are displayed in the tables below.

Table 6. C-EDGE TN Primary Efficacy Results

Treatment Regimen	SVR12 (FAS) (n=316) GZR/EBR x 12 weeks
SVR Achieved (%)	299 (94.6)
95% CI [^] , p-value*	91.5, 96.8 <0.0001
SVR Not Achieved	17 (5.4)
Non-virologic failure	4 (1.3)
Death	2 (0.6)
LTF/Missing Value	1 (0.3)
Adverse Event Discontinuation	1 (0.3)
Virologic failure	13 (4.1)
Breakthrough	1 (0.3)
Relapse	12 (3.8)
1a	9 (2.8)
1b	1 (0.3)
(b) (4)	

[^]Clopper-Pearson exact method

*One-sided Exact test, alpha=0.025 based on test for true proportion=0.73.

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Reviewer Comment: The overall SVR12 rate of 95% (95% CI 92%, 97%) far exceeds the pre-specified reference rate of 73% and is reasonably within the efficacy range of more recently approved treatments for GT 1 infection. Importantly, the use of baseline screening for NS5A resistance associated polymorphisms in GT 1a infected subjects will further improve efficacy (further discussion below). Overall, this trial supports efficacy of GZR/EBR in HCV TN patients, particularly with GT 1 infection which comprise the majority population in this trial.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 7. C-EDGE TN SVR12 Subgroup Analysis

SVR12	Immediate Treatment Group (n=316)	
	% (n/N)	95% CI*
Baseline HCV RNA (IU/mL)		
≤ 800,000	100.0 (94/94)	96.2, 100.0
> 800,000	92.3 (205/222)	88.0, 95.5
HCV genotype		
1a	91.7 (144/157)	86.3, 95.5
1b	98.5 (129/131)	94.6, 99.8
4	100.0 (18/18)	81.5, 100.0
(b) (4)		
Cirrhosis		
Yes	97.2 (68/70)	90.1, 99.7
No	93.9 (231/246)	90.1, 96.6
Fibrosis Stage		
F0-F02	93.8 (197/210)	89.7, 96.7
F3-F4	96.2 (102/106)	90.6, 99.0

*Clopper-Pearson exact method

Source: FDA Statistical Review, Dr. LaRee Tracy

Reviewer Comment:

A higher SVR rate in subjects with baseline HCV RNA <800,000 IU/mL (compared to HCV RNA >800,000 IU/mL) and in subjects infected with GT 1b (compared to GT 1a) is consistent with previous trials evaluating HCV treatment. In contrast, equal efficacy and a trend toward higher SVR rates in cirrhotics (compared to non-cirrhotics) was less expected, and this finding is supported by a numerically higher SVR rate in subjects with advanced fibrosis or cirrhosis (F3-F4) compared to subjects with no or less advanced fibrosis (F0-F2). This trend is beneficial for subjects with cirrhosis.

The number of subjects with GT 4 infection is relatively small, but an SVR12 rate of 100% in this population is highly favorable. See Section 7.1.2 for pooled data analysis of TN GT 4 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

Subjects with GT 6 infection had the lowest SVR12 rates, (b) (4). See Section 7.1.2 for pooled data analysis of TN GT 6 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

Clinical Review
 Sarita Boyd, PharmD
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 NDA 208261
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Additional Analyses Conducted on the Individual Trial

The table below presents pertinent analysis of SVR12 by baseline NS5A polymorphisms in GT 1 infected subjects. This analysis excludes subjects who failed treatment due to reasons other than virologic failure because baseline NS5A polymorphisms would not impact failure for “other” reasons. Overall ten GT 1a and one GT1b infected subject experienced virologic failure based on SVR12 analysis. Lists “A” and “B” contain polymorphisms at the same five amino acid positions, but list B contains additional substitutions at those positions. Please refer to Dr. Komatsu’s virology review for additional details and analyses.

Table 8. C-EDGE TN SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms

	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
SVR12	144/154 (94%)	129/130 (99%)	142/145 (98%)	2/9 (22%)	113/113 (100%)	16/17 (94%)	133/135 (99%)	11/19 (58%)	111/111 (100%)	18/19 (95%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, Y93C/H/N polymorphism
 B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S polymorphism
 Source: FDA Virology Reviewer Dr. Takashi Komatsu

Reviewer Comment: There was a strong trend toward reduced efficacy in GT 1a infected subjects with baseline NS5A polymorphisms at positions 28, 30, 31, 58, and 93. Furthermore, the presence of baseline NS5A polymorphisms appears to explain the majority of virologic failures. SVR12 rates in subjects without baseline NS5A polymorphisms (98-99%) are consistent with the overall SVR12 rate in GT 1b infected subjects (99%); these SVR rates are presented for the purpose of comparison and are solely based on baseline NS5A polymorphisms as they do not account for subjects who failed for reasons other than virologic failure. The impact of polymorphisms in GT 1b infected subjects was minimal because only one GT 1b infected subject experienced virologic failure.

6.2. C-EDGE COINFECTION (P061)

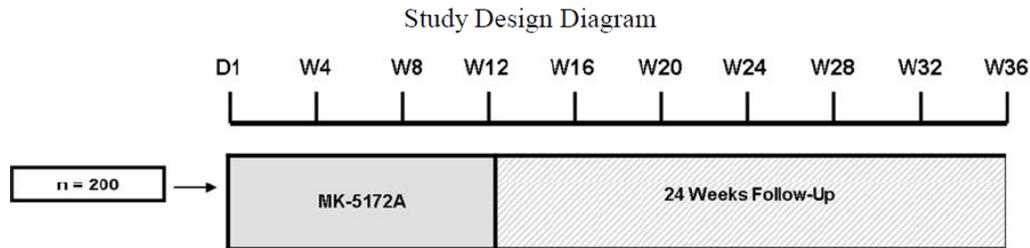
6.2.1. Study Design

Overview

C-EDGE COINFECTION (P061) was a Phase 3 open-label clinical trial that assessed the efficacy and safety of GZR/EBR FDC for 12 weeks in TN cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 infection and HIV coinfection. See Section 6.1.1 for methods to determine the presence or absence of cirrhosis.

Clinical Review
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NDA 208261
Zepatier (elbasvir and grazoprevir)

Figure 2. C-EDGE COINFECTION Trial Design



Source: P061v01 CSR

The trial began on June 11, 2014, and was completed on February 13, 2015. The NDA submission contains primary efficacy and safety results. The trial was conducted at 37 centers across Australia (2), Canada (2), Denmark (3), France (3), Germany (3), Israel (3), Spain (3), United Kingdom (2), and the U.S. (18).

Study Endpoints

The primary efficacy and safety endpoints were the same as for C-EDGE TN described in Section 6.2.1.

Statistical Analysis Plan

The FAS population, which consisted of all allocated subjects who received at least one dose of study treatment, was pre-specified as the primary population for efficacy analysis, with Missing=Failure approach. For the primary efficacy analysis to estimate the proportion of subjects achieving SVR12, a Wald test was planned to ascertain whether the true SVR12 is at least 70%, the historical reference rate (derived from the Phase 2 trial of sofosbuvir in HCV GT 1 subjects coinfecting with HIV [Photon-1] after adjusting for the expected proportion of subjects with cirrhosis in this study and an expected improved safety profile related to an IFN-free regimen). The All Subjects as Treated population was pre-specified as the population for safety analysis.

6.2.2. Study Results

Patient Disposition

Of the 261 subjects screened, 218 were enrolled, and all subjects received at least one dose of therapy. One subject prematurely discontinued treatment at TW2 due to use of nevirapine, a prohibited concomitant medication. Two subjects prematurely discontinued the trial; both were lost to follow up.

Clinical Review
 Sarita Boyd, PharmD
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 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Demographic Characteristics

Baseline demographics and characteristics were as follows:

- Male sex 84%
- Mean age 49 years (range 21-71)
- Race: White 77%, Black 17%, Asian 3%
- U.S. region 38%
- Mean BL HCV RNA 6.0 log₁₀ IU/mL (range 3.8-7.2)
- HCV GT 1a 66%, GT 1b 20%, GT 4 13%, GT 6 0.5% (1 subject)
- Hepatic stage: cirrhosis (F4) 16%, advanced fibrosis (F3) 11%

Antiretroviral treatment generally consisted of a raltegravir-, dolutegravir-, or rilpivirine-based regimen with 78% of subjects also receiving tenofovir.

Efficacy Results - Primary Endpoint

Overall, 207/218 subjects (95.0%; 95% CI 91.2, 97.5; p<0.0001) achieved SVR12. Four (1.8%) subjects experienced non-virologic failure due to lost to follow-up (n=3) or early discontinuation (n=1). Seven (3.2%) subjects experienced virologic failure, all due to relapse.

Reviewer Comment: The overall SVR12 rate and lower bound of the 95% CI far exceed the pre-specified reference rate of 73% and is consistent with efficacy results in HCV monoinfected subjects. Importantly, the use of baseline screening for NS5A resistance associated polymorphisms in GT 1a infected subjects may further improve efficacy (further discussion below). Overall, this trial supports efficacy of GZR/EBR in TN HIV coinfecting patients with HCV GT 1 or 4.

SVR12 rates by subgroup are displayed in the table below.

Table 9. C-EDGE COINFECTION SVR12 Subgroup Analysis

SVR12	GZR/EBR (n=218)	
	% (n/N)	95% CI*
Baseline HCV RNA (IU/mL)		
≤ 800,000	96.7 (88/91)	90.7, 99.3
> 800,000	93.7 (119/127)	88.0, 97.2
HCV genotype[^]		
1a	94.4 (136/144)	89.4, 97.6
1b	95.5 (42/44)	84.5, 99.4
4	96.4 (27/28)	81.7, 99.9

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

GZR/EBR (n=218)		
SVR12	% (n/N)	95% CI*
Cirrhosis		
Yes	100 (35/35)	90.0, 100.0
No	94.0 (172/183)	89.5, 97.0
Fibrosis Stage		
F0-F2	95.0 (152/160)	90.4, 97.8
F3	87.0 (20/23)	66.4, 97.2
F4	100 (35/35)	90.0, 100.0

Reviewer Comment: Notably, all subjects with cirrhosis achieved SVR12. The numerically higher rate of SVR in cirrhotic subjects (compared to non-cirrhotic subjects) in this trial is consistent with C-EDGE TN results. Unlike in C-EDGE TN, SVR rates in GT 1a and 1b infected subjects were similar. However, the individual SVR rates for both GT 1 subtypes and GT 4 were high (94-96%). See Section 7.1.2 for pooled data analysis of TN GT 4 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

(b) (4)

See Section 7.1.2 for pooled data analysis of TN GT 6 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

Additional Analyses Conducted on the Individual Trial

The table below presents pertinent analysis of SVR12 by baseline NS5A polymorphisms in GT 1 infected subjects. This analysis excludes subjects who failed treatment due to reasons other than virologic failure because baseline NS5A polymorphisms would not impact failure for “other” reasons. Overall five GT 1a and one GT 1b infected subject experienced virologic failure based on SVR12 analysis. Please refer to Dr. Komatsu’s virology review for additional details and analyses.

Table 10. C-EDGE COINFECTION SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms

	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
SVR12	133/138 (96%)	42/43 (98%)	130/134 (97%)	3/4 (75%)	37/38 (97%)	5/5 (100%)	125/128 (98%)	8/10 (80%)	36/37 (97%)	6/6 (100%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, Y93C/H/N polymorphism

B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S polymorphism

Source: FDA Virology Reviewer Dr. Takashi Komatsu

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Reviewer Comment: For GT 1a, a relatively low number of subjects had baseline NS5A polymorphisms and the SVR12 rate with or without polymorphisms was relatively high at 96%. Unlike in C-EDGE TN, baseline NS5A polymorphisms do not explain the majority of virologic failures; only 2/5 virologic failures may have been due to baseline polymorphisms. Similar to C-EDGE TN, the impact of baseline polymorphisms in GT 1b infected subjects was minimal because only one GT 1b infected subject experienced virologic failure.

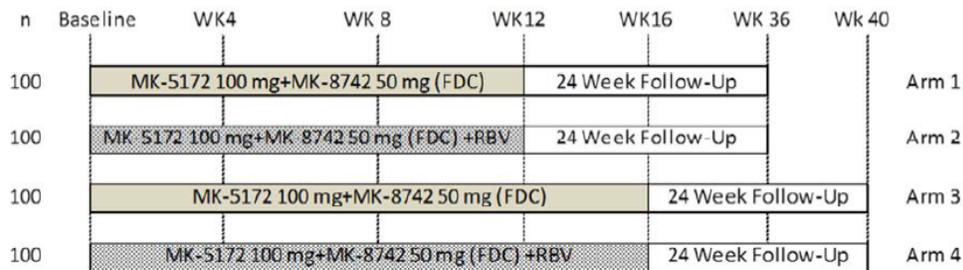
6.3. C-EDGE TE (P068)

6.3.1. Study Design

Overview and Objective

C-EDGE TE (P068) was a Phase 3 randomized (1:1:1:1), parallel-group, open-label clinical trial. The regimens compared were GZR/EBR +/- RBV for 12 weeks and GZR/EBR +/- RBV for 16 weeks. The patient population consisted of TE cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 who failed prior treatment with PR. Prior relapsers were capped at approximately 20%. HCV monoinfected and HIV coinfecting subjects were included. See Section 6.1.1 for methods to determine the presence or absence of cirrhosis.

Figure 3. C-EDGE TE Trial Design



FDC=Fixed Dose Combination

Source: P068v01 CSR

The trial began on June 11, 2014, and was completed on March 13, 2015. The trial was conducted at 65 centers across Australia (3), Canada (5), Denmark (2), Finland (1), France (3), Israel (5), Korea (3), Malaysia (3), Netherlands (3), New Zealand (3), Poland (3), Puerto Rico (2), Spain (3), Taiwan (1), and the U.S. (25).

Study Endpoints

The primary efficacy and safety endpoints were the same as for C-EDGE TN described in Section

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

6.2.1.

Statistical Analysis Plan

The Statistical Analysis Plan is similar to that of C-EDGE COINFECTION except the pre-specified SVR12 reference rate was 58% (derived from simeprevir Phase 2 registrational trial in TE subjects after adjusting for the expected proportion of subjects that were null or partial responders in this study and an expected improved safety profile related to an IFN-free regimen).

6.3.2. Study Results

Patient Disposition

Patient disposition across all four treatment groups is displayed below.

Table 11. C-EDGE TE Patient Disposition

	GZR/EBR	GZR/EBR+ RBV	GZR/EBR	GZR/EBR + RBV	Total
Treatment Duration	12 Weeks		16 Weeks		
Screened not randomized					62
Randomized	105	104	105	106	420
Received Assigned Treatment (FAS)	105 (100)	104 (100)	105 (100)	106 (100)	420
Premature Trial D/C	3 (2.9)	1 (1.0)	1 (1.0)	1 (0.9)	6 (1.4)
Death	1 (1.0)	0	0	0	1 (0.2)
LTF	0	0	0	1 (0.9)	1 (0.2)
Non-compliance	0	0	1 (1.0)	0	1 (0.2)
Subject withdrawal	2 (1.9)	1 (1.0)	0	0	3 (0.7)
Premature Treatment D/C	1 (1.0)	1 (1.0)	4 (3.8)	5 (4.7)	11 (2.6)
Adverse Event	1 (1.0)	1 (1.0)	0	4 (3.8)	6 (1.4)
Lack of Efficacy	0	0	3 (2.9)	0	3 (0.7)
Non-Compliance	0	0	1 (1.)	0	1 (0.2)
Physician Decision	0	0	0	1 (0.9)	1 (0.2)

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Table of Demographic Characteristics

The table below describes the baseline demographics and characteristics for subjects in the FAS.

Clinical Review
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 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 12. C-EDGE TE Subject Demographics and Characteristics

	GZR/EBR (N=105)	GZR/EBR+ RBV (N=104)	GZR/EBR (N=105)	GZR/EBR + RBV (N=106)
Treatment Duration	12 Weeks		16 Weeks	
Characteristic (%)				
Gender (Male)	66 (62.9)	72 (69.2)	69 (65.7)	64 (60.4)
Age (years)				
Mean (+/-se)	55.7 (1.0)	55.5 (0.8)	54.9 (1.0)	55.0 (0.9)
Range	25-76	23-75	31-73	19-77
% ≥ 65 years	16.2	11.5	15.2	11.3
Race				
White	66 (62.9)	70 (67.3)	72 (68.6)	78 (73.6)
African American/Black	23 (21.9)	24 (23.1)	9 (8.6)	15 (14.2)
Asian	15 (14.3)	9 (8.6)	22 (21.0)	10 (9.4)
Other	1 (1.0)	1 (1.0)	2 (1.9)	3 (2.8)
Baseline HCV RNA Log₁₀ (IU/mL)				
Mean (+/-SD)	6.3 (0.5)	6.3 (0.5)	6.3 (0.5)	6.2 (0.6)
Median	6.3	6.3	6.4	6.2
Range	4.3, 7.5	5.0, 7.4	4.9, 7.5	3.7, 7.4
Baseline HCV RNA (IU/mL)				
≤ 800,000	24 (22.9)	22 (21.2)	19 (18.1)	28 (26.4)
> 800,000	81 (77.1)	82 (78.8)	86 (81.9)	78 (73.6)
HCV Genotype				
1a	61 (58.1)	60 (57.7)	48 (45.7)	58 (54.7)
1b	34 (32.4)	29 (27.9)	48 (45.7)	36 (34.0)
1 other	1 (1.0)	0	0	2 (1.9)
4	9 (8.6)	15 (14.4)	5 (4.8)	8 (7.5)
6	0	0	4 (3.8)	2 (1.9)
Prior HCV Treatment				
P/R Null Responder	49 (46.7)	44 (42.3)	46 (43.8)	43 (40.6)
P/R Partial Responder	21 (20.0)	22 (21.2)	21 (20.0)	23 (21.7)
P/R Relapser	35 (33.3)	38 (36.5)	38 (36.2)	40 (37.7)
Hepatic Stage				
Non-Cirrhotic	68 (64.8)	69 (66.3)	67 (63.8)	69 (65.1)
Cirrhotic	37 (35.2)	35 (33.6)	38 (36.2)	37 (34.9)
Fibrosis Stage				
F0-F2	49 (46.7)	55 (52.9)	55 (52.4)	56 (52.8)
F3	19 (18.1)	14 (13.5)	12 (11.4)	13 (12.3)
F4	37 (35.3)	35 (33.7)	38 (36.2)	37 (34.9)
Fibroscan® Hepatitis Score (kPa)				
Subjects with Data (% total)	50 (47.6)	53 (51.0)	67 (63.8)	51 (48.1)
Mean (SD)	15.2 (11.5)	14.3 (9.5)	14.2 (12.5)	14.5 (11.4)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

	GZR/EBR (N=105)	GZR/EBR+ RBV (N=104)	GZR/EBR (N=105)	GZR/EBR + RBV (N=106)
Treatment Duration	12 Weeks		16 Weeks	
Characteristic (%)				
Median	11.7	10.2	9.1	10.4
Range	2.9, 53.3	4.9, 41	4.3, 67.8	3.8, 54.2
HIV Status				
Positive	6 (5.7)	5 (4.8)	6 (5.7)	5 (4.7)
Negative	99 (94.2)	99 (92.2)	99 (94.3)	101 (95.2)
Region				
US	54 (51.4)	52 (50.0)	42 (40.0)	47 (44.3)
Europe	15 (14.3)	30 (28.8)	27 (25.7)	25 (23.6)
Asia Pacific	20 (19.0)	12 (11.5)	21 (20.0)	18 (17.0)
Canada	10 (9.5)	4 (3.8)	10 (9.5)	9 (8.5)
Middle East	6 (5.7)	6 (5.8)	5 (4.8)	7 (6.6)

^Missing: GZR/EBR+RBV (12 weeks) n=2; GZR/EBR (12 weeks) n=1

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Reviewer Comment: There was an imbalance across groups with respect to HCV GT and race. HCV GT imbalance may impact overall SVR rates in each treatment group; therefore, subgroup analysis by HCV GT may be more useful and is available below. Asian race is associated with higher GZR exposures, which may impact safety (see Section 8.5.1).

Efficacy Results - Primary Endpoint

SVR12 results overall and by subgroup are displayed in the tables below.

Table 13. C-EDGE TE Primary Efficacy Results

	GZR/EBR (N=105)	GZR/EBR+ RBV (N=104)	GZR/EBR (N=105)	GZR/EBR + RBV (N=106)
Treatment Duration	12 Weeks		16 Weeks	
SVR Achieved (%)	97 (92.4)	98 (94.2)	97 (92.4)	103 (97.2)
95% CI^	85.5, 96.7	87.9, 97.9	85.5, 96.7	92.0, 99.4
SVR Not Achieved	8 (7.6)	6 (5.8)	8 (7.6)	3 (2.8)
Non-virologic failure	2 (1.9)	0 (0.0)	1 (1.0)	3 (2.8)
LTF/Missing Value	0	0	1	2
AE Discontinuation^	1 (1.0)	0	0	1 (0.9)
Early Termination**	1 (1.0)	0	0	0
Virologic failure	6 (5.7)	6 (5.8)	7 (6.7)	0 (0.0)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

<i>Relapse</i>	6	6	4	0
<i>1a</i>	5	4	3	0
<i>1b</i>	0	1	1	0
<i>4</i>	1	1	0	0
<i>Breakthrough</i>	0	0	1	0
<i>Rebound</i>	0	0	2	0

^Clopper-Pearson exact method

*One-sided Exact test, alpha=0.025 (two-sided) based on test for true proportion=0.58.

**Physician decision to remove subject from treatment

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Reviewer Comment: The overall SVR12 rate of 92-97% across all arms far exceeds the pre-specified reference rate of 58%. Longer treatment duration (16w) and addition of RBV together improved efficacy and minimized the risk of virologic failure. The 16w/RBV regimen achieved the highest SVR rate of 97% and is within the efficacy range of more recently approved treatments for GT 1 infected subjects. Furthermore, there were no virologic failures in the 16w/RBV arm, whereas 6-7% of subjects receiving any of the other three regimens (12w, 12w/RBV, and 16w) experienced virologic failure, mainly relapse. The primary analysis of this trial supports efficacy of GZR/EBR (optimal duration 16 weeks with the addition of RBV) in PR-experienced patients. However, removal of GT 1 infected subjects with baseline NS5A resistance associated polymorphisms substantially increases efficacy of the 12w (no RBV) arm based on post-hoc analysis (further discussion below).

Table 14. C-EDGE TE SVR12 Subgroup Analysis

% (95% CI)	GZR/EBR (N=105)	GZR/EBR+ RBV (N=104)	GZR/EBR (N=105)	GZR/EBR + RBV (N=106)
Treatment Duration	12 Weeks		16 Weeks	
SVR12				
Baseline HCV RNA				
≤ 800,000 IU/mL	95.8 (78.9, 99.9)	95.5 (77.2, 99.9)	100.0 (82.4, 100.0)	100.0 (87.7, 100.0)
> 800,000 IU/mL	91.4 (83.0, 96.5)	93.9 (86.3, 98.0)	90.7 (82.5, 95.9)	96.2 (89.2, 99.2)
HCV genotype**				
1a	90.2 (79.8, 96.3)	93.3 (83.8, 98.2)	93.8 (82.8, 98.7)	94.8 (85.6, 98.9)
1b	100.0 (89.7, 100.0)	96.6 (82.2, 99.9)	95.8 (85.8, 99.5)	100.0 (90.3, 100.0)
4	77.8 (40.0, 97.2)	93.3 (68.1, 99.8)	60.0 (14.7, 94.7)	100.0 (63.1, 100.0)
(b) (4)				
Cirrhosis				
Yes	89.2 (74.6, 97.0)	88.6 (73.3, 96.8)	92.1 (78.6, 98.3)	100.0 (90.5, 100.0)
No	94.1 (85.6, 98.4)	97.1 (89.9, 99.7)	92.5 (83.4, 97.5)	95.7 (87.8, 99.1)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

% (95% CI)	GZR/EBR (N=105)	GZR/EBR+ RBV (N=104)	GZR/EBR (N=105)	GZR/EBR + RBV (N=106)
Treatment Duration	12 Weeks		16 Weeks	
SVR12				
Prior HCV trt history				
P/R Null Responder	91.8 (80.4, 97.7)	88.6 (75.4, 96.2)	91.3 (79.2, 97.6)	95.4 (84.2, 99.4)
P/R Partial Responder	81.0 (58.1, 94.6)	95.5 (77.2, 99.9)	95.2 (76.2, 99.9)	95.7 (78.1, 99.9)
P/R Relapser	100.0 (90.0, 100.0)	100.0 (90.8, 100.0)	92.1 (78.6, 98.3)	100.0 (91.2, 100.0)

^other race omitted due to small counts

**GT 1 other omitted due to small counts

Source: FDA Statistical Reviewer, Dr. LaRee Tracy

Reviewer Comment:

A higher SVR12 rate in subjects with baseline HCV RNA <800,000 IU/mL (compared to HCV RNA >800,000 IU/mL) and in subjects infected with GT 1b (compared to GT 1a) is consistent with previous trials including C-EDGE TN.

PR-experienced subjects with cirrhosis (compared to without cirrhosis) had similar SVR12 rates with longer treatment duration (16w and 16w/RBV) but numerically lower SVR12 rates with shorter duration (12w and 12w/RBV).

With respect to prior treatment history, there was a high SVR12 rate in the 16w/RBV arm for subjects regardless of the type of PR failure.

The number of subjects with GT 4 infection is relatively small and imbalanced across arms, but the addition of RBV appears to increase efficacy in this subpopulation.

There were only six GT 6 infected subjects, none of whom received either of the 12 week regimens. (b) (4)

Additional Analyses Conducted on the Individual Trial

The table below presents pertinent analysis of SVR12 by baseline NS5A polymorphisms in GT 1 infected subjects. This analysis excludes subjects who failed treatment due to reasons other than virologic failure because baseline NS5A polymorphisms would not impact failure for “other” reasons. Overall across all four arms, ten GT1a and two GT1b infected subjects experienced virologic failure based on SVR12 analysis. Please refer to Dr. Komatsu’s virology review for additional details and analyses.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 15. C-EDGE TE SVR12 in GT 1 Infected Subjects with and without Baseline NS5A Polymorphisms

GZR/EBR Regimen	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
12w	54/59 (92%)	34/34 (100%)	52/53 (99%)	2/6 (33%)	32/32 (100%)	2/2 (100%)	48/49 (98%)	6/10 (60%)	32/32 (100%)	2/2 (100%)
12w/RBV	20/22 (91%)	10/11 (91%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)
16w	45/48 (94%)	46/47 (98%)	43/43 (100%)	2/5 (40%)	39/39 (100%)	7/8 (88%)	42/42 (100%)	3/6 (50%)	38/38 (100%)	8/9 (89%)
16w/RBV	55/55 (100%)	36/36 (100%)	51/51 (100%)	4/4 (100%)	33/33 (100%)	3/3 (100%)	49/49 (100%)	6/6 (100%)	33/33 (100%)	3/3 (100%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, Y93C/H/N polymorphism
 B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S polymorphism
 Source: FDA Virology Reviewer Dr. Takashi Komatsu

Reviewer Comment: Longer treatment duration and addition of RBV (16w/RBV arm) together appear to overcome the effect of baseline NS5A polymorphisms as the SVR12 rate was 100% (i.e., no virologic failures). For the other three treatment arms, there was a trend toward reduced efficacy in GT 1a infected subjects with baseline NS5A polymorphisms. Furthermore, the presence of baseline NS5A polymorphisms appears to explain the majority of virologic failures. For GT 1a, SVR12 rates in the absence of baseline NS5A polymorphisms in the 12w arm (98-99%) are higher than the SVR12 rate with or without polymorphisms in the 12w arm (92%) and are similar to the SVR12 rates in the 16w/RBV arm (100%); these SVR rates are presented for the purpose of comparison solely based on baseline NS5A polymorphisms as they do not account for subjects who failed for reasons other than virologic failure. The impact of polymorphisms in GT 1b infected subjects was minimal because only two GT 1b infected subjects experienced virologic failure, and neither occurred in the 12w (no RBV) arm.

6.4. C-SALVAGE (P048)

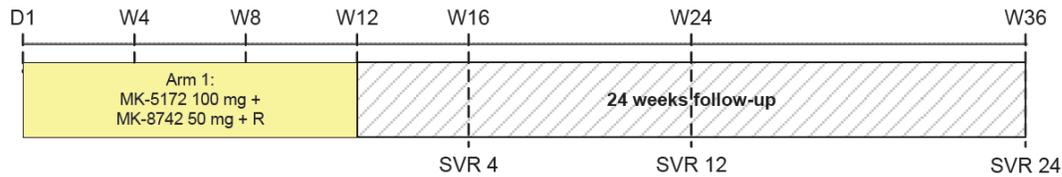
6.4.1. Study Design

Overview

C-SALVAGE was an open-label, single-arm Phase 2 clinical trial. TE cirrhotic and non-cirrhotic subjects with HCV GT 1 who failed prior treatment with a DAA (boceprevir, telaprevir, simeprevir, or sofosbuvir) + PR were eligible. All enrolled subjects received GZR + EBR + RBV for 12 weeks. Subjects must have received at least 4 weeks of prior DAA treatment, and approximately 80% must have met virologic failure criteria with or without RAVs on the prior regimen.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Figure 4. C-SALVAGE Trial Design



Source: P048v01 CSR

The trial began on May 23, 2014, and was completed on January 28, 2015. The trial was conducted at 14 centers across Austria (2), Israel (5), Spain (3), and the U.S. (4).

Study Endpoints

The primary efficacy and safety endpoints were the same as for C-EDGE TN described in Section 6.2.1.

Statistical Analysis Plan

There were no formal hypotheses for this trial as it was intended to be a hypothesis generating trial.

6.4.2. **Study Results**

Patient Disposition

Of the 97 subjects screened, 79 were enrolled, and all subjects received at least one dose of therapy. One subject prematurely discontinued treatment due to an AE. One subject prematurely discontinued the trial after experiencing relapse at FU4.

Table of Demographic Characteristics

The following table displays baseline demographics and characteristics. Of note, the majority of prior failures occurred with telaprevir/PR or boceprevir/PR and none with sofosbuvir/PR.

Table 16. C-SALVAGE Subject Demographics and Characteristics

Characteristic	N (%)
Gender (Male)	59 (60.8)
Age (years)	
Mean (+/-se)	54.4 (1.1)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Characteristic	N (%)
Range	23, 75
Race	
White	77 (97.5)
African American	2 (2.5)
Region	
US	18 (22.8)
Non-US	61 (77.2)
Baseline HCV RNA Log₁₀ (IU/mL)**	
Mean (+/-SD)	6.04 (0.44)
Median	6.03
<=800,000 IU/mL	27 (34.2)
>800,000 IU/mL	52 (65.8)
HCV Genotype	
1a	30 (38.0)
1b	49 (62.0)
Prior DAA	
Boceprevir	28 (35.4)
Telaprevir	43 (54.4)
Simeprevir	8 (10.1)
Sofosbuvir	0 (0)
Prior Mode of Virologic Failure	
PR + DAA Relapser	26 (32.9)
PR + DAA Nonresponder	16 (20.3)
PR + DAA Breakthrough	8 (10.1)
PR Tail Breakthrough	16 (20.3)
PR + DAA Non-virologic Failure	13 (16.5)
Fibrosis Stage	
Cirrhotic	34 (43.0)
Non-Cirrhotic	45 (57.0)

Sources: FDA Statistical Reviewer, Dr. LaRee Tracy, and p048v01 CSR

Efficacy Results - Primary Endpoint

Overall, 76/79 subjects (96.2%; 95% CI 89.3, 99.2) achieved SVR12. All three failures were due to relapse. One relapser had received two prior DAA-containing regimens, one with telaprevir and one with faldaprevir, which was a violation of entry criteria. In GT 1a and 1b infected subjects, 93% and 98% achieved SVR12, respectively.

Additional Analyses Conducted on the Individual Trial

Analysis of SVR12 by baseline NS5A polymorphisms in GT 1 infected subjects is summarized below. This analysis excludes subjects who failed treatment due to reasons other than virologic

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

failure because baseline NS5A polymorphisms would not impact failure for “other” reasons. Overall, two GT 1a infected subjects and one GT 1b infected subject experienced virologic failure based on SVR12 analysis. Please refer to Dr. Komatsu’s virology review for additional details and analyses.

GT1a: Using List A, 28/29 (97%) vs. 0/1 (0%) subjects without and with baseline NS5A polymorphisms, respectively, achieved SVR12. Using List B, 25/26 (96%) vs. 3/4 (75%) subjects without and with NS5A polymorphisms, respectively, achieved SVR12.

GT1b: Using List A, 45/45 (100%) vs. 3/4 (75%) subjects without and with baseline NS5A polymorphisms, respectively, achieved SVR12. Using List B, 44/44 (100%) vs. 4/5 (80%) subjects without and with NS5A polymorphisms, respectively, achieved SVR12.

Source: Adapted from Dr. Komatsu’s virology review. Refer to Table 8 footnote for Lists A and B.

Reviewer Comment: There were too few virologic failures in this trial to determine the impact of baseline NS5A polymorphisms. Two of the three virologic failures had baseline NS5A polymorphisms.

Dr. Komatsu’s virology analysis showed achievement of SVR12 in 4/4 (100%), 7/8 (88%), and 2/2 (100%) GT 1a infected subjects with NS3 V36A/M, R155K, and V36M+R155K substitution at baseline, respectively. These substitutions were the most common treatment-emergent substitutions for boceprevir, simeprevir, and telaprevir failures. There were not enough GT 1b infected subjects with key NS3 baseline resistance substitutions to evaluate the impact of detectable resistance mutations on efficacy.

Reviewer Comment: C-SALVAGE results support an indication for treatment of HCV GT 1a and 1b infection in subjects who previously failed treatment with a PI (boceprevir, telaprevir, or simeprevir) plus PR. Although the number of GT 1a infected subjects with baseline NS3 resistance substitutions is low, efficacy in this subgroup was high overall (93%, 13/14) and is not expected to differ for GT 1b infection.

^{(b) (4)} However, an indication should not be granted for these populations without efficacy data, particularly in the presence of baseline NS3 resistance substitutions.

6.5. C-SCAPE (P047 Part B)

6.5.1. Study Design

Overview

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

C-SCAPE Part B was a Phase 2 randomized (1:1), open-label clinical trial that assessed the efficacy and safety of GZR + EBR +/- RBV for 12 weeks in TN non-cirrhotic subjects with HCV GT 4, 5, and 6 infection. Note: Part A and Part B Arm 1 are not discussed because these arms enrolled HCV GT 2 infected subjects and therefore not relevant for this NDA.

Study Endpoints

The primary efficacy endpoint was the same as for C-EDGE TN described in Section 6.2.1.

Statistical Analysis Plan

There were no formal statistical hypotheses for this trial as it was a hypothesis generating trial.

6.5.2. Study Results

Patient Disposition

In the GZR/EBR arm, 17/19 subjects completed treatment with one discontinuation due to an AE and one discontinuation due to lack of efficacy. All 19 subjects in the GZR/EBR + RBV arm completed treatment and follow-up.

Baseline Demographics and Characteristics

Baseline demographics and characteristics were similar to those described in Phase 3 trials, except for factors outlined in the study overview for this trial.

Efficacy Results - Primary Endpoint

In HCV GT 4 infected subjects treated with and without RBV, 10/10 (100%) and 9/10 (90%) subjects, respectively, achieved SVR12. One subject did not achieve SVR12 due to lost to follow-up after FW8 at which time point the HCV RNA result was TND.

Reviewer Comment: This trial enrolled very few numbers of GT 4 infected subjects, but the results were favorable and supported selection of GZR/EBR without RBV as the regimen to evaluate in Phase 3 trials in TN subjects. See Section 7.1.2 for pooled data analysis of TN GT 4 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

(b) (4)

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Reviewer Comment: [REDACTED] (b) (4)
See Section 7.1.2 for pooled data analysis of TN GT 6 infected subjects from C-SCAPE, C-EDGE TN, and C-EDGE COINFECTION.

Virologic failure occurred in 3/4 (75%) HCV GT5-infected subjects treated with GZR/EBR. As a result, protocol amendments to C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE subsequently excluded GT 5-infected subjects. [REDACTED] (b) (4)

One subject in each arm (GZR/EBR with or without RBV) was discovered to have GT 1 infection post randomization and both achieved SVR12.

6.6. C-SURFER (P052)

6.6.1. Study Design

Overview

Protocol 052 is a randomized, parallel-group, multi-site, multi-national, placebo-controlled trial in Stage 4 or 5 CKD subjects infected with GT 1 HCV, with or without prior treatment experience and with or without cirrhosis. Definitions of CKD and ESRD were based on the National Kidney Foundation (United States): Stage 4 is defined as estimated glomerular filtration rate (eGFR) of 15-29 mL/min/1.73 m²; Stage 5 (ESRD) is defined as eGFR < 15 ml/min/1.73m² or need for renal replacement therapy. Enrollment of non-dialysis subjects was capped at 20% in order to enrich the study population with ESRD subjects, for whom data are most needed.

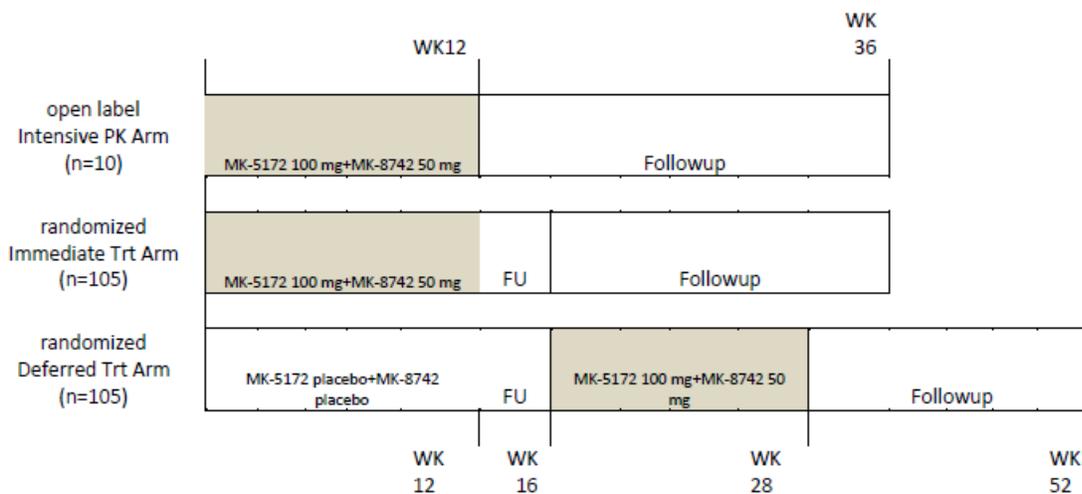
To be eligible for trial participation, subjects had to be ≥ 18 years of age with documented chronic (> 6months) GT1 HCV infection and Stage 4 or 5 CKD. Both TN and TE subjects were eligible, regardless of prior treatment outcome (null responder, partial responder, and relapser). Subjects with decompensated liver disease and subjects co-infected with HIV or Hepatitis B virus were excluded, as were subjects receiving peritoneal dialysis and subjects with new or worsening cardiovascular or cerebrovascular disease in the 3 months prior to study enrollment.

Eligible subjects who provided written informed consent were randomized 1:1 to either the immediate treatment group (ITG) or deferred treatment group (DTG). Subjects in the ITG received GZR 100 mg/ EBR 50 mg once daily for 12 weeks with 24 weeks follow-up once dosing was complete. Subjects in the DTG received placebo during the initial 12 week treatment period; after a 4 week unblinding period, these subjects received GZR 100 mg/EBR 50mg once daily for 12 weeks followed by an additional 24 weeks of follow-up. Randomization was stratified according to baseline dialysis and diabetes status.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

In addition, a small group of subjects were enrolled in an open-label intensive PK arm and received the same treatment as the ITG subjects. Half of these subjects were dialysis patients and the other half were non-dialysis patients. Figure 5 provides a graphical overview of the study design.

Figure 5. C-SURFER Trial Design



Source: Figure 9-1 of Applicant's P052 Clinical Study Report

Study Endpoints

The primary efficacy endpoint was SVR12, the same as for C-EDGE TN described in Section 6.2.1.

Statistical Analysis Plan

The primary hypothesis was that subjects treated with GZR + EBR for 12 weeks would achieve an SVR12 rate higher than the historical SVR12 rate of 45%, which was based on studies of HCV-infected subjects with Stage 3-5 CKD treated with interferon monotherapy and non-CKD subjects treated with PR. This hypothesis was evaluated for subjects in the ITG and intensive PK group combined, and it was tested at a two-sided significance level (type-I error) of 0.05. A 95% confidence interval (CI) was also constructed for the SVR12 rate. The trial was designed to enroll 105 patients each in the ITG and DTG groups along with 10 additional patients enrolled in an intensive PK/ITG cohort. Therefore, given a sample size of n=115, the trial was expected to have at least 95% power to demonstrate that the SVR12 rate of GZR/EBR is higher than the reference value of 45%, with an overall 1-sided 0.025 alpha level, and a 10% missing SVR12 rate due to death or early study discontinuation.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

The primary efficacy analysis population used for FDA analyses was the Full Analysis set (FAS), which included all subjects in the ITG and intensive PK group who received at least one dose of study medication. The primary analysis set used by the Applicant was the modified FAS (mFAS), which includes all members of the FAS but excluded subjects with missing data due to death or discontinuation for reasons unrelated to study drug or reasons other than liver disease, study drug, or response to HCV treatment. The Applicant elected to use the mFAS rather than the FAS because patients with advanced CKD 4/5, especially those with hemodialysis-dependent CKD5, have a high incidence of major cardiovascular events that may lead to death or to withdrawal from the study. The applicant believed that removal of this potential confounder of HCV efficacy would allow for a more fair comparison to non-CKD-patients in other trials in which such high cardiovascular mortality was not expected.

6.6.2. Study Results

Subject Disposition

A total of 328 subjects were screened, of which 237 subjects were randomized to one of the three arms: ITG, DTG or intensive PK. All subjects who were assigned to a treatment group received at least one dose of study medication. Subject disposition is summarized in Table 17.

Table 17. C-SURFER Subject Disposition

	ITG	DTG	Intensive PK/ITG
Randomized	112	114	11
Premature Trial Discontinuation (all randomized)	7 (6.3)	11 (9.6)	0
Adverse Event	0	4 (3.5)	0
Death	1 (0.9)	4 (3.5)	0
LTF	2 (1.8)	1 (0.9)	0
Non-compliance	1 (0.9)	0	0
Physician decision	1 (0.9)	0	0
Subject withdrawal	1 (0.9)	2 (1.8)	0
Screen Failure	1 (0.9)	0	0
Received Assigned Treatment (FAS)	111 (100)	113 (99.1)	11 (100)
Premature Treatment Discontinuation	5 (4.5)	6 (5.3)	0
Adverse Event	0	5 (4.4)	0
Death	1 (0.9)	0	0
Kidney Transplant	1 (0.9)	0	0
LTF	1 (0.9)	1 (0.9)	0
Non-Compliant	1 (0.9)	0	0
Subject Withdrawal	1 (0.9)	0	0
Modified Full Analysis Set (mFAS) ^	105 (93.8)	113 (99.1)	11 (100)

Reasons given for not receiving treatment: ITG (n=1)=screening failure; DTG (n=1): AE

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

^Reasons listed for exclusion from the mFAS: subject withdrawal due to transportation issues, LTF unrelated to study medication (n=2), death due to cardiorespiratory arrest, non-compliance due to hospitalization of acute appendicitis surgery, and withdrawn by investigator due to violent behavior
 Source: Biometrics Review by Dr. LaRee Tracy

Reviewer Comment: Despite the Applicant’s concerns for high rates of premature discontinuation due to cardiovascular events, the vast majority of subjects were able to complete this initial phase of the trial. Upon review of the outcomes of subjects excluded in the mFAS (as above), the FDA review team determined that the FAS was the more appropriate choice for efficacy analyses.

Demographic and Baseline Disease Characteristics

C-SURFER was a multinational trial which enrolled subjects across the world in order to gain representation from various racial groups. The trial was conducted at 79 centers in 12 countries: 48 sites in the United States; 5 each in Canada and Israel; 4 in France; 3 each in Lithuania and Spain; 2 each in Australia, Estonia, Korea, Netherlands, and Sweden; and 1 in Argentina. As previously stated, both TE and TN experienced subjects were enrolled; however, given the limited options available to CKD subjects, the majority of subjects were TN. Non-cirrhotic subjects as well as subjects with compensated cirrhosis were eligible, but the majority of subjects were non-cirrhotic. More than 75% of subjects were dialysis-dependent and approximately 25% were also diabetic. Demographic and baseline disease characteristics are summarized in Table 18.

Table 18. C-SURFER Demographic and Baseline Disease Characteristics (FAS)

Characteristic (%)	ITG (n=111)	DTG (n=113)	Intensive PK (n=11)
Gender (Male)	81 (73.0)	80 (70.8)	11 (100)
Age (years)			
Mean (+/-se)	56.5 (0.9)	55.2 (0.9)	58.2 (2.9)
Range	31-76	28-80	41-66
% ≥ 65 years	20 (18.0)	18 (15.9)	2 (18.2)
Race*			
White	55 (49.6)	48 (42.9)	6 (54.6)
African American	50 (45.1)	53 (47.3)	5 (45.4)
Asian	4 (4.5)	9 (8.0)	0
Other	1 (0.9)	2 (1.8)	0
IL28 Genotype			
CC	30 (27.0)	30 (26.6)	2 (18.2)
Non-CC	79 (71.2)	83 (73.4)	9 (81.8)
Missing	2 (1.8)	0	0
Baseline HCV RNA Log10 (IU/mL)**			
Mean (+/-SD)	5.93 (0.76)	5.97 (0.67)	6.04 (0.67)
Median	6.02	6.03	6.24

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Characteristic (%)	ITG (n=111)	DTG (n=113)	Intensive PK (n=11)
HCV Genotype			
1a	53 (47.7)	59 (52.2)	10 (90.9)
1b	58 (52.3)	53 (46.9)	1 (0.9)
1 other	0	1 (0.9)	0
Prior HCV Treatment Naïve (Y)	91 (82.0)	88 (77.9)	10 (90.1)
Hepatic Stage			
Non-Cirrhotic [^]	104 (93.7)	107 (93.9)	11 (100)
Randomization Strata			
Diabetes/on dialysis	29 (26.1)	28 (24.8)	3 (27.3)
Diabetes/not on dialysis	9 (8.1)	8 (7.1)	3 (27.3)
No diabetes/on dialysis	57 (51.4)	59 (52.2)	3 (27.3)
No diabetes/not on dialysis	16 (14.4)	18 (15.9)	2 (18.2)
Diabetes (Y)	38 (34.2)	36 (31.9)	6 (54.5)
On dialysis (Y)	86 (77.5)	87 (77.0)	6 (54.5)
Region			
US	69 (62.2)	73 (64.6)	9 (81.8)
Canada	4 (3.6)	2 (1.8)	0
Europe	25 (22.5)	22 (19.5)	2 (18.2)
Other	13 (11.7)	16 (14.2)	0

*Race missing for one subject in the DTG, **baseline HCV RNA Missing for one DTG subject, ^ Cirrhosis (No) includes Metavir F0 to F2, Metavir F3, and No evidence of cirrhosis by Fibro Test Score. Status missing for one subject in the ITG group
Source: Biometrics review by Dr. LaRee Tracy

Efficacy Results – Primary Endpoint

Of the 122 subjects in the FAS, 115 achieved SVR12 (94%). Among subjects with GT1a HCV, 61/63 achieved SVR12 (97%); among subjects with GT1b HCV, 54/63 achieved SVR12 (86%). The group of 7 seven subjects who did not achieve SVR included 1 relapser (GT1b) and 7 subjects with missing data for reasons unrelated to study treatment, which were discussed in Table 17 (study disposition). The results are summarized in Table 19. SVR12 rates using the mFAS, as proposed by the applicant, are provided for comparison.

Table 19. Proportion of subjects achieving SVR12 in C-SURFER

	SVR12 (FAS) (n=122)	SVR12 (mFAS) (n=116)
SVR Achieved (%)	115 (94.3)	115 (99.1)
<i>95% CI[^]</i>	88.5, 97.7	95.3, 100.0
<i>p-value*</i>	<0.0001	<0.0001
SVR Not Achieved	7 (5.7)	1 (0.9)
Virologic Failure: Relapse	1 (0.8)	1 (0.9)
Non-virologic Failure: Missing data for reasons unrelated to treatment	6 (4.9)	NA

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

^Clopper-Pearson exact method

*One-sided exact test, true $p=0.53$ based on historical estimate

Source: Biometrics review by Dr. LaRee Tracy

The one subject who relapsed was a 59 year old white male with diabetes mellitus, hypertension, and ulcerative colitis. He was infected with GT1b HCV and had failed treatment with PR in the past. He was non-cirrhotic at the time of study entry and his baseline viral load was 7,265,725 IU/mL. The subject quickly achieved viral suppression and had HCV RNA values of TND from treatment week 3 onwards until follow-up week 12, at which time his viral load was 38,625 IU/mL. Repeat testing for confirmation revealed a viral load of 446,776 IU/mL. His ALT and AST were normal until his relapse, at which point both values trended upward: ALT rose from 32 to 74 IU/L and AST rose from 34 to 94 IU/L. Baseline RAVs included NS3 Y56F/Y and NS5A L31M; at relapse, the virus had reverted to wildtype NS3, but maintained L31M and added the Y93H NS5A RAV.

Two additional relapses have been noted thus far among subjects who have completed follow-up through Week 24.

- Subject AN608408 was a 55 year old treatment-naïve, non-cirrhotic white male infected with GT1a HCV. His baseline viral load was 2,272,577 IU/mL but he quickly achieved virologic suppression and was TND from treatment week 3 onwards. At follow-up week 24, his viral load was 1,050,609 IU/mL and relapse was confirmed with repeat HCV RNA. At baseline, this subject had wild-type NS3 virus and NS5A L31L/M, M28M/V, and Q30Q/R RAVs. Resistance testing at the time of failure was notable for NS5A Q30R and L31M RAVs.
- Subject AN607021 was a 60 year old treatment-naïve, non-cirrhotic black female infected with GT1a HCV and baseline viral load of 1,104,634 IU/mL. She was TND at treatment week 1 and remained so until follow-up week 24, at which time she relapsed with a viral load of 742,048 IU/mL. At baseline, the subject had NS3 Q80K and NS5A L31M RAVs; post-baseline sequencing results were not available at the time of NDA submission.

Reviewer Comment: The overall SVR12 rate of 94% (95% CI 89%, 98%) far exceeds the historical rate of 45% and is comparable to rates of efficacy observed in the C-EDGE TN, C-EDGE TE, AND C-EDGE COINFECTION trials. The lack of ribavirin does not seem to compromise efficacy. Hence, the trial results support the efficacy of GZR/EBR for 12 weeks for the treatment of HCV GT 1 in subjects with CKD 4/5.

As will be further discussed in Section 7, presence of key baseline RAVs lowers the probability of viral eradication. Hence, alternative treatment options are advised for subjects harboring these key RAVs at baseline. The effect of baseline polymorphisms is again evident in C-SURFER, in which each of the 3 subjects who relapsed had at least one of the key RAVs at baseline. Unfortunately, alternative treatment options are unavailable (at the time this review was

finalized) for dialysis-dependent subjects. Based on the current data, the optimal treatment strategy for this population remains unclear. There is some suggestion from C-EDGE TE that prolonging the total treatment course to 16 weeks and adding ribavirin may improve outcomes. However, given the small number of subjects in this cohort, these trends must be interpreted with caution. In addition, ribavirin has an unacceptable safety profile in the CKD 5 population and longer treatment courses have not been formally studied. The safety implications of prolonged treatment will be explored further in Section 8.

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 were assessed. The results are summarized in Table 20.

Table 20. C-SURFER SVR12 Subgroup Analysis

	Immediate + Intensive PK GZR/EBR Arms (n=122)	
SVR12	% (n/N)	95% CI**
Age (years)		
< 65	95.0 (95/100)	88.7, 98.4
≥ 65	90.9 (20/22)	70.8, 98.9
Gender		
Male	95.6 (88/92)	89.2, 98.8
Female	90.0 (27/30)	73.5, 97.9
Race		
Caucasian	95.1 (58/61)	86.3, 99.0
Non-Caucasian*	93.4 (57/61)	84.1, 98.2
Region		
US	93.6 (73/78)	85.7, 97.9
Non-US*	95.5 (42/44)	84.5, 99.4
Baseline HCV RNA (IU/mL)		
≤ 800,000	94.3 (50/53)	84.3, 98.8
> 800,000	94.2 (65/69)	85.8, 98.4
HCV genotype		
1a	96.8 (61/63)	89.0, 99.6
1b	91.5 (54/59)	81.3, 97.2
IL28 Genotype		
CC	87.5 (28/32)	71.0, 96.5
TC	98.2 (53/54)	90.1, 100.0

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

SVR12	Immediate + Intensive PK GZR/EBR Arms (n=122)	
	% (n/N)	95% CI**
TT	97.1 (33/34)	84.7, 99.9
Cirrhosis		
Yes	85.7 (6/7)	42.1, 99.6
No	94.8 (109/115)	89.0, 98.1
Prior HCV treatment history		
Naive	95.1 (96/101)	88.8, 98.4
P/R Experienced	90.5 (19/21)	69.6, 98.8
Baseline Diabetes		
Yes	90.9 (40/44)	78.3, 97.5
No	96.2 (75/78)	89.2, 99.2
Baseline CKD Stage		
Stage 4	100 (22/22)	84.6, 100.0
Stage 5	93.0 (93/100)	86.1, 97.1
Baseline Dialysis		
Yes	93.5 (86/92)	86.3, 97.6
No	96.7 (29/30)	82.8, 99.9

^Include n=11 subjects randomized to the intensive PK ITG group

*n=55African-American, n=5 Asian, n=1 other

**Clopper-Pearson exact method

Source: Biometrics review by Dr. LaRee Tracy

Reviewer Comment: Response to treatment was relatively uniform for each of the demographic and disease characteristics analyzed. As seen in the other pivotal efficacy studies, traditionally hard-to-treat groups, such as TE subjects and subjects with cirrhosis, had high rates of efficacy. However, these results should be interpreted with caution given the small number of TE and cirrhotic subjects.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Treatment-Naïve Trials

Overall SVR12 rates were 95% in both C-EDGE TN and C-EDGE COINFECTION, supporting efficacy of GZR/EBR (12 weeks duration without RBV) in TN HCV GT 1 or 4 infected subjects

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

with or without HIV coinfection. The most common reason for failure was relapse, which may be minimized through baseline NS5A polymorphism screening for some patient populations (see Section 7.1.2). Reducing the risk of virologic failure, if possible, would not only improve the chance of SVR12 but would also minimize the consequence of developing NS3/4A and NS5A resistance.

(b) (4)

Table 21. C-EDGE TN, C-EDGE COINFECTION, and C-SCAPE Primary SVR12 Results

Trial	C-EDGE TN	C-EDGE COINFECTION	C-SCAPE
Regimen	GZR/EBR 12 Weeks N=316	GZR/EBR 12 Weeks N=218	EBR + GZR 12 Weeks N=14
Overall SVR	95% (299/316)	95% (207/218)	86% (12/14)
Outcome for subjects without SVR			
Breakthrough	<1% (1/316)	0% (0/218)	7% (1/14)
Relapse	4% (12/316)	3% (7/218)	0% (0/14)
Other [†]	1% (4/316)	2% (4/218)	7% (1/14)

[†]Other includes subjects who discontinued due to AE, lost to follow-up, or subject withdrawal.

Treatment-Experienced Trials

One Phase 3 trial (C-EDGE TE) evaluated four treatment regimens, GZR/EBR +/- RBV for 12 or 16 weeks, in PR-experienced subjects, and one Phase 2 trial (C-SALVAGE) evaluated one regimen, GZR/EBR + RBV for 12 weeks, in PI/PR-experienced subjects. The latter trial included subjects who previously failed boceprevir, simeprevir, or telaprevir. Because only one trial evaluated each TE population, and both TE populations are distinct from one another from the standpoint of potential baseline drug resistance, overall results were not integrated or compared to one another. However, SVR12 results in both respective trials support indications for PR-experienced and PI/PR-experienced GT 1 or 4 infected subjects.

(b) (4)

7.1.2. Subpopulations

Genotype 1

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

The SVR12 rates in TN GT 1 infected subjects with 12w of GZR/EBR were 95% in both C-EDGE TN and C-EDGE COINFECTION. In both trials, GT 1b infected subjects had higher SVR12 rates (96-98%) compared to GT 1a infected subjects (92-94%).

In PR-experienced GT 1a infected subjects in C-EDGE TE, SVR12 rates increased from 90% to 95% with increased treatment duration of GZR/EBR from 12w to 16w and the addition of RBV. In contrast, SVR12 was 100% in PR-experienced GT 1b infected subjects receiving either 12w of GZR/EBR or 16w of GZR/EBR + RBV; SVR12 was also high (96-97%) for regimens in between. The table below displays the pooled analysis of SVR12 by baseline NS5A polymorphisms for TN GT 1a and 1b infected subjects in Phase 2 and Phase 3 trials who received at least 12w of GZR/EBR; as previously stated, this analysis excludes subjects who failed for reasons other than virologic failure. The rationale for pooling is to increase the sample size because the number of virologic failures per individual trial is relatively small. The most compelling data in the table are highlighted.

Table 22. SVR12 by Baseline NS5A Polymorphisms in TN and PR-Experienced GT 1 Infected Subjects: Pooled Analysis

SVR12 (%)	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
Pooled Treatment-Naïve Subjects from C-EDGE TN, C-EDGE COINFECTION, C-SURFER, and C-WORTHY										
GZR/EBR 12w	397/416 (95%)	241/243 (99%)	383/393 (97%)	14/23 (61%)	211/212 (99%)	30/31 (97%)	365/372 (99%)	32/44 (73%)	207/208 (100%)	34/35 (97%)
Pooled PR-Experienced Subjects from C-EDGE TE, C-SURFER, and C-WORTHY										
GZR/EBR 12w	83/90 (92%)	54/56 (96%)	81/83 (98%)	2/7 (29%)	48/48 (100%)	6/8 (75%)	77/79 (98%)	6/11 (55%)	48/48 (100%)	6/8 (75%)
GZR/EBR+RBV 12w	72/76 (95%)	42/43 (98%)	68/69 (99%)	4/7 (57%)	37/37 (100%)	5/6 (83%)	65/66 (98%)	7/10 (70%)	37/37 (100%)	5/6 (83%)
GZR/EBR 16w or 18w	61/65 (94%)	61/62 (98%)	58/58 (100%)	3/7 (43%)	53/53 (100%)	8/9 (89%)	57/57 (100%)	4/8 (50%)	52/52 (100%)	9/10 (90%)
GZR/EBR+RBV 16w or 18w	74/74 (100%)	50/50 (100%)	70/70 (100%)	4/4 (100%)	42/42 (100%)	8/8 (100%)	68/68 (100%)	6/6 (100%)	42/42 (100%)	8/8 (100%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, Y93C/H/N polymorphism

B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S polymorphism

Source: FDA Virology Reviewer Dr. Takashi Komatsu (adapted)

Reviewer Comment: This analysis indicates screening for baseline NS5A polymorphisms would be greatly beneficial in TN GT 1a infected subjects by decreasing the risk of virologic failure. The difference in SVR12 rates in TN GT 1a infected subjects with and without baseline NS5A polymorphisms, using List A or B, is compelling (26-36%). Non-virologic failures, not accounted for in the table, will decrease SVR12 rates but are not expected to differ in patients with or

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

without polymorphisms.

The impact of baseline NS5A polymorphisms in TN GT 1b infected subjects is minimal to none in both individual and pooled analyses. SVR12 rates are high (97-100%) regardless of polymorphisms.

Because pooled analysis for PR-experienced subjects is split by treatment regimen (duration and use of RBV), each of the four treatment arms contain fewer overall subjects compared to the pooled TN group. In GT 1a infected subjects who received 12w (no RBV), baseline NS5A polymorphisms in List B account for 5/7 (71%) virologic failures. Similarly, in GT 1a infected subjects who received 12w/RBV or 16w (no RBV), baseline polymorphisms in List B account for 3/4 and 4/4 virologic failures, respectively. All four GT 1b infected subjects who experienced virologic failure in the 12w +/- RBV and 16w (no RBV) arms combined had baseline NS5A polymorphisms. In contrast, no GT 1a or 1b infected subject in the 16w(or 18w)/RBV arm experienced virologic failure, including the 14 subjects who had baseline NS5A polymorphisms.

Cumulatively, the data in GT 1a PR-experienced subjects support either GZR/EBR for 12w in the absence of NS5A polymorphisms or for 16w with RBV in the absence of baseline genotypic testing. The former approach is preferred because baseline resistance testing is commercially available and would allow for regimen simplification and elimination of potential RBV-associated toxicity. Both approaches result in high SVR12 rates of 99-100%, which signifies a virologic failure rate of 0-1% but doesn't account for non-virologic failure. The rate of non-virologic failure in the 12w (no RBV) arm and 16w/RBV arms of C-EDGE TE alone was 2% and 3%, respectively, and is not expected to differ in patients with or without polymorphisms. See Section 8.4 for safety analysis of each treatment arm.

A similar approach for GT 1b PR-experienced subjects may be considered because all virologic failures had baseline NS5A polymorphisms, though the total number of virologic failures was very small (n=4). Moreover, the overall SVR12 rate was 100% (34/34) in subjects who received 12w (no RBV) in the pivotal Phase 3 trial C-EDGE TE, and the lower bound of the 95% CI in both the 12w and 16w/RBV arms was 90%.

SVR12 rates of 100% with 16w/RBV in subjects with baseline polymorphisms are based on relatively few subjects: 6/6 GT 1a and 8/8 GT 1b infected subjects. Though the data suggest this regimen may overcome baseline NS5A resistance, confirmatory data would be optimal given the consequences of resistance.

FDA Virologist Dr. Komatsu analyzed the emergence of resistance substitutions in pooled Phase 2 and Phase 3 trials including TN and TE GT 1 infected subjects who received at least 12 weeks of GZR/EBR +/- RBV. In GT 1a infected subjects with baseline NS5A polymorphisms who

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

experienced virologic failure, 25/26 (96%) and 28/29 (97%) subjects using List A and List B, respectively, developed either NS3 or additional NS5A resistance substitutions; 15/26 (58%) subjects developed both NS3 and additional NS5A resistance substitutions. Though small, 6/6 GT 1b infected subjects with baseline polymorphisms developed additional resistance substitutions. Treatment failure with development of resistance will likely impact the ability to successfully retreat with current treatment options, ledipasvir/sofosbuvir, dasabuvir + ombitasvir/paritaprevir/ritonavir, or simeprevir /sofosbuvir. Please see Dr. Komatsu's virology review for more details.

Reviewer Comment: This analysis demonstrates the consequences of virologic failure in subjects with baseline NS5A polymorphisms. Additional resistance emerged in almost all subjects, substantially compromising future treatment options based on currently marketed options. Therefore, reducing the risk of virologic failure through baseline NS5A polymorphism screening will have clinically meaningful benefits including (1) an increased chance of SVR12, and (2) a reduced risk of developing multi-drug resistance.

The prevalence of baseline NS5A polymorphisms in U.S. GT 1a and 1b infected subjects is 8-12% and 11-12%, respectively. These rates are comparable to the frequency in other clinical development programs to date and are similar between sex and race. Please see Dr. Komatsu's virology review for more details.

Reviewer: Because GT 1 (and specifically GT 1a) is the most common HCV subtype in the U.S., a prevalence rate of NS5A baseline polymorphisms in up to 11% of GT 1a infected subjects includes a substantial portion of the HCV population. Furthermore, commercially available assays for NS5A testing for HCV GT 1 are currently available and report variants that represent at least 10-25% of the viral population. This type of reporting is clinically relevant based on the testing employed in clinical trials and results analyzed during this review.

Genotype 4

In TN GT 4 infected subjects, the SVR12 rate was 90-100% in each individual trial (C-EDGE TN, C-EDGE COINFECTION, and C-SCAPE) and 96% (54/56) when pooled. One (2%) subject experienced virologic failure due to relapse and one subject was lost to follow-up.

Reviewer Comment: These data support efficacy of GZR/EBR (12w duration without RBV) in TN GT 4 infected subjects.

In PR-experienced GT 4 infected subjects, the SVR12 rate ranged 60-100% across four arms with different treatment durations (12 or 16 weeks) with or without RBV. Overall, two subjects experienced virologic failure in each of the 12w arms (with and without RBV), both due to

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

relapse.

Table 23. C-EDGE TE SVR12 in GT 4 Infected Subjects

SVR12 (95% CI)	GZR/EBR 12w (N=105)	GZR/EBR+ RBV 12w (N=104)	GZR/EBR 16w (N=105)	GZR/EBR + RBV 16w (N=106)
HCV GT4	78% (7/9)	93% (14/15)	60% (3/5)	100% (8/8)

Reviewer Comment: Numerically the 16w/RBV arm performed the best with 100% efficacy, but this arm included only eight subjects. The 12w (no RBV) and 16w (no RBV) arms also contained very small numbers of GT 4 infected subjects, and the 12w/RBV arm contained the highest number of subjects though had one virologic failure. Limited data in GT 4 PR-experienced subjects make it difficult to determine efficacy of each regimen in this population without extrapolating from the FAS. The challenge with extrapolating from the FAS is that the FAS included mostly GT 1 infected subjects, and regimen selection for these subjects is optimally determined based on the absence of baseline NS5A polymorphisms. The impact of baseline polymorphisms in GT 4 infected subjects is unknown.

When pooled by RBV use, 10/14 (71%, 95% CI 42, 92) subjects receiving GZR/EBR (no RBV) for 12 or 16 weeks compared to 22/23 (96%, CI 78, 100) subjects receiving GZR/EBR + RBV for 12 or 16 weeks achieved SVR12. When pooled by treatment duration, 21/24 (88%) and 11/13 (85%) subjects receiving 12w or 16w, respectively, of GZR/EBR +/- RBV achieved SVR12.

Reviewer Comment: The purpose of such pooling was to explore whether RBV and/or increased treatment duration improved SVR12 as suggested by the small number of GT 4 infected subjects in the 16w/RBV arm. In addition, efficacy in the 12w/RBV arm also appeared promising, despite one failure, due to a higher number of subjects; the pooled analyses is an also attempt to probe whether 12w/RBV is sufficient. Based on these pooled analyses, there is a clear trend that the addition of RBV appears to improve the SVR12 rate, while increased treatment duration to 16w appears similar to 12w.

As of the time of this review, there are no IFN-sparing regimens approved for treatment of PR-experienced GT 4 infected subjects with cirrhosis. SVR12 in GT 4 PR-experienced subjects with and without cirrhosis was 76% (13/17) and 95% (19/20), respectively, when pooling all treatment arms. Consistent with the above pooled analyses, there was a trend toward higher efficacy in both cirrhotics and non-cirrhotics with the addition of RBV. SVR12 in subjects who received GZR/EBR + RBV (pooled 12w/16w) with cirrhosis was 89% (8/9, 95% CI 52, 100) and without cirrhosis was 100% (14/14, 95% CI 77, 100).

Reviewer Comment: The small number of subjects in each arm as well as the imbalance across

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

arms makes it challenging to determine the optimal regimen for GT 4 infected PR-experienced subjects. Because of currently limited treatment options for GT 4 PR experienced subjects, particularly with cirrhosis, it is optimal to approve this product for this patient population if efficacy can be established.

In support of approval, TN trials demonstrate adequate efficacy of GZR/EBR in GT 4 infected subjects; this finding validates antiviral activity of GZR/EBR against HCV GT 4, unlike GTs 2, 3, and 5. Prior failure with a PR generally occurred (historically) due to host-related reasons rather than drug resistance, and these patients like TN patients have not been previously exposed to PIs or any other DAAs.

Overall, GZR/EBR + RBV appears to have adequate efficacy for an indication in GT 4 PR-experienced subjects. A more conservative approach from an efficacy standpoint is to recommend 16w duration. However, if 12w duration is equally efficacious, as the data trend, then it is optimal to minimize RBV exposure from a safety and tolerability perspective. Though the occurrence of RBV-related AEs is higher with four additional weeks duration, the AEs are generally manageable based on safety analyses and is acceptable in exchange for improved efficacy and decreased emergence of drug resistance. Notably, the impact of increased GZR/EBR exposure from 12w to 16w on safety is minimal (see Section 8.4).

Therefore, GZR/EBR + RBV for 16 weeks for PR-experienced GT 4 infected subjects is recommended. The risk of RBV-related toxicity with four additional weeks of treatment is outweighed by the potential benefit of optimizing the regimen.

(b) (4)

Genotype 6

The overall SVR12 rate with GZR/EBR (12w duration without RBV) in TN GT 6 infected subjects was (b) (4) based on pooled results from C-EDGE TN, C-EDGE COINFECTION, and C-SCAPE. An additional four subjects in C-SCAPE received GZR/EBR + RBV for 12 weeks, and three of these subjects achieved SVR12. Even fewer PR-experienced GT 6 infected subjects were included in the clinical development program; six subjects were included in C-EDGE TE and were represented in only two of the four treatment arms. Two of the six subjects received GZR/EBR + RBV for 16 weeks.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Reviewer Comment:

(b) (4)

(b) (4)

(b) (4)

Cirrhosis

The Applicant's definition of cirrhosis included a Fibroscan result of >12.5 kPa, which was agreed to by the Division prior to trial commencement. Statistical reviewer Dr. LaRee Tracy performed a sensitivity analysis for a stricter Fibroscan cut off of >14.5 kPa for cirrhosis. In C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE, the use of >12.5 kPa or >14.5 kPa to define cirrhosis did not meaningfully alter the SVR12 rates in cirrhotics or comparisons to non-cirrhotics. Please see Dr. Tracy's statistical review for additional details.

Reviewer Comment: A stricter definition of cirrhosis by Fibroscan results maintained high efficacy for subjects with cirrhosis. In C-EDGE TN and C-EDGE COINFECTION, SVR12 remained numerically higher in subjects with cirrhosis compared to subjects without cirrhosis. One of two failures with cirrhosis (>14.5 kPa) across these two trials had a baseline NS5A polymorphism, while the second failure was due to missing data. These analyses support high SVR12 rates in cirrhotics compared to non-cirrhotics previously discussed.

Sex and Race

SVR12 results in C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE did not vary substantially based on sex or race. As previously mentioned, the presence of baseline NS5A polymorphisms, which does substantially impact efficacy in subpopulations such as GT 1a infection, is not associated with any particular sex or race.

7.1.1. Onset, Duration, and Durability of Efficacy Effects

The primary efficacy endpoint was SVR12 regardless of the onset of virologic suppression on treatment. Generally, HCV RNA not detected 12 weeks after the end of treatment has been durable with respect to HCV treatment.

Two GT 1a infected subjects each in C-WORTHY and C-SURFER achieved SVR12 and subsequently relapsed failing to achieve SVR24 and ultimately failing to achieve a virologic cure.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Three of the four subjects had baseline NS5A polymorphisms in List A. These subjects are not included in the failures discussed above as the primary endpoint was SVR12. SVR24 analysis is necessary to evaluate the durability of efficacy, particularly in subjects with baseline NS5A polymorphisms who achieved SVR12. The submission did not include complete SVR24 results for all clinical trials.

7.1.2. Dose and Dose-Response

See Section 4.4.2 for GZR and EBR dose selection. This section summarizes the Clinical Pharmacology review team's exposure-efficacy analysis.

Exposure-response analyses were conducted using data from seven Phase 2 and Phase 3 trials in which GZR (100 mg) and EBR (20 or 50 mg) were co-administered with or without RBV in GT 1, 4, or 6 infected subjects. Analyses showed that GZR exposures were not significant predictors of SVR12 ($p=0.574$ for AUC_{0-24h} and $p=0.306$ for C_{trough}), which is expected because a previous Phase 2 trial demonstrated that GZR 100 mg or higher saturated SVR12.

In contrast, EBR exposures were significant predictors of SVR12 ($p<0.001$ for both). Additional significant covariates identified for an exposure-relationship relationship were treatment duration, baseline \log_{10} HCV RNA, and presence or absence of baseline resistance to NS5A inhibitors, the latter of which was the most important predictor. Though the SVR12 response rate is near 100% across the entire EBR exposure range in the absence of baseline NS5A resistance, there was a concentration-dependent SVR12 rate in the presence of baseline NS5A resistance. In subjects with baseline NS5A resistance, the predicted SVR12 rate with 20 mg and 50 mg was 60% and 80%.

Reviewer Comment: The GZR 100 mg dosage cap imposed due to safety concerns is further supported by extensive exposure-efficacy analyses. Exposure-efficacy analyses further support EBR 50 mg as the selected dosage for optimal efficacy given the impact and prevalence of baseline NS5A polymorphisms. EBR at higher dosages may have further improved efficacy in the presence of polymorphisms, but dosages higher than 50 mg were not evaluated by the Applicant.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional considerations on benefit in the postmarket setting to discuss in this section.

7.2.2. Other Relevant Benefits

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

The dosage form and dosing schedule are beneficial from a convenience perspective in that GZR/EBR is a FDC one tablet once daily regimen that can be taken without regard to food. The addition of RBV, however, for some populations will require additional tablets and twice daily dosing. These regimens overall add to the treatment armamentarium of IFN-free treatments for HCV GT 1 and 4.

7.3. Integrated Assessment of Effectiveness

The efficacy of GZR/EBR was established in five clinical trials (three Phase 3, one Phase 2/3, and one Phase 2) with a total of 1155 HCV infected patients. The trials varied in terms of the treatment regimen, treatment duration, patients' HCV GT, and patients' prior treatment experience. These five trials provide substantial evidence of effectiveness of GZR/EBR based on SVR12, considered a virologic cure, in the following populations, some of which differ from the Applicant's proposal:

- (1) TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms (12 weeks duration)
- (2) TN and PR-experienced GT 1b infected subjects (12 weeks duration)
- (3) PI/PR-experienced GT 1 infected subjects (12 weeks duration with RBV)
- (4) TN GT 4 infected subjects (12 weeks duration)
- (5) PR-experienced GT 4 infected subjects (16 weeks duration with RBV)
- (6) CKD Stage 4 or 5 including patients on hemodialysis (same regimens as above, except RBV is not recommended as stated in #3 and #5)

With GZR/EBR therapy, SVR12 ranged from 92% to 100% depending on patient and viral factors as well as overall versus subgroup analysis. Efficacy was similar in patients with or without cirrhosis, with or without HIV coinfection, and with CKD with or without receipt of hemodialysis. Importantly, GZR/EBR is the first IFN-free regimen for treatment of HCV in CKD patients receiving hemodialysis, satisfying an unmet medical need. GZR/EBR is also another highly effective RBV-free single tablet once daily treatment option for TN and PR-experienced GT 1 infection and for TN GT 4 infection. GZR/EBR with RBV is a highly effective option for PI/PR-experienced GT 1 infection and PR-experienced GT 4 infection.

(b) (4)

SVR12 rates are reasonably high but might be even higher for GT 1a infection if subjects with baseline NS5A polymorphisms were excluded from trial entry. Based on post-hoc analysis showing improved efficacy when excluding those with baseline NS5A polymorphisms, baseline NS5A resistance testing is strongly recommended for all TN and TE GT 1a infected patients. Specifically, the virologic failure rate decreased from 5% to 1% in pooled TN GT 1a infected

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

subjects. In PR-experienced GT 1a infected subjects, the virologic failure rate decreased from 8% to 2% with 12 weeks of GZR/EBR when excluding subjects with baseline NS5A polymorphisms. In PR-experienced GT 1 infected subjects overall, post-hoc screening for baseline NS5A polymorphisms improved efficacy with GZR/EBR for 12 weeks (from an SVR12 rate of 92%), making it more comparable to GZR/EBR + RBV for 16 weeks (SVR12 rate of 97%). The latter regimen was the most effective regimen based on primary analysis of the C-EDGE TE FAS.

The potential consequences of treating subjects with GZR/EBR who have baseline NS5A substitutions are serious. Not only are subjects at greater risk of virologic failure, but development of additional resistance in the event of virologic failure appears highly likely. In pooled clinical trials, GT 1a infected subjects with baseline NS5A polymorphisms who experienced virologic failure developed either NS3 resistance substitutions or additional NS5A resistance substitutions (96%) or developed both (58%). Development of additional resistance substitutions limits the use of other treatment options that are currently available. Therefore, the benefit of baseline NS5A resistance testing in the recommended population is to increase the chance for SVR12 and decrease the risk of developing additional resistance substitutions.

Though favorable, the virologic success rate with 16 weeks of GZR/EBR + RBV in GT 1a infected subjects with baseline NS5A polymorphisms (6/6) was based on too few subjects to recommend this regimen in this population. Treatment of all GT 1a infected subjects with GZR/EBR + RBV for 16 weeks without screening for baseline polymorphisms is not recommended. This approach would result in overtreatment of approximately 90% of GT 1a infected patients. Additionally, the safety profile of this regimen is suboptimal compared to 12 weeks of GZR/EBR without RBV.

Baseline NS5A resistance testing is not necessary for TN GT 1b infected patients based on SVR12 rates of 96-98% and minimal impact of baseline NS5A polymorphisms in clinical trials. Baseline testing may be considered for TE GT 1b infected patients to maximize potential efficacy and minimize the risk of virologic failure based on the trends observed in C-EDGE TE. In Phase 2 and Phase 3 trials, all six GT 1b infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistance, limiting future treatment options. However, SVR12 in GT 1b subjects treated with GZR/EBR for 12 weeks was 96% overall, generally supporting the use of this regimen with or without baseline resistance testing.

8 Review of Safety

8.1. Safety Review Approach

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Pivotal Phase 3 trials C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE were analyzed individually and included in the pooled safety population for the majority of safety analyses. Individual analysis of C-EDGE TN was critical because this trial included a placebo arm for the purpose of safety comparison. Individual analysis of C-EDGE TE was useful for comparing safety across four different treatment arms. Phase 2 trial C-SALVAGE was also analyzed either individually or as part of pooled analyses with Phase 3 trials. Though the safety profile of GZR/EBR in PI/PR-experienced subjects (C-SALVAGE) is not expected to differ from the Phase 3 population (TN and PR-experienced), C-SALVAGE provides additional safety information for 12 weeks of GZR/EBR + RBV. Deaths occurring in any submitted Phase 2 or Phase 3 trial were reviewed and assessed.

A thorough hepatic safety review was conducted as it was the key GZR-associated safety issue identified during drug development and has a known association with marketed HCV NS3/4A PIs. The pooled hepatic safety population included subjects who received GZR/EBR at the dosages and durations proposed for marketing; subjects who received placebo were analyzed for general comparison.

Dr. Sarita Boyd conducted the above safety analyses which are presented in Sections 8.4 and 8.5. Unless otherwise specified, clinical trial data were independently analyzed using the SDTM datasets for P060, P061, and P068 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. Prabha Viswanathan conducted the primary safety analysis of C-SURFER, which is presented in Section 8.6. C-SURFER was not pooled with any other trial for analyses presented in Sections 8.4 and 8.5 because subjects with underlying CKD Stage 4 or 5 represent a considerably different patient population and thereby have potentially different safety concerns.

The Applicant submitted a Safety Update Report (SUR) two months after the original NDA submission. Trials included in the SUR include those ongoing at the time of the original submission and four additional ongoing trials that were not included previously. Deaths, SAEs, discontinuations due to AEs, and hepatic ECIs 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 GZR and/or EBR at any dose and as a part of various regimens.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 24. Safety Database: Population and Size

Individuals exposed to GZR and/or EBR in this development program for the indication under review N=4143 (includes 218 placebo-treated subjects who received or are receiving GZR/EBR during the deferred treatment period)				
Clinical Trial Groups	GZR	EBR	GZR and EBR	Placebo
Phase 1 HCV uninfected subjects: 1300				
Phase 1 HCV-infected subjects: 139				
Phase 2/3 Database (n=2704)	2486	2041	2041	218

Excluding subjects who received deferred treatment, 1747 subjects received GZR 100 mg and EBR 50 mg for at least 12 weeks, and 360 subjects received GZR 100 mg and EBR 50 mg for 16-18 weeks.

8.2.2. Relevant characteristics of the safety population:

Characteristics of subjects in pooled Phase 2 and Phase 3 trials (n=2704) were as follows:

- Age (years) 18-35 (n=250), 36-50 (n=731), 51-64 (n=1432), ≥ 65 (n=291)
- Male (n=1657), Female (n=1047)
- White (n=2014), Black (n=403), Asian (n=235), Multiple (n=35), Other (n=17)
- Non-cirrhotic (n=2092), Cirrhotic (n=611), Unknown (n=1)
- HCV GT 1a (n=1445), GT 1b (n=961), GT 1-other (n=13), GT 2 (n=56), GT 3 (n=82), GT 4 (n=111), GT 5 (n=8), GT 6 (n=28)
- Treatment-naïve (n=1984), Treatment-experienced (n=720)
- HCV monoinfected (n=2406), HCV/HIV coinfecting (n=298)

Early results from P003 established a dose-response relationship for GZR-related ALT elevations. Therefore, factors such as age, sex, and race that increase GZR exposure are important when assessing safety of GZR/EBR.

8.2.3. Adequacy of the safety database:

The safety database for both products is comprehensive and adequate to assess safety of GZR/EBR for the proposed indication, dosage regimen, duration of treatment, and patient population.

8.3. Adequacy of Applicant’s Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

There were no identified issues regarding data integrity. For Phase 3 trials, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment. In addition, available autopsy reports were obtained and confirmed to be accurately summarized by the Applicant.

The quality of the submission was adequate to perform most of the safety review for GZR/EBR. Jump Start service analyzed data fitness and found no major issues that would preclude performing a safety review. However, two components of the ISS dataset were missing which would have created difficulty in reviewing safety data in a comprehensive and timely manner. We requested the Applicant submit a revised ISS dataset with inclusion of the placebo (DTG) subjects from C-SURFER (as agreed to at the pre-NDA meeting) and a treatment emergent flag. The Applicant complied with the request.

8.3.2. **Categorization of Adverse Events**

There were no identified issues with respect to recording, coding, and categorizing AEs. The Applicant categorized SAEs in accordance with standard, regulatory definitions. The Applicant did not use a toxicity grading scale to categorize the severity of AEs but instead used the following definitions:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity
- Severe: incapacitating with inability to work or do usual activity

Life-threatening events were reported as SAEs. These definitions are generally consistent with those used to estimate severity of clinical AEs in the DAIDS toxicity table.

The Applicant used the Division of AIDS (DAIDS) criteria (version 1.0, December 2004) to grade individual laboratory assessments, with three exceptions. Hemoglobin was graded according to the DAIDS scale for HIV-negative subjects by absolute values only, and not by changes from baseline. GGT and direct bilirubin were graded according to the National Cancer Institute (NCI) Common Terminology for AEs (version 4.03, June 2010). The Applicant's approach was reasonable.

The clinical reviewers verified the Applicant's translation of verbatim terms to preferred terms for C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SURFER.

8.3.3. **Routine Clinical Tests**

Routine clinical evaluation and laboratory testing occurred at pre-specified regular intervals: Treatment Weeks (TW) 1, 2, 4, 6, 8, 10, 12, and when applicable TW16; Follow-up (FU) weeks 4, 8, 12, 16, 20, and 24. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs and inspection of parameters including

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

vital signs, physical examinations, 12-lead ECGs, standard laboratory safety tests, as well as HIV RNA and CD4 counts at specified time points. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

8.4. Safety Results

The table below displays an overall safety summary of individual Phase 3 trials and C-SALVAGE.

Table 25. Safety Overview: C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE

	C-EDGE TN (P060)		C-EDGE Co-infection (P061)	C-EDGE TE (P068)				C-SALVAGE (P048)
	ITG 12w N=316	DTG pbo N=105		12w N=218	12w N=105	12w/RBV N=104	16w N=105	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Deaths	2 (1)	0	0	0	0	0	0	0
SAEs	9 (3)	3 (3)	2 (1)	4 (4)	3 (3)	3 (3)	4 (4)	4 (5)
D/C d/t AE	3 (1)	1 (1)	0	1 (1)	1 (1)	0	5 (5)	1 (1)
D/C d/t hepatic AE	2 (1)	0	0	0	0	0	0	0
Hepatic ECI ¹	5 (1)	0	3 (1)	0	2 (2)	3 (3)	0	0
Late ALT/AST inc	4 (1)	0	2 (1)	0	1 (1)	3 (3)	0	0
AE All	213 (67)	72 (69)	161 (74)	74 (71)	85 (82)	77 (73)	95 (90)	63 (80)
AE Related	114 (36)	41 (39)	75 (34)	41 (39)	67 (64)	46 (44)	81 (76)	45 (56)
AE mild	197 (62)	64 (61)	148 (68)	71 (67)	80 (77)	70 (67)	89 (84)	56 (71)
AE mod	71 (22)	29 (28)	60 (28)	17 (16)	30 (29)	24 (22)	38 (36)	18 (23)
AE severe	12 (4)	4 (4)	3 (1)	6 (6)	4 (4)	4 (4)	6 (6)	3 (4)

¹Hepatic ECIs include any one of the following occurrences from the initiation of therapy through 14 days following treatment and not associated with virologic failure: (1) first instance of ALT or AST >500 IU/L, (2) first instance of ALT or AST >3x baseline and >100 IU/L, or (3) first instance of ALP >3x ULN.

Reviewer Comment: The high level safety overview and general comparison to placebo suggests that GZR/EBR has a relatively favorable safety profile. The addition of RBV appears to impact overall safety and tolerability. Detailed safety analyses are included below.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

8.4.1. Deaths

C-EDGE TN (P060), C-EDGE COINFECTION (P061), and C-EDGE TE (P068)

Two treatment-emergent deaths and one death after early treatment discontinuation occurred in Phase 3 clinical trials, which are summarized below. One additional death occurred during screening (myocardial infarction) and was unrelated to study drug.

P060, AN 435637 (ITG GZR/EBR x 12 w); Cause of death: Ventricular arrhythmia

A 63-year-old cirrhotic white male with HCV monoinfection and past medical history significant for hypertension, cerebral atherosclerosis, Gilbert's disease, and Factor XIII deficiency completed 12 weeks of study medication and achieved undetectable HCV RNA from TW6 through EOT. One AE of worsening hypertension (BP not reported) was reported on treatment, which was considered mild and not related to study treatment. He had no notable laboratory findings at any time. Two weeks after EOT, he was found deceased at home. The main autopsy finding was central second degree atherosclerosis of the coronary vessels. Toxicology showed blood alcohol 0.41 g/kg, which corresponds to a blood alcohol content of 0.04%. The investigator reported malignant ventricular arrhythmia and assessed the death as not related to study drug but presumably due to an arrhythmia from autopsy-documented coronary disease.

Reviewer Comment: The autopsy report was requested and reviewed. The subject's death was unlikely related to study treatment. There was no evidence of cardiac toxicity during treatment based on reported AEs, laboratory results, vital signs, and ECG results. At the time of death, systemic exposure of GZR/EBR was unlikely given the half-life of both drugs.

P060, AN 435142 (ITG GZR/EBR x 12 w); Cause of death: Strangulated hernia

A 59-year-old non-cirrhotic white male with HCV monoinfection and an otherwise relatively unremarkable past medical history presented to the ED with right lower quadrant abdominal pain at TW2. Abdominal CT results were consistent with acute appendicitis, a small hiatal hernia, and bilateral, small fat-containing inguinal hernias. He underwent an emergent laparoscopic appendectomy, which revealed an inflamed, non-perforated appendix. He was discharged with no complications noted. He contacted the site that day and appeared to be having an unremarkable post-operative course. The next day, his daughter found him deceased. The autopsy showed the death was a result of complications of gastroesophageal strangulation due to a hiatal hernia. The medical examiner noted that there was no evidence to suggest death resulted from study treatment and that strangulation of the GI tract is a known complication of a hernia, and the leakage of GI contents leads to a deadly systemic reaction.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Reviewer Comment: The autopsy report was requested and reviewed. The subject's death was unlikely related to study treatment based on autopsy results and natural complication of a hernia.

P068, AN680405 (GZR/EBR x 12 w); Cause of death: Cancer

A 54-year-old white male with HCV GT 4 infection, compensated cirrhosis, and a history of a partial response to prior treatment with PR was hospitalized for new-onset, rapidly progressing ascites, increasing ammonia levels, and elevated creatinine beginning during TW3. He continued to progress despite treatment and developed renal failure, gram-negative sepsis, and bacterial peritonitis. The subject stopped study medication before TW4, at which time laboratory results were unremarkable with the exception of decreased hemoglobin (10.6 g/dL) and increased serum creatinine (2.2 mg/dL). From the time of randomization to treatment discontinuation, there was no evidence of hepatic decompensation. He died 22 days after treatment discontinuation. An autopsy determined the cause of death was lymphoma with abdominal scatter and infiltration in the pericardium. The investigator considered the AEs and death to be unrelated to study medication.

Reviewer Comment: The autopsy report was requested and reviewed. The subject's death was unlikely related to study treatment based on autopsy results showing previously undiagnosed lymphoma with abdominal involvement.

Supportive Safety Database

Three additional deaths were reported in the supportive or ongoing Phase 2 and Phase 3 clinical trial database. One subject in C-WORTHY died as a passenger in a motor vehicle accident while on treatment which was unrelated to study drug. One death occurred during post-treatment follow up and one death occurred after early treatment discontinuation, which are summarized below. Deaths that occurred in C-SURFER are discussed in Section 8.6.

Protocol 059, AN609001 (GZR [50 mg]/EBR x 12 w); Cause of death: Hepatic failure

A 63-year-old white male with Child-Pugh B cirrhosis (screening score: 7) and medical history significant for anemia, ascites, esophageal varices, portal vein thrombosis, and splenomegaly-associated thrombocytopenia achieved HCV RNA TND from TW4 through EOT. At TW9 he developed new-onset spontaneous bacterial peritonitis (SBP), which was treated and resolved by TW11. He subsequently completed 12 weeks of study medication. In the follow-up phase he developed a cerebral infarction, SBP, and hepatic failure. At FU4, he died due to progressive hepatic failure. SBP was not associated with increases in ALT, AST, or total bilirubin, nor did the subject experience a late ALT/AST elevation event while on treatment. The investigator did not attribute the events to study medication.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Reviewer Comment: It is difficult to determine whether the events were solely due to the subject's underlying hepatic disease or whether study treatment contributed at all to the course of events which progressed while on treatment. Though the subject did not experience any increases in liver enzymes, which is known effect of GZR, or significant changes in other laboratory parameters from baseline, data with GZR/EBR in the Child-Pugh B patient population are limited. Therefore, these events which ended in the subject's death are possibly related to study treatment. Because the proposed indication for GZR/EBR is not extended to subjects with Child-Pugh B cirrhosis, this event does not directly impact the approvability of the drug in the proposed patient population. Furthermore, the proposed recommendation in the label is that GZR/EBR is (b) (6) in patients with moderate hepatic impairment (Child-Pugh B). Consideration to strengthen the recommendation to a contraindication may be warranted. This case was also discussed with Dr. Poonam Mishra (hepatologist) who added that this subject was rather advanced at baseline with likely Child Pugh C cirrhosis and agreed that a contraindication may be warranted.

P062, AN 232470 (GZR/EBR x 12 w [ITG] vs. placebo [DTG]); Cause of death: Pneumonia

Note: P062 (C-EDGE CO-STAR) is an ongoing Phase 3 randomized, placebo-controlled, double-blind trial in TN subjects with HCV GT 1, 4, or 6 who are also on opiate substitution therapy; a high-level safety summary for this trial was included in the NDA submission.

A 60-year-old non-cirrhotic, white male with a past medical history significant for severe pulmonary fibrosis was hospitalized during TW4 after worsening dyspnea and chest x-ray showing a left upper lobe infiltrate and underlying chronic disease. He received treatment for pneumonia, and study medication was stopped. After three days of hospitalization, a chest CT showed diffuse pulmonary fibrosis, paraseptal emphysema, and pleural/parenchymal scarring within both apices; there was development of diffuse ground-glass opacification of both lungs, nonspecific in appearance. The subject was intubated in the ICU and subsequently developed bacteremia and fungemia. He was made "do not resuscitate" and expired after three weeks of hospitalization. As of the NDA cutoff date, the subject's treatment assignment was still blinded. The death was assessed as not related to study drug.

Reviewer Comment: The subject's death was unlikely related to study drug given the subject's underlying severe pulmonary disease and the course and nature of the event.

Safety Update Report

Two additional deaths were reported in ongoing Phase 2 and Phase 3 clinical trials. One subject on blinded therapy committed suicide; this case is described below and includes original details reported as well as follow-up information requested by the Division. One subject receiving

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

placebo died due to bacterial pneumonia. Any additional deaths in C-SURFER are discussed in Section 8.6.

P067, AN 106831 (GZR/EBR or placebo x 12 w); Cause of death: Suicide

Note: P067 is an ongoing Phase 3 randomized (3:1, ITG: DTG), blinded trial in TN, non-cirrhotic or cirrhotic GT 1, 4, or 6 infected Asian subjects. Immediate treatment consists of GZR/EBR 100/50 mg for 12 weeks. This trial was not included in the original submission.

A 50-year-old non-cirrhotic Korean female experienced suicidal ideation during TW6 of blinded treatment with GZR/EBR or placebo. This event was assessed as severe and not related to study drug. Insomnia was also reported as unrelated and ongoing. The subject visited the hospital for the TW8 visit at which time suicidal ideation was ongoing. The subject refused to see a psychiatrist, withdrew consent without explanation, and left the hospital in a hurry. Hospital personnel called the subject a few hours later and discovered from a police officer that she had committed suicide. The subject had no known medical problems, including depression or other psychiatric illness, at study entry and was not taking any concomitant medications. Her only known risk factor for HCV transmission was a blood transfusion, and she had no known history of injection drug use. It is currently unknown whether the subject was receiving GZR/EBR or placebo, though ALT and AST declined rapidly after blinded treatment initiation.

Reviewer Comment: Though the trial currently remains unblinded, the subject was likely receiving GZR/EBR rather than placebo based on the ALT/AST trends. This event is of interest because it occurred on treatment and in the absence of any known confounding factors. It is difficult to assess causality without additional information, which may not be available.

8.4.2. **Serious Adverse Events**

C-EDGE TN (P060)

SAEs of any grade occurred at a similar rate in both arms: 9/316 (3%) and 3/105 (3%) subjects receiving GZR/EBR and placebo, respectively, for 12 weeks. All SAEs in both arms were assessed as unrelated to study drug by the investigator. No SAE occurred in more than one subject, and none led to early discontinuation of study drug. The following SAEs occurred in the GZR/EBR ITG arm: ventricular arrhythmia (see Section 8.4.1), Meniere's disease, upper abdominal pain, hiatus hernia strangulated (see Section 8.4.1), accidental overdose (of clonidine), multiple fractures (due to fall), muscular weakness (due to pre-existing myasthenia), renal colic, and skin ulcer (due to fall and paper clip stick).

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

C-EDGE COINFECTION (P061)

SAEs of any grade occurred in 2/218 (1%) subjects receiving GZR/EBR for 12 weeks, and none were related to study drug per the investigator. SAEs included convulsion and pneumonia, both of which occurred and resolved on study treatment.

C-EDGE TE (P068)

Similar rates of SAEs of any grade (3-4%) occurred across all four arms, with no specific trends based on duration (12 vs. 16 weeks) or use of RBV. There was an overall trend of GI-related events, which occurred in three of the four arms (see table below), with ascites resulting in early treatment discontinuation and fatality (see Section 8.4.1), gastrointestinal inflammation resulting in early treatment discontinuation (see Section 8.4.3), and abdominal pain deemed as related to study drug (described below). One additional GI-related SAE, infectious colitis, was related to food-borne illness and unrelated to study treatment. All three fractures had a plausible alternate explanation.

Table 26. All Reported SAEs in C-EDGE TE

GZR/EBR 12w	GZR/EBR + RBV 12w	GZR/EBR 16w	GZR/EBR + RBV 16w
Angina unstable/CAD	Abdominal pain/TIA	Loss of consciousness	Anemia
Ascites	Infectious colitis	Lymphocytosis	Colitis/GI inflammation
Hip fracture	Uterine polyp	Overdose	Rib fracture
Sudden hearing loss			Tibia fracture

CAD = coronary artery disease, TIA = transient ischemic attack, GI = gastrointestinal

Drug-Related SAEs per Investigator

AN681215: The subject is a 53-year-old black female with HCV GT 1a without cirrhosis. SAEs abdominal pain and transient ischemic attack (TIA) occurred separately on study treatment and each led to hospitalization. Both events were considered related to study drug by the investigator because no alternate explanation was available. However, the subject had a history of TIA and hypertension as well as abdominal pain prior to study entry. Abdominal pain was not associated with abnormalities in laboratory studies, including hepatic enzymes, abdominal ultrasound, EGD, or hepatobiliary scan. Both events resolved without changes to study treatment.

One additional subject had a drug-related SAE per the investigator. However, the SAE anemia was related only to RBV, which is not unexpected, and was considered serious due to accidental overdose of RBV; the subject took 1000 mg daily instead of 800 mg daily as prescribed. Anemia improved after the subject began taking the correct dose of RBV.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Summary of Pooled Analysis (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE)

No specific SAE was reported in more than one subject. However, hearing-related SAEs Meniere's disease and sudden hearing loss are of interest due to occurrence in one subject each (described below). The pattern of both events differ, with one event resolving on treatment without recurrence and MRI results suggesting the incident was associated with possible infection.

AN435146: The subject is a 58-year-old white male with medical history of tinnitus. He experienced dizziness on D12 of treatment, which led to treatment of presumed Meniere's disease. Symptoms progressed leading to hospitalization approximately 4 weeks later. The subject received mannitol and ondansetron which led to improvement and discharge the next day. The subject completed dosing; however, the event was unresolved. A larger review of AEs under the Ear and Labyrinth Disorders SOC for all submitted Phase 2 and Phase 3 trials (except C-SURFER) revealed no additional patterns or concerns.

AN682045: The subject was a 64-year-old Asian female. Around TW6, she experienced severe vertigo with sudden onset hearing loss along with mild vomiting, dizziness, and tinnitus. She was hospitalized and treated with intra-auricular dexamethasone. MRI showed mild fluid collection in the mastoid air cells. The event resolved after four days, and the subject completed treatment without any other reported hearing incidents.

Overall, 25/954 (3%) subjects in Phase 3 trials who received GZR/EBR with or without RBV and regardless of treatment duration experienced an SAE, and two (< 1%) were drug-related per the investigator. The incidence of SAEs was not altered by the use of RBV, longer treatment duration, cirrhosis, HIV coinfection, or prior PR treatment failure.

Reviewer Comment: Overall, the SAEs in Phase 3 trials do not raise significant safety concerns as there were no concerning trends and all were unrelated or unlikely related to GZR/EBR per narrative review. Generally, subjects either had an alternate explanation for the SAE, experienced resolution of SAE with continued study treatment, or experienced negative dechallenge. I agree with the investigator assessments of unrelated SAEs.

Phase 2 Trial: C-SALVAGE (P048)

Four of 79 (5%) subjects experienced an SAE, none of which were related to study treatment GZR/EBR + RBV for 12 weeks. The events were COPD (worsening of pre-existing condition), laryngeal squamous cell carcinoma, bacterial pharyngitis, and UTI. The investigator's assessments were reasonable.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Safety Update Report

No treatment-emergent SAEs occurred in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, or C-SALVAGE in the update period.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

C-EDGE TN (P060)

Discontinuations due to AEs were infrequent in both arms, with 3/316 (1%) and 1/105 (1%) in the GZR/EBR and placebo arms, respectively. Two GZR/EBR-treated subjects discontinued study drug due to ALT/AST elevations, as required by protocol, and one subject discontinued early due to anxiety and palpitations. The placebo-treated subject discontinued early due to pruritic rash.

AN 436615: This is a 52-year-old cirrhotic Asian female with HCV GT 1b and elevated baseline ALT/AST (75/57 U/L) with no other notable baseline laboratory abnormalities. After normalization at TW2, ALT/AST increased to 199/167 U/L (6x/4x ULN) at TW8 and peaked at TW10 at 702/459 U/L (20x/12x ULN), which met criteria for a hepatic ECI (ALT >500 U/L) and discontinuation of study drug. Total and direct bilirubin increased to 1.3 and 0.46 mg/dL, respectively, at TW10, and INR increased to 1.3 at TW10. Absolute eosinophil count remained WNL though the percentage increased to 8.8% at TW8, after which it normalized. After treatment discontinuation on Day 70, laboratory values gradually normalized in less than two months. Of note, one day prior to initiation of the event, the subject was diagnosed with URI in a local clinic and given medications for cough that were taken for 3-4 days. The subject remained asymptomatic throughout the event, and there were no notable findings from additional hepatic work-up. Despite completing only 10 weeks of treatment, the subject achieved SVR12.

AN 436026: This is a 67-year-old non-cirrhotic African American female with HCV GT 1b and elevated baseline ALT/AST (94/99 U/L) with no other notable baseline laboratory abnormalities. After normalization at TW2, ALT/AST increased to 399/338 U/L (12x/9x ULN) at TW10 and peaked around TW11 at 474/352 U/L with eosinophil increase to 5.1%, which met criteria for a hepatic ECI (ALT/AST >3x baseline) and discontinuation of study drug (ECI + eosinophilia >5%). After treatment discontinuation on Day 78, laboratory values gradually normalized within one month. The subject remained asymptomatic throughout the event, and there were no additional notable findings. Despite completing only 11 weeks of treatment, the subject achieved SVR12.

Reviewer Comment: The two hepatic ECI events leading to treatment discontinuation appear related to study drug based on known safety profile of GZR, temporal relationship including time

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

to onset, and positive dechallenge. The level of increases in hepatic enzymes are concerning, particularly if monitoring and management becomes suboptimal in a post-marketing setting outside of a highly monitored clinical trial. While it is reassuring that subjects remained asymptomatic and had complete resolution of events upon dechallenge, these subjects were carefully monitored with specific discontinuation criteria in place to avoid or minimize more significant hepatic safety events beyond laboratory abnormalities. Furthermore, these two subjects had GT 1b infection and achieved SVR12 despite 10-11 weeks of treatment. In a broader setting, especially in GT 1a patients, achievement of SVR12 in subjects who discontinue early due to hepatic laboratory abnormalities may be less common.

AN 435074: The subject is a 59-year-old Asian female with HCV GT 1a infection without cirrhosis. She had a history of anxiety, depression, and palpitations, for which she was not taking any medications at study entry. Anxiety and palpitations started on the same day the subject started study treatment and persisted, leading the subject to discontinue treatment on Day 4. She recovered from the events less than three months later. The investigator considered the AEs related to study drug.

Reviewer Comment: While it is possible the events are related to study drug, it is also possible the events were due to pre-existing conditions considering the subject's past medical history and persistent of events for almost three months after discontinuation. The subject also had limited exposure to study drug.

C-EDGE COINFECTION (P061)

There were no discontinuations due to AEs in this trial.

C-EDGE TE (P068)

Discontinuations due to AEs occurred at a higher rate in the 16w/RBV arm (5/106, 5%) compared to the other three treatment arms (0-1%). One subject (AN 680405) in the 12w arm discontinued due to ascites which ended in fatality (see Section 8.4.1). One subject (AN 681242) in the 12w/RBV arm discontinued RBV only on Day 3 due to related affect lability, which quickly resolved, and the subject went on to achieve SVR12. No subjects in the 16w arm discontinued due to AEs. Narratives for discontinuations due to AEs in the 16w/RBV arm are summarized below.

AN 682098: This subject is a 53-year-old non-cirrhotic white male with HCV GT 1a with past medical history notable for psychiatric illness including depression and was taking multiple psychiatric medications at study entry. The subject reportedly stopped taking all study drugs on Day 88 due to moderate depression, and depression resolved three days later. At FU4 HCV RNA

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

was undetectable, but the subject did not return for FU12 visit and was lost to follow up. The investigator assessed depression as not related to study drug.

Reviewer Comment: Although the subject has a history of depression, it is possible that RBV and/or GZR/EBR exacerbated the condition given the positive dechallenge.

AN 682085: This subject is a 55-year-old non-cirrhotic multi-racial male with HCV GT 1a who had general compliance problems throughout the study. He experienced non-serious AEs dysphagia, confusional state, dyspnea, and anxiety approximately two weeks after treatment initiation that the investigator deemed unrelated. The investigator discontinued study treatment due to non-serious AEs and subject's habitual drug use.

Reviewer Comment: The narrative does not contain enough information to assess potential causality.

AN 680041: This subject is a 53-year-old cirrhotic white male with HCV GT 1a with no history of psychiatric illness. He developed fatigue and depression on treatment and discontinued only ribavirin after experiencing suicidal ideation. Suicidal ideation resolved but depression continued after EOT. The investigator assessed both events as related to study drugs. AT FU11 HCV RNA was undetectable.

Reviewer Comment: I agree suicidal ideation and depression appear related to RBV, and it is difficult to rule out contribution of GZR/EBR to depression.

AN 682030: This subject is a 68-year-old non-cirrhotic white male. He experienced dyspnea, palpitations, and presyncope and a 3 g/dL decrease in hemoglobin from baseline to a nadir of 11.6 g/dL, prompting discontinuation of ribavirin before TW5. Persistence of symptoms and moderate nausea led to discontinuation of GZR/EBR at TW6; the investigator deemed the events related to study drug. ECG was normal. Hemoglobin normalized within one month and additional AEs resolved 2-3 months after treatment discontinuation. Subsequently he was hospitalized for a kidney stone. Despite less than 6 weeks of treatment, the subject achieved SVR24.

Reviewer Comment: I agree that AEs appear related to RBV given its known safety profile and that GZR/EBR possibly contributed to symptoms.

AN 680809: This subject is a 52-year-old cirrhotic white male with HCV GT 4a and PMH significant for esophageal varices and diabetes mellitus. Starting at TW2 he developed bouts of bloody diarrhea and abdominal pain. The first episode was an SAE diagnosed as right-sided colitis and was treated with antibiotics. Following CTdocumented resolution, the AEs returned

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

along with chills and fever. At TW14 a second SAE occurred with the same symptoms. CT scan showed colonic edema and decreased C3 complement, and blood cultures were positive for streptococcus B. Study medications were discontinued at TW15. Significant laboratory abnormalities during treatment included increase in total bilirubin from baseline with the first peak at TW1 and a second peak at TW14 (at time of second SAE), and decrease in hemoglobin to a nadir of 11.2 g/dL. All laboratory values normalized after treatment discontinuation. ALT/AST were elevated at baseline and normalized by TW4 with no subsequent increase. The investigator initially assessed the first SAE as unrelated and the second SAE as related but changed both assessments to unrelated after recurrence of abdominal pain one month after treatment discontinuation. CT showed portal hypertension, and ultrasound showed portal vein thrombosis.

Reviewer Comment: I agree the SAEs are unlikely related to study drugs and more likely related to underlying disease and/or infection given the time course and recurrence of events.

Summary of Pooled Analysis (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE)

Overall, 10/954 (1%) subjects in Phase 3 trials who received GZR/EBR with or without RBV and regardless of treatment duration discontinued study drug due to an AE, and six were at least possibly drug-related per the investigator. I agree with the investigator's causality assessments, except one additional case appears at least possibly related. Discontinuations due to AE were more common in subjects treated with GZR/EBR + RBV (6/210, 3%) vs. GZR/EBR alone (4/744, 1%), and two of these subjects discontinued RBV alone but continued GZR/EBR. Although discontinuations were also more common with 16 weeks (5/211, 2%) vs. 12 weeks (5/743, 1%) of treatment, only two occurred between TW12 and TW16 and all occurred in the 16w/RBV group. Therefore, treatment duration did not appear to impact discontinuations due to AEs and any difference was driven by the use of RBV. Additionally, cirrhosis did not substantially alter the incidence of discontinuations due to AE, and no HIV coinfecting subjects discontinued due to an AE.

The most common AEs by SOC leading to discontinuation were Psychiatric disorders, which mainly consisted of mood-related AEs such as anxiety, depression, and suicidal ideation. These events appear most likely related to RBV as 4/5 psychiatric AEs occurred in RBV-treated subjects. Only one subject discontinued due to symptomatic decrease in hemoglobin, also likely related to RBV. Overall, there appears to be an increased risk of treatment discontinuations due to AEs with the addition of RBV, and the AEs are consistent with the known safety profile of RBV. However, Phase 3 trial results do not raise specific concerns related to GZR/EBR.

Phase 2 Trial: C-SALVAGE (P048)

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

One of 79 (1%) subjects discontinued GZR/EBR + RBV (12 week treatment) due to dehydration, dysphagia, and vomiting. These events were not related to study drug but rather to radiation therapy for laryngeal carcinoma.

Safety Update Report

No discontinuations due to AEs occurred in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, or C-SALVAGE in the update period.

8.4.4. Significant Adverse Events

See Section 8.3.2 for the Applicant's definitions of mild, moderate, severe AEs.

C-EDGE TN: P060

Severe AEs regardless of causality occurred in 4/316 (4%) and 12/105 (4%) subjects in the GZR/EBR ITG and placebo/DTG arms, respectively. In the GZR/EBR ITG arm, severe AEs were considered related in three cases (ALT increased, AST increased, and anxiety). In the placebo/DTG arm, one severe AE (hepatic enzyme increased) was assessed as drug-related. Increases in hepatic enzymes are a known GZR-related effect (see Section 8.5.1.).

C-EDGE COINFECTION (P061)

Three (1%) subjects experienced severe AEs, none of which were considered related to study drug.

C-EDGE TE (P068)

Severe AEs regardless of causality occurred at a similarly low rate (4-6%) in all four treatment arms, and drug-related severe AEs occurred at a very low rate (0-3%) with no clear differences based on RBV use or length of treatment duration. Severe drug-related AEs consisted of abdominal pain and TIA (12w/RBV); asthenia and fatigue (12w/RBV); malaise (12w/RBV arm); asthenia (16w arm); and fatigue (16w/RBV arm). There was a pattern of asthenia, fatigue, and malaise, which may be related to the RBV component of the regimen, although one subject who received GZR/EBR alone also experienced severe asthenia. Of note, there was a similar incidence of fatigue in the GZR/EBR and placebo arms in C-EDGE TN.

Pooled Analysis (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Related and Severe AEs

	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
	N (%)	N (%)	N (%)	N (%)	N (%)
All Severe AEs	4 (4)	22 (3)	4 (4)	7 (4)	6 (6)
Related Severe AEs	1 (1)	3 (<1%)	1 (1)	3 (2)	1 (1)

Specific events are discussed for each trial above. Pooling of 12-week arms and addition of subjects in C-SALVAGE did not change the incidence or nature of severe AEs. Overall, severe AEs occurred very infrequently in all trials across treatment arms and did not differ based on duration of treatment, use of RBV, or presence of cirrhosis.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

C-EDGE TN: P060

Overall, subjects treated with GZR/EBR in the ITG arm (213/316, 67%) experienced a similar rate of AEs regardless of causality compared to subjects treated with placebo in the DTG (72/105, 69%). The most common AEs ($\geq 5\%$) in the GZR/EBR ITG arm were headache, fatigue, nausea, and arthralgia; the rate of these AEs was similar with placebo in the DTG arm. The only AEs that occurred at a higher rate ($\geq 2\%$ difference) in the GZR/EBR ITG arm compared to placebo/DTG were upper respiratory tract (URI) infection and vomiting. More AEs occurred at a higher rate ($\geq 2\%$ difference) in the placebo/DTG arm compared to the GZR/EBR ITG arm and included pruritis, insomnia, muscle spasms, dizziness, musculoskeletal pain, anxiety, dysguesia, and diarrhea.

Related AEs also occurred at a similar overall rate in the GZR/EBR ITG arm (114/316, 36%) compared to the placebo/DTG arm (41/105, 39%). Related AE terms and differences in rates between arms were similar to those reported regardless of causality.

C-EDGE COINFECTION: P061

Overall, 74% (161/218) of subjects experienced any AE and 34% (75/218) experienced a drug-related AE, similar to HCV monoinfected subjects in C-EDGE TN. The most common AEs were similar to those seen in C-EDGE TN, with additional AEs diarrhea, URI, insomnia, nasopharyngitis, and upper abdominal pain occurring in $\geq 5\%$ of subjects.

C-EDGE TE: P068

Overall, the rate of any AE was similar in the GZR/EBR (no RBV) 12w vs. 16w arms at 70%

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

(74/105) and 73% (77/105), respectively; the rates were also similar to those seen in C-EDGE TN and C-EDGE COINFECTION. However, the rate of any AE was higher in the GZR/EBR + RBV 12w arm at 82% (85/104) and further increased with longer duration of RBV in the GZR/EBR + RBV 16w arm at 90% (95/106). A similar pattern was observed for related AEs with 39% and 43% in the non-RBV-containing 12w and 16w arms, respectively, compared to 64% and 76% in the RBV-containing 12w and 16w arms, respectively. Based on these comparisons, duration of GZR/EBR treatment did not substantially impact the rate of AEs in the absence of RBV, while RBV drove an increase in AEs overall and with longer duration.

A comparison of PTs between pooled arms of GZR/EBR with and without RBV is portrayed in the following table. The same analysis of related AEs produced similar results. There were no notable differences between cirrhotic and non-cirrhotic subjects with or without RBV, except increased incidence of pruritis and rash in cirrhotic patients taking RBV. Established RBV-related AEs, such as anemia, fatigue, and dyspnea, occurred more frequently in the RBV-containing arms.

Table 27. C-EDGE TE: Treatment-Emergent Adverse Events in Pooled Arms +/- RBV, Regardless of Relatedness and Severity ($\geq 5\%$ difference between arms)

Preferred Term	GZR/EBR x 12w or 16w (n=210)	GZR/EBR+RBV x 12w or 16w (n=210)
	N (%)	N (%)
Fatigue	37 (18)	60 (29)
Nausea	13 (6)	33 (16)
Anemia	0	29 (14)
Accidental overdose	4 (2)	29 (14)
Dyspnea (includes DOE)	3 (1)	30 (14)
Pruritus	6 (3)	22 (10)
Insomnia	11 (5)	21 (10)
Vomiting	2 (1)	16 (8)
Dyspnea exertional	1 (<1)	11 (5)

When pooling arms based on treatment duration, most AEs occurred at a similar rate with 16w vs. 12w of GZR/EBR +/- RBV (none $\geq 5\%$ difference). Only diarrhea, myalgia, and constipation occurred at a higher rate (by 3-4%) with 16w vs. 12w of treatment and in at least 5% of subjects treated for 16w. However, these differences decreased when considering relatedness of the AE to study treatment.

Pooled Analysis (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

The two tables below display pooled analysis of AEs by SOC and PT, respectively, based on treatment regimen and duration. Subjects in both RBV-containing arms and especially with 16w duration experienced more AEs in every SOC. PTs in the second table represent the major drivers for each SOC. Ear and labyrinth disorders were driven by vertigo and tinnitus, which didn't meet the threshold for inclusion in the table. The majority of AEs were mild or moderate. See Section 8.4.4 for analysis of severe AEs. Highlighted cells represent treatment arms with the highest rates of AEs per SOC or PT.

Table 28. Pooled Analysis of Study Treatment-Related AEs by SOC Occurring in at least 5% of Subjects in Any Arm (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

System Organ Class (SOC)	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
	N (%)	N (%)	N (%)	N (%)	N (%)
All	41 (39)	230 (36)	46 (44)	112 (61)	81 (76)
Blood and lymphatic system disorders	0	1 (<1)	0	19 (10)	19 (18)
Ear and labyrinth disorders	0	7 (1)	5 (5)	3 (2)	0
Gastrointestinal disorders	18 (17)	93 (15)	13 (12)	39 (21)	25 (24)
General disorders	12 (11)	84 (13)	22 (21)	61 (33)	37 (35)
Investigations	1 (1)	13 (2)	2 (2)	9 (5)	12 (11)
Metabolism and nutrition disorders	1 (1)	14 (2)	0	8 (4)	5 (5)
Musculoskeletal and connective tissue disorders	3 (3)	24 (4)	9 (8)	10 (5)	12 (11)
Nervous system disorders	15 (14)	80 (13)	17 (16)	37 (20)	26 (25)
Psychiatric disorders	9 (9)	48 (8)	10 (10)	24 (13)	21 (20)
Respiratory, thoracic and mediastinal disorders	2 (2)	6 (1)	3 (3)	17 (9)	19 (18)
Skin and subcutaneous tissue disorders	9 (9)	32 (5)	7 (7)	25 (14)	22 (21)

Table 29. Pooled Analysis of Treatment-Related AEs by PT Occurring in at least 5% of Subjects in Any Arm (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
Preferred term (PT)	N (%)	N (%)	N (%)	N (%)	N (%)
Fatigue	10 (10)	68 (11)	14 (13)	42 (23)	27 (25)
Headache	9 (9)	61 (10)	13 (12)	26 (14)	18 (17)
Anemia	0	0	0	18 (10)	17 (16)
Dyspnea ¹	1 (1)	4 (1)	1 (1)	12 (7)	15 (14)
Nausea	5 (5)	31 (5)	2 (2)	21 (11)	13 (12)
Rash events ²	1 (1)	9 (1)	0	11 (6)	11 (11)
Pruritus events ³	7 (7)	8 (1)	2 (2)	11 (6)	11 (10)
Asthenia	2 (2)	17 (3)	8 (8)	20 (11)	9 (8)
Insomnia	3 (3)	14 (2)	4 (4)	13 (7)	6 (6)
Dyspepsia	1 (1)	5 (1)	0	5 (3)	6 (6)
Myalgia	0	6 (1)	3 (3)	5 (3)	6 (6)
Vomiting	0	5 (1)	0	7 (4)	6 (6)
Irritability	2 (2)	12 (2)	2 (2)	4 (2)	5 (5)
Cough	1 (1)	3 (<1)	1 (1)	8 (4)	5 (5)
Decreased appetite	0	10 (2)	0	7 (4)	5 (5)

¹Includes dyspnea and dyspnea exertional

²Includes dermatitis, dermatitis allergic, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, skin irritation, and urticaria

³Includes pruritis, pruritis allergic, and pruritis generalized

Reviewer Comment: Fatigue, headache, and nausea were the most common AEs reported across trials with GZR/EBR without RBV but occurred at relatively similar rates compared to placebo. No notable differences appeared with increased duration of GZR/EBR without RBV from 12 to 16 weeks, with the exception of asthenia. Subjects treated with GZR/EBR with RBV had a notably higher rate of most AEs compared to GZR/EBR without RBV and to placebo, whether the regimen was administered for 12 or 16 weeks. These data show RBV substantially increases the risk of most AEs, but GZR/EBR does not increase the risk of known RBV-related AEs.

8.4.6. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in pooled Phase 3 trials and C-SALVAGE. 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 GZR/EBR

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

compared to placebo. Neither treatment duration nor addition of RBV was associated with a higher rate of grade 3/4 abnormalities, except elevated bilirubin in RBV-containing arms. Overall, laboratory analyses did not reveal any new significant safety concerns.

See Section 8.5.1 for detailed discussion of ALT, AST, bilirubin, alkaline phosphatase, and INR abnormalities. Grade 3 ALT elevations occurred more frequently in subjects who received GZR/EBR without RBV for 16 weeks (5%) compared to other treatment groups (0-1%); however, the frequency was higher compared to the 16w/RBV group (0%) and lower compared to placebo (9%). Grade 4 ALT elevations were infrequent (1%) and observed only in the largest treatment group, GZR/EBR without RBV for 12 weeks. AST elevations were also infrequent and occurred at a similar rate in subjects receiving GZR/EBR vs. placebo. Of note, ALT/AST elevations in placebo-treated subjects are presumably due to untreated HCV infection, whereas ALT/AST elevations in GZR/EBR-treated subjects are likely due to drug.

One subject experienced grade 4 total bilirubin elevation (indirect and direct bilirubin) beginning at TW6 and resolving at FU4; the subject received GZR/EBR + RBV for 12 weeks without treatment interruption or concomitant hepatic symptoms or events. One subject experienced grade 4 direct bilirubin elevation (>5x ULN) and discontinued treatment at TW14 due to unrelated GI inflammation (see Section 8.4.3). One subject with a grade 4 INR elevation experienced a bleeding event of hematochezia which resolved on treatment; three subjects with a grade 4 INR elevation reported no AEs during the study. No grade 3 or 4 alkaline phosphatase elevations occurred (not shown below; see Section 8.5.1).

No GZR/EBR-treated subject who experienced a grade 4 lipase elevation reported an AE of pancreatitis. One subject experienced concomitant upper abdominal pain, but both the abdominal pain and lipase elevation resolved rapidly and with continued treatment.

CK elevations grade 1-4 occurred in slightly more subjects treated with GZR/EBR (9%) compared to placebo (6%); the majority of CK elevations in GZR/EBR-treated subjects were grade 1 (6%) or grade 2 (2%). No subject with a grade 2-4 creatine kinase (CK) elevation was receiving concomitant treatment with a statin. None of the five GZR/EBR-treated subjects who experienced a grade 4 creatine kinase (CK) elevation reported associated clinical AEs. Three GZR/EBR-treated subjects with grade 3 CK elevations reported myalgia, musculoskeletal pain, and muscle spasms, respectively, all of which resolved with continued treatment.

Grade 3 and 4 hematologic abnormalities were uncommon, particularly in the non-RBV groups. Low hemoglobin was more prevalent in RBV groups, which is not unexpected due to RBV-induced hemolysis. Grade 3 and 4 neutropenia occurred in one GZR/EBR-treated subject each, but neither was associated with any clinical AEs and both represented an isolated drop. Grade 3 thrombocytopenia occurred rarely and at a slightly lower rate with GZR/EBR compared to

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

placebo; these subjects generally had low platelets at baseline, and none were associated with clinical AEs. No subject experienced grade 4 thrombocytopenia.

Table 30. Pooled Analysis of Treatment-Emergent Chemistry Laboratory Abnormalities (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

Lab Test	Emergent Toxicity Grade	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
		N (%)	N (%)	N (%)	N (%)	N (%)
ALT	Grade 1	26 (25%)	16 (3%)	7 (7%)	1 (1%)	3 (3%)
	Grade 2	20 (19%)	6 (1%)	0 (0%)	0 (0%)	1 (1%)
	Grade 3	9 (9%)	5 (1%)	5 (5%)	1 (1%)	0 (0%)
	Grade 4	0 (0%)	5 (1%)	0 (0%)	0 (0%)	0 (0%)
AST	Grade 1	26 (25%)	15 (2%)	7 (7%)	1 (1%)	3 (3%)
	Grade 2	18 (17%)	10 (2%)	2 (2%)	2 (1%)	1 (1%)
	Grade 3	2 (2%)	2 (<1%)	3 (3%)	0 (0%)	0 (0%)
	Grade 4	1 (1%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Total Bilirubin	Grade 1	4 (4%)	37 (6%)	9 (9%)	46 (25%)	27 (25%)
	Grade 2	4 (4%)	15 (2%)	1 (1%)	31 (17%)	20 (19%)
	Grade 3	0 (0%)	2 (<1%)	0 (0%)	9 (5%)	9 (8%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Direct Bilirubin	Grade 1	5 (5%)	20 (3%)	2 (2%)	39 (21%)	11 (10%)
	Grade 2	1 (1%)	9 (1%)	2 (2%)	24 (13%)	10 (9%)
	Grade 3	1 (1%)	3 (<1%)	0 (0%)	3 (2%)	5 (5%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Albumin (low)	Grade 1	3 (3%)	17 (3%)	2 (2%)	0 (0%)	7 (7%)
	Grade 2	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
INR	Grade 1	14 (13%)	90 (4%)	12 (11%)	54 (30%)	25 (24%)
	Grade 2	0 (0%)	16 (3%)	0 (0%)	5 (3%)	3 (3%)
	Grade 3	1 (1%)	6 (1%)	0 (0%)	2 (1%)	0 (0%)
	Grade 4	0 (0%)	1 (<1%)	1 (1%)	2 (1%)	0 (0%)
GGT	Grade 1	26 (25%)	23 (4%)	4 (4%)	8 (4%)	5 (5%)
	Grade 2	12 (11%)	12 (2%)	2 (2%)	2 (1%)	3 (3%)
	Grade 3	8 (8%)	4 (1%)	0 (0%)	1 (1%)	3 (3%)
Amylase	Grade 1	9 (9%)	104 (16%)	14 (13%)	20 (11%)	17 (16%)
	Grade 2	2 (2%)	18 (3%)	1 (1%)	3 (2%)	2 (2%)
	Grade 3	4 (4%)	15 (2%)	2 (2%)	4 (2%)	4 (4%)
	Grade 4	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lipase	Grade 1	17 (16%)	123 (19%)	21 (20%)	37 (20%)	20 (19%)
	Grade 2	8 (8%)	85 (13%)	16 (15%)	18 (10%)	9 (8%)
	Grade 3	2 (2%)	21 (3%)	5 (5%)	4 (2%)	7 (7%)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Lab Test	Emergent Toxicity Grade	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
		N (%)	N (%)	N (%)	N (%)	N (%)
	Grade 4	3 (3%)	12 (2%)	0 (0%)	3 (2%)	1 (1%)
Creatinine	Grade 1	1 (1%)	9 (1%)	1 (1%)	2 (1%)	0 (0%)
	Grade 2	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
	Grade 3	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Creatine Kinase	Grade 1	4 (4%)	47 (7%)	4 (4%)	5 (3%)	3 (3%)
	Grade 2	1 (1%)	10 (2%)	3 (3%)	2 (1%)	2 (2%)
	Grade 3	0 (0%)	3 (<1%)	2 (2%)	1 (1%)	2 (2%)
	Grade 4	1 (1%)	4 (1%)	0 (0%)	1 (1%)	0 (0%)

Table 31. Pooled Analysis of Treatment-Emergent Hematology Laboratory Abnormalities (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE)

Lab Test	Emergent Toxicity Grade	Placebo x 12w (n=105)	GZR/EBR x 12w (n=639)	GZR/EBR x 16w (n=105)	GZR/EBR + RBV x 12w (n=183)	GZR/EBR + RBV x 16w (n=106)
		N (%)	N (%)	N (%)	N (%)	N (%)
Hemoglobin (low)	Grade 1	4 (4%)	12 (2%)	1 (1%)	34 (19%)	15 (14%)
	Grade 2	0 (0%)	3 (<1%)	0 (0%)	10 (5%)	17 (16%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	7 (4%)	4 (4%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Leukocytes (low)	Grade 1	1 (1%)	7 (1%)	0 (0%)	3 (2%)	2 (2%)
	Grade 2	0 (0%)	2 (<1%)	0 (0%)	2 (1%)	0 (0%)
	Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Neutrophils (low)	Grade 1	4 (4%)	21 (3%)	5 (5%)	5 (3%)	1 (1%)
	Grade 2	0 (0%)	7 (1%)	1 (1%)	1 (1%)	0 (0%)
	Grade 3	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
	Grade 4	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Platelets (low)	Grade 1	6 (6%)	35 (5%)	6 (6%)	5 (3%)	6 (6%)
	Grade 2	14 (13%)	49 (8%)	9 (9%)	5 (3%)	5 (5%)
	Grade 3	2 (2%)	3 (<1%)	0 (0%)	2 (1%)	1 (1%)

C-EDGE COINFECTION: HIV RNA

All subjects maintained HIV suppression defined as HIV RNA < 20 copies/mL at the last available treatment visit or post-treatment follow-up visit.

The mean change from baseline in CD3+CD4+ cell count was +57 cells/mm³ at TW12 and +33

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

cells/mm³ at FU12.

Reviewer Comment: GZR/EBR treatment did not interfere with HIV virologic suppression or immunologic response.

8.4.7. **Vital Signs**

Changes in systolic blood pressure, diastolic blood pressure, and heart rate in subjects receiving GZR/EBR in Phase 3 trials were similar to changes that occurred in subjects receiving placebo. Clinical events, such as hypertension and palpitations, occurred at a low rate in both GZR/EBR- and placebo-treated subjects and did not appear clinically significant based on a thorough cardiac analysis (see Section 8.5.2).

8.4.8. **Electrocardiograms (ECGs)**

During Phase 3 trials, no subject discontinued treatment due to an ECG abnormality. Overall, 23/954 (2%) GZR/EBR-treated subjects had an on-treatment QTcF interval between 450-480 msec. Among these 23 subjects, six subjects had QTcF interval prolongation at screening between 450-480 msec.

One subject (068_142000006) had an on-treatment QTcF interval prolongation > 480 msec, specifically 485 msec at TW16. At the screening visit, this subject's ECG showed 1st degree AV block and QTcF interval of 452 msec. No related AEs were reported for this subject.

Two subjects each had an ECG abnormality of QT prolongation reported as an AE by the investigator. One subject (068_142000009) had a QTcF interval of 456 msec at TW16 compared to 446 msec at screening, and one subject (068_151000001) had a QTcF interval of 445 msec at TW12 compared to 449 msec at screening. Neither finding was associated with a clinical AE.

Reviewer Comment: GZR/EBR did not cause meaningful ECG changes or concerns based on Phase 3 clinical trials as well as thorough QT trials (see Section 8.4.9).

8.4.9. **QT**

The Applicant conducted thorough QT (TQT) trials for both GZR and EBR, and the FDA Interdisciplinary Review Team (IRT) for QT studies review both trials. Neither drug was associated with significant QTc prolongation. The largest upper bounds of the 2-sided 90% CI for the mean differences between GZR 1600 mg and placebo and between EBR 700 mg and placebo were below 10 msec, the threshold for regulatory concern as described in the ICH E14 guidelines. Both of the largest lower bounds of the two-sided 90% CI in the GZR study and EBR

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

study for $\Delta\Delta\text{QTcF}$ for moxifloxacin were greater than 5 msec, indicating that assay sensitivity was established. Please refer to the IRT-QT review for full details.

8.4.10. Immunogenicity

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

The structure of GZR contains a sulfonamide moiety. During the NDA review, FDA requested the Applicant assess whether subjects with a documented sulfa allergy had a greater incidence or severity of rash and other AEs associated with allergic reactions. The Applicant responded that clinical trials of GZR did not include systematic collection of drug allergy history, but they were able to review clinical safety data in subjects who reported a history of sulfa allergy at enrollment. The Applicant stated that subjects with a documented history of sulfa allergy did not have a greater incidence of these events compared to all subjects in their integrated safety population. Furthermore, the Applicant clarified that the structure of GZR includes an acyl-sulfonamide, which is different from the sulfonamide structure found in “sulfa” drugs associated with allergic reactions. Additionally, preclinical studies found no signals or findings of phototoxicity, skin sensitization, or antigenicity related to GZR. The Applicant pointed out that many sulfonamide containing drugs are not associated with drug allergy and are approved without a sulfa allergy warning, including Viekira Pak which has an acyl-sulfonamide component.

Reviewer Comment: The Applicant makes a reasonable argument that the structure of GZR is not generally associated with allergic reactions, and that Viekira Pak, which has a similar sulfonamide structure, does not contain a Warning for patients with a history of sulfa allergy. Available clinical trial data with GZR/EBR further support the notion that this structure does not pose an increased risk of allergic reactions in patients with a history of sulfa allergy. Therefore, it is reasonable not to include such a Warning or Precaution at this time for GZR/EBR, as proposed by the Applicant. CMC reviewer Dr. George Lunn is also of the opinion that GZR does not have any concerning structures.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hepatobiliary Events

The hepatic safety population for this review consists of 1558 subjects who received GZR 100 mg and EBR 50 mg with or without RBV for at least 12 weeks in Phase 2 trials C-WORTHY, C-SCAPE, and C-SALVAGE, and Phase 3 trials C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE. Additionally, subjects in the DTG/placebo arm of C-EDGE TN were evaluated. Trials 003, 038, and 039 were not included due to one or more of the following reasons: (1) administration of

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

GZR >100 mg daily, (2) administration of GZR without EBR or with EBR < 50 mg, and/or (3) co-administration of PR. Trials 058A (non-IND, Japanese trial) and 059A (Child-Pugh B trial) were also not included because they are ongoing with preliminary data through FU4 instead of FU12. Trial 074 was not included because the regimen included sofosbuvir.

The following table displays key baseline characteristics for the hepatic safety population.

Table 32. Pooled Hepatic Safety Population: Baseline Characteristics

	GZR/EBR +/- RBV x 12-18w (n=1558)	Placebo (n=105)
	N (%)	N (%)
Age (y)		
18-35	131 (8)	9 (9)
36-50	422 (27)	25 (24)
51-64	841 (54)	53 (50)
≥ 65	164 (11)	18 (17)
Sex		
Female	586 (38)	49 (47)
Male	972 (62)	56 (53)
Race		
White	1190 (76)	73 (70)
Black	204 (13)	18 (17)
Asian	133 (9)	12 (12)
Cirrhosis	457 (29)	22 (21)
Genotype		
1a	830 (53)	54 (51)
1b	512 (33)	40 (38)
4	103 (7)	8 (8)
6	25 (2)	3 (3)

Among GZR/EBR-treated subjects in the hepatic safety population, the mean baseline ALT was 67 U/L in non-cirrhotic subjects and 102 U/L in cirrhotic subjects. Treatment with GZR/EBR resulted in a rapid decrease from baseline in mean ALT levels which is consistent with reduction in viral load and hepatic inflammation caused by HCV infection. Approximately 1% of subjects experienced a post-baseline ALT elevation of Grade 3 or 4, and the rate was similarly low between subjects with or without cirrhosis and those receiving GZR/EBR with or without RBV. No Grade 4 and infrequent Grade 3 bilirubin elevations occurred in subjects who were not receiving RBV, while a higher rate occurred in RBV-treated subjects, likely due to RBV-induced hemolysis. Most subjects were asymptomatic and experienced improvement or resolution by the end of treatment or during the follow-up period. No subjects experienced Grade 3 or Grade 4 ALP elevations. The following table displays the worst baseline toxicity grade (that was

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

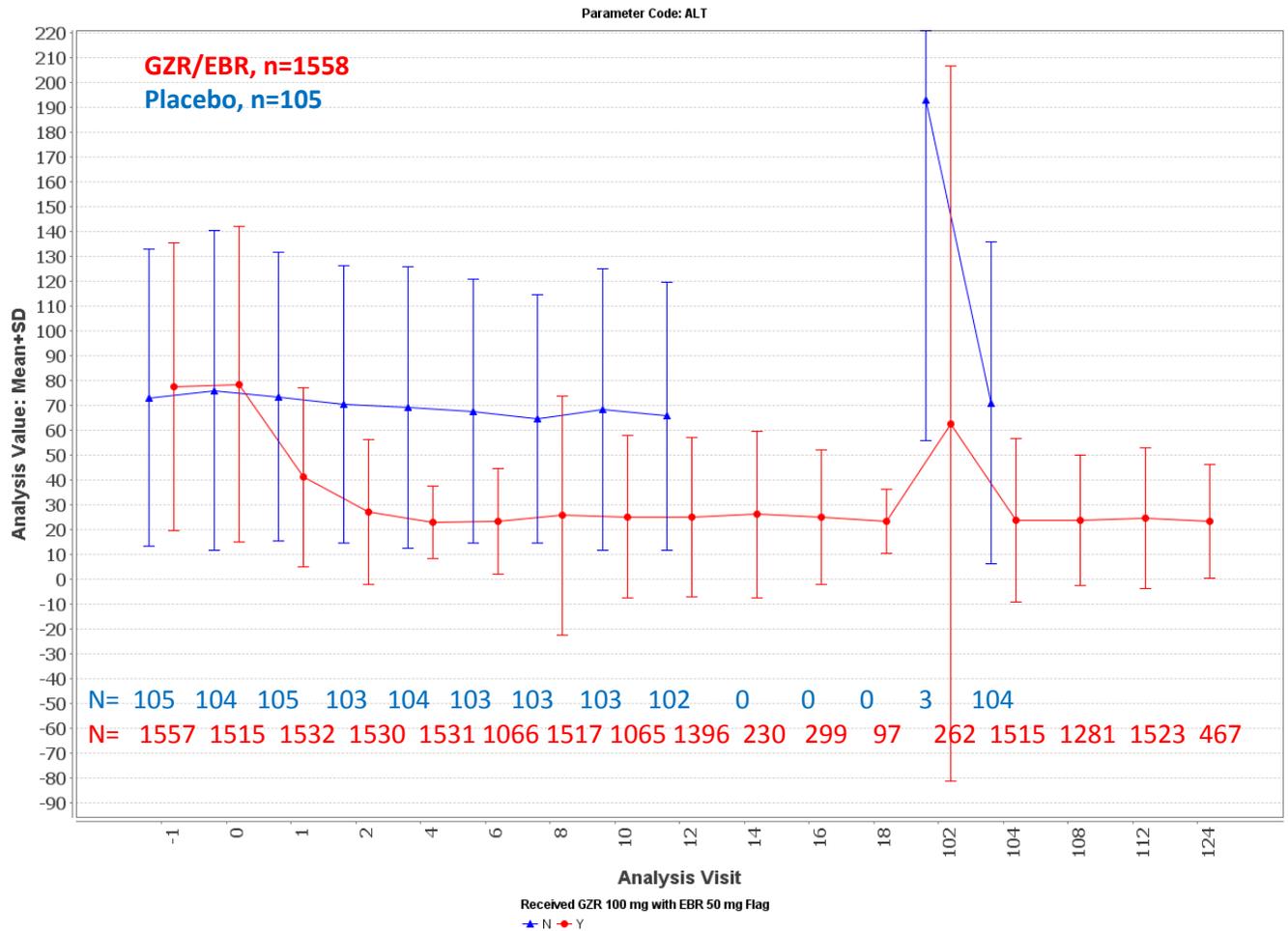
also worse than baseline) for ALT, AST, ALP, and total bilirubin in placebo- and GZR/EBR-treated subjects. GZR/EBR-treated subjects are subdivided by inclusion or exclusion of RBV as well as presence or absence of cirrhosis.

Table 33. Hepatic Laboratory Abnormalities in the Hepatic Safety Population: Worst Post-Baseline Toxicity Grade and Worse than Baseline

Laboratory Parameter and Toxicity Grade	Placebo x 12w	GZR/EBR x 12-18 w		GZR/EBR +/- RBV x 12-18 w	
	(n=105)	No RBV (n=961)	RBV (n=597)	Non-Cirrhotic (n=1100)	Cirrhotic (n=457)
	N (%)	N (%)	N (%)	N (%)	N (%)
ALT					
G1: 1.25 – 2.5 x ULN	26 (25)	27 (3)	11 (2)	31 (3)	7 (2)
G2: >2.5 – 5.0 x ULN	20 (19)	10 (1)	3 (<1)	10 (1)	3 (1)
G3: 5.1 – 10.0 x ULN	9 (9)	11 (1)	2 (<1)	7 (1)	6 (1)
G4: >10.0 x ULN	0	6 (1)	1 (<1)	6 (<1)	1 (<1)
AST					
G1: 1.25 – 2.5 x ULN	26 (25)	28 (3)	9 (2)	28 (3)	9 (2)
G2: >2.5 – 5.0 x ULN	18 (17)	14 (1)	4 (1)	13 (1)	5 (1)
G3: 5.1 – 10.0 x ULN	2 (2)	6 (1)	1 (<1)	5 (<1)	2 (<1)
G4: >10.0 x ULN	1 (1)	3 (<1)	0	2 (<1)	1 (<1)
ALP					
G1: 1.25 – 2.5 x ULN	1 (1)	50 (5)	23 (4)	25 (2)	48 (11)
G2: >2.5 – 5.0 x ULN	0	1 (<1)	1 (<1)	0	2 (<1)
G3: 5.1 – 10.0 x ULN	0	0	0	0	0
G4: >10.0 x ULN	0	0	0	0	0
Total Bilirubin					
G1: 1.1 – 1.5 x ULN	4 (4)	56 (6)	137 (23)	116 (11)	77 (17)
G2: 1.6 – 2.5 x ULN	4 (4)	22 (2)	93 (16)	54 (5)	61 (13)
G3: 2.6 – 5.0 x ULN	0	3 (<1)	34 (6)	24 (2)	13 (3)
G4: >5.0 x ULN	0	0 (0)	1 (<1)	0	1 (<1)

The following figure illustrates the mean (and SD) ALT from baseline through the end of treatment (TW12, TW16, or TW18, respectively) and throughout the follow-up period. All placebo-treated subjects received 12 weeks of treatment and 4 weeks of blinded follow up. FU2 (Analysis Visit 102) was generally not a regularly scheduled study visit; therefore, ALT values at this time point are likely skewed by subjects receiving interim laboratory testing due to previously elevated enzymes. Placebo-treated subjects had a similar mean baseline ALT value, which remained relatively unchanged throughout the 12 weeks of treatment and 4-week follow-up period. The AST pattern was similar to the ALT pattern (not shown). Overall, treatment of HCV with GZR/EBR resulted in ALT and AST improvement compared to placebo.

Figure 6. Mean ALT from Baseline through Follow-Up Week 24 in the Hepatic Safety Population



Pre-specified Hepatic Laboratory Abnormalities and Events

Following identification of a safety signal in an early Phase 2 trial (see Section 3.2), hepatobiliary events were a focus of subsequent Phase 2 and Phase 3 trials. The following hepatic safety measures were pre-specified in all the trials used for hepatic safety analysis:

1. Late ALT or AST elevations defined as >5x ULN occurring after TW4 in subjects with an occurrence of ALT/AST ≤ULN between TW2 and TW4.
2. Hepatic ECI defined with the following criteria from initiation of study therapy through 14 days following treatment and not associated with virologic failure:
 - a. First instance of ALT or AST >500 IU/L
 - b. First instance of ALT or AST >3x baseline AND >100 IU/L
 - c. First instance of alkaline phosphatase >3x ULN

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

3. Discontinuation Due to Liver-Related Events, defined per protocol as:
 - a. ALT or AST increases to >500 IU/L
 - b. ALT or AST increases to >3x baseline, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2x ULN and/or INR increases from baseline and is >1.5 (unless the subject is on anticoagulation)
 - c. ALT or AST increases to >3x the nadir value, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2x ULN and/or INR increases from baseline and is >1.5 (unless the subject is on anticoagulation)
 - d. ALT or AST increases to >3x the nadir value, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following AEs that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to GZR: nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%)
 - e. ALP increases to >3x ULN, a simultaneous increase in total bilirubin >2x ULN, and other causes of elevated ALP are excluded

The pre-specified hepatic abnormalities outlined above include those that are less likely to be a result of underlying hepatic disease. While they may be drug-related, etiologies other than study drug and underlying HCV infection are possible. Because of the known hepatic safety signal with GZR, this review also evaluated late ALT or AST elevations that fell outside the pre-specified criteria.

As displayed in the following table, treatment with GZR/EBR for at least 12 weeks resulted in a low but increased incidence of pre-specified hepatic abnormalities, including late ALT or AST elevations >5x ULN, compared to placebo. Importantly, no placebo-treated subjects experienced an increase in liver enzymes >5x ULN, which supports the notion that late ALT/AST elevations of this degree are likely drug-related rather than disease-related; however, the number of placebo-treated subjects was substantially lower than treated subjects, which is notable given the low incidence. The incidence of ALT/AST elevation >2x ULN was higher with placebo compared to study drug, likely due to untreated HCV infection.

Of note, I excluded two ECIs in GZR/EBR-treated subjects that the Applicant included because one subject (036200007) experienced ALT >500 U/L on Day 1 prior to study drug administration and the drug was discontinued after three days, and one subject (035600002) experienced hepatic laboratory abnormalities four weeks after the end of treatment.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 34. Liver Abnormalities and Events in the Hepatic Safety Population: GZR/EBR vs. Placebo

Event	GZR/EBR +/- RBV x 12-18w (n=1558)	Placebo x 12w (n=105)
	N (%)	N (%)
Pre-specified Hepatic Lab Abnormality or Event ¹	18 (1.2)	0
Pre-specified Late ALT/AST Elevation ²	12 (0.8)	0
Late ALT/AST Elevation ³	4 (0.3)	0
Late ALT/AST Elevation ⁴	19 (1.2)	4 (3.8)
Late ALT/AST Elevation ⁵	17 (1.1)	34 (32)

¹ Late ALT/AST elevation² or Hepatic ECI or Discontinuation due to Pre-specified Liver Event

² ALT or AST elevation >5 x ULN after TW4 with a normal ALT or AST between TW2 and TW4

³ ALT or AST elevation >5 x ULN after TW4 without a normal ALT or AST between TW2 and TW4

⁴ ALT or AST elevation >2 x ULN after TW4 with a normal ALT or AST between TW2 and TW4

⁵ ALT or AST elevation >2 x ULN after TW4 without a normal ALT or AST between TW2 and TW4

In the GZR/EBR group, the incidence of pre-specified hepatic abnormalities and all “other” pooled late ALT/AST elevations was not proportionately higher based on presence of cirrhosis or HIV coinfection, addition of RBV, or duration of treatment (analyses not shown).

Of the 18 pre-specified hepatic abnormalities or events, late ALT/AST elevation was the most common event. The following table summarizes mean ALT and AST values from baseline through FU4 for the 12 subjects who experienced a pre-specified late ALT/AST elevation event.

Table 35. Mean Liver Enzyme Results in Subjects with a Pre-specified Late ALT/AST Elevation Event

N=12	Baseline	Nadir	Peak	EOT ¹	FU4
ALT (U/L)	68	19	396	249	24
AST (U/L)	65	24	221	151	28

¹ Three subjects discontinued at the time of peak ALT/AST, and therefore, the EOT values for these subjects are the same as the peak values. If these three subjects are removed from the EOT, the mean EOT ALT and AST falls to 89 U/L and 63 U/L, respectively.

EOT = end of treatment, FU4 = Follow-up visit four weeks after end of treatment

Normal range (Central lab): ALT [10-33 U/L], AST [10-36 U/L]

Other than baseline ALT and AST elevations, all 12 subjects had normal baseline hepatic laboratory parameters, including bilirubin. On treatment ALT and AST nadir occurred between TW2 and TW8 (mean Study Day 36 and 24, respectively). ALT increased a mean of 18x the nadir (range 7 - 40 times the nadir) to peak levels; AST increased a mean of 9x the nadir (range 4 - 21 times the nadir) to peak levels.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

At the time of peak ALT and AST levels, three subjects also had a Grade 1 total bilirubin elevation ranging from 1.2-1.3 mg/dL, although a repeat test in one subject showed a Grade 2 elevation of 2.0 mg/dL. Four additional subjects had Grade 1 total bilirubin elevations, which occurred after the peak ALT or AST time point. Five of the seven subjects with total bilirubin elevations had an elevated direct bilirubin level ranging from 0.46 - 0.65 mg/dL. Two of these subjects were treated with RBV, but the elevations are unlikely related to RBV-induced hemolysis given the time course of bilirubin elevation and increase in direct bilirubin.

Hepatic-related symptoms did not occur in 11 of the 12 subjects; one subject experienced abdominal pain two days after onset of the late ALT/AST elevation event. All events completely resolved, defined as ALT, AST, and total bilirubin levels within normal limits. Most events resolved by FU4 and some as early as end of treatment, but some resolved as late as FU12. All subjects achieved SVR12 except for one GT 6-infected subject who relapsed at FU4 (baseline HCV RNA was >15 million).

Additional details for all 18 subjects with a pre-specified hepatic abnormality or event, including the 12 subjects with a pre-specified late ALT/AST elevation event, are available in the Appendix (Section 13.3).

Three of the 18 subjects discontinued study drug early due to pre-specified criteria (two subjects had ALT >500 U/L and one subject had ALT/AST >3x the nadir value and >100 U/L and eosinophils >5%). Despite discontinuation at TW8 or TW10, all three subjects achieved SVR12. Two additional subjects met discontinuation criteria at TW12 due to ALT or AST >3x the nadir value and >100 U/L and elevated INR (1.8) in one subject and eosinophils >5% in one subject; however, treatment was already complete. Although seemingly rare, the need for discontinuation at TW12 is not optimal in a subject who requires 16 weeks of treatment to maximize efficacy and achieve SVR12 (i.e., subjects with baseline NS5A polymorphisms or prior PR experience).

Lab parameters other than ALT, AST, and bilirubin were generally within normal limits unless otherwise specified. The Applicant selected eosinophils >5% as part of discontinuation criteria to set a low threshold to prompt further investigation. The two subjects (040900004 and 058500004) with an eosinophil result of 5.1% and 8.8%, respectively, who either discontinued study drug or met discontinuation criteria at the end of treatment were asymptomatic and maintained a normal absolute eosinophil count and would not likely require treatment discontinuation in clinical practice based on the information provided. A third subject (010100001) with an eosinophil result of 5.3% did not discontinue study drug because the investigator deemed the event not related to study drug. Overall, four subjects had an eosinophil result >7% (ULN), one of whom had a history of chlonorchiasis and eosinophilia prior

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

to treatment. The absolute eosinophil count for all subjects remained within normal limits with the exception of the subject with chronic chlonorchiasis.

Three cases of late ALT/AST elevations had potential confounders that may have contributed to each event. Subject 040800006 experienced virologic rebound at FU4. Because the event occurred relatively late in this subject at TW12, it is possible that virologic failure contributed; however, the subject's HCV RNA result was TND at TW12 (end of treatment) making it less likely. Subject 150300004 had a medical history of chronic chlonorchiasis, which likely contributed to eosinophilia, but the pattern of ALT/AST elevation was consistent with the other cases. Lastly, Subject 016300003 drank four glasses of champagne the night before the onset of late ALT/AST elevation and was concomitantly taking etifoxine, a drug with hepatotoxic potential, and Kudzu root. Although these factors may have contributed to the event and specifically resulted in further elevated ALT/AST, the event was consistent with other cases. The role of GZR/EBR in the late ALT/AST elevation events cannot be ruled out in any of these three cases.

Two hepatic ECIs had confounding factors that may plausibly explain each event. Subject 078200005 experienced a relatively low ALT elevation of 104 U/L at TW6 along with a higher AST elevation and increases in CK and indirect bilirubin. The subject admitted to recent strenuous workouts, which likely caused the event given the pattern of laboratory abnormalities and rapid resolution within five days after abstaining from heavy workouts. In Subject 050000004 ALT, AST, ALP, and bilirubin elevations along with acute onset nausea and pruritis at TW2 appear related to biliary stent blockage diagnosed by abdominal ultrasound. GZR/EBR was temporarily discontinued for three days while the subject underwent endoscopic intervention. The event resolved immediately after resumption of GZR/EBR, and the subject completed treatment without any recurrent or additional abnormalities. These two hepatic ECIs were probably not related to study drug.

The following table shows baseline characteristics in various populations that experienced one or more hepatic events. Proportionately more subjects who were older than 65 years of age, female, Asian, or infected with HCV GT 1b experienced a pre-specified hepatic abnormality, including late ALT/AST elevation. GZR exposures are independently higher in subjects older than 65 years of age, female, and Asian, which may explain the higher incidence of pre-specified hepatic events. However, exposures are also higher in cirrhotic subjects, yet they did not experience a higher incidence of hepatic abnormalities compared to non-cirrhotic subjects. Furthermore, GT 1b-infected subjects have similar exposures as GT 1a-infected subjects, yet the incidence of hepatic abnormalities was higher in GT 1b-infected subjects. While an exposure-response relationship for hepatic abnormalities has been demonstrated and appears contributory, drug exposures may not be the only factor.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 36. Baseline Characteristics in Subjects who Experienced a Hepatic Event

	GZR/EBR +/- RBV x 12-18 w			Placebo x 12w
	Pre-specified Late ALT/AST Elevation ¹ N=12	Pre-specified Hepatic Lab Abnormality or Event ² N=18	Pooled Other Late ALT/AST Elevation ³ N=39	Pooled Other Late ALT/AST Elevation ³ N=38
Age (y)				
18 - 64	9/1394 (0.6)	15/1394 (1.1)	33/1394 (2.4)	31/87 (36)
≥ 65	3/164 (1.8)	3/164 (1.8)	6/164 (3.7)	7/18 (39)
Sex				
Male	2/972 (0.2)	6/972 (0.6)	22/972 (2.3)	19/56 (34)
Female	10/586 (1.7)	12/586 (2.0)	17/586 (2.9)	19/49 (40)
Race				
White	7/1190 (0.6)	10/1190 (0.8)	27/1190 (2.3)	28/73 (38)
Black	1/204 (0.5)	3/204 (1.5)	6/204 (2.9)	5/18 (28)
Asian	4/133 (3.0)	5/133 (3.8)	6/133 (4.5)	4/13 (31)
Cirrhosis				
Y	4/457 (0.9)	4/457 (0.9)	13/457 (2.8)	11/22 (50)
N	8/1100 (0.7)	14/1100 (1.3)	26/1100 (2.4)	27/83 (33)
HCV GT				
1a	2/830 (0.2)	7/830 (0.8)	18/830 (2.2)	20/54 (37)
1b	8/512 (1.6)	9/512 (1.8)	18/512 (3.5)	17/40 (43)

The denominators for each subgroup were derived from Table X above.

¹ ALT or AST elevation >5 x ULN after TW4 with a normal ALT or AST between TW2 and TW4

² Late ALT/AST elevation¹ or Hepatic ECI or Discontinuation due to Pre-specified Liver Event

³ Pooled: ALT or AST elevation >5 x ULN after TW4 without a normal ALT or AST between TW2 and TW4 or ALT or AST elevation >2 x ULN after TW4 with or without a normal ALT or AST between TW2 and TW4

Safety Update Report

Of the 929 subjects who received GZR 100 mg and EBR 50 mg or placebo in the update period, two subjects (P058 AN105122 and P065 AN 480622) experienced a late ALT/AST elevation event as previously defined. Both subjects experienced peak ALT elevation at TW8, remained asymptomatic, and experienced complete resolution. One subject discontinued treatment due to protocol specifications (ALT > 500 U/L). Both events were similar to those reported in the original NDA submission.

Exposure-Safety Analysis

The clinical pharmacology review team's exposure safety analyses are summarized here. Please see Drs. Su-Young Choi and Luning (Ada) Zhuang's review for full details. Exposure-safety analyses focused on the incidence of late ALT/AST elevations based on data from 13 Phase 2 and Phase 3 trials in which subjects received GZR dosages of 25 - 800 mg daily. As expected,

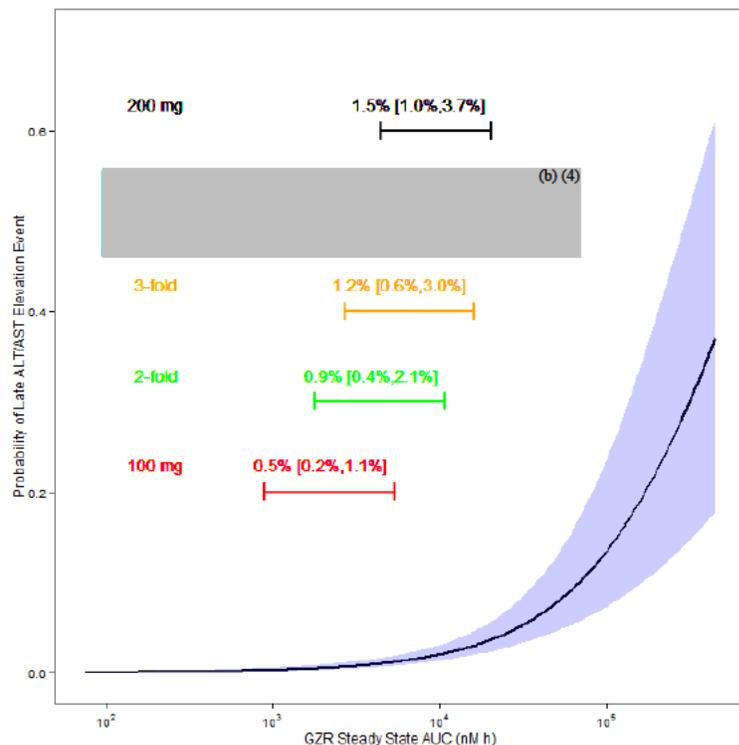
Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

analysis showed the late ALT/AST elevation event was correlated with GZR exposures. No other covariates were identified as significant predictors.

The Applicant analyzed the relationship between the predicted rate of late ALT/AST elevation events compared to the fold change in GZR exposure 100 mg in a reference population. The reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected subjects (i.e., subjects not expected to have higher GZR exposures) receiving GZR 100 mg in Phase 2 or Phase 3 studies. The predicted rate of late ALT/AST elevation events in the reference population was 0.5% with GZR 100 mg. The predicted rates with increased GZR exposures of 5-fold (corresponding to GZR 200 mg) and 13-14-fold (corresponding to GZR 200 – 400 mg) were approximately 2% and 5%, respectively. The Applicant proposes (b) (4) for GZR exposures is acceptable from a safety perspective.

The clinical pharmacology review team conducted an independent assessment of the exposure-response relationship between late ALT/AST elevations and GZR exposure (see Figure below). They concluded that a 3-fold upper bound is more appropriate and has proposed dosage adjustments for certain intrinsic and extrinsic factors based on this boundary. For example, a 3-fold increase in exposure results in a late ALT/AST elevation event rate up to 3% (upper bound), which is the event rate that may be attained by Asians receiving GZR 100 mg.

Figure 7. Exposure-Safety Evaluation for GZR



The red line represents the 90% prediction interval of GZR exposure covered by a dose of 100 mg and the number above the line shows the median (90%) predicted safety event rate for those exposures. The green and yellow bars represent a 2- and 3-fold increase in GZR exposure, respectively, compared to that of 100 mg. Source: Clinical Pharmacology reviewers Drs. Choi and Zhuang

Reviewer Comment: The (b) (4) for GZR safety exposure proposed by the Applicant is high. This degree of increased exposures may result in up to a (b) (4) event rate of late ALT elevations, or a median of (b) (4) which is still more than double the rate that occurred with GZR 100 mg in clinical trials. A 3-fold upper bound and justification proposed by the clinical pharmacology review team is more reasonable. One remaining concern is a potential interaction between intrinsic and extrinsic factors resulting in an additive increase in GZR exposure, which may further increase the rate of late ALT elevation events. For example, an Asian, female, or elderly patient who may intrinsically have increased GZR exposures may take a permitted interacting drug that further increases exposures (above 3-fold). In this case a 2-fold upper bound limit for GZR safety exposure may be more acceptable and account for both intrinsic and extrinsic factors.

However, based on review of the specific increases in GZR exposures in the multitude of drug interaction studies conducted by the Applicant (see Clinical Pharmacology review), it appears a 3-fold upper bound is reasonable. Ketoconazole and ritonavir were the only drugs that

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

increased GZR exposures between 2- and 3-fold; all other interactions either increased GZR exposures well below 2-fold or substantially higher than 3-fold. Potential additive effects of drug interactions and intrinsic factors resulting in <2-fold and 20-50% increase in GZR exposures, respectively, appear to fall within a reasonable safety margin based on exposure-safety modeling (likely well below 3-fold). Furthermore, the late ALT elevation event is well characterized in Phase 2 and Phase 3 trials and appears manageable with adequate monitoring.

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. All of the subjects in the hepatic safety population for GZR/EBR had chronic HCV infection and 29% (457/1558) were classified as having cirrhosis. Subjects in early Phase 2 trials received PR, and the administration of IFN is known to increase the risk of hepatitis exacerbations and hepatic failure, particularly in patients with underlying cirrhosis; these subjects are not included in the hepatic safety population as GZR/EBR will not be recommended in a regimen with PR. Despite the limitations of Hy's Law in the chronic HCV infected population, the Hy's Law laboratory criteria were used for capturing all potential DILI cases in order to conservatively evaluate the relevant subjects in the clinical safety database (i.e., hepatic safety population).

One GZR/EBR-treated subject and one placebo-treated subject met numerical criteria for Hy's Law. Subject 002400002, who was receiving GZR/EBR + RBV for a 12-week treatment course in C-SALVAGE, had an ALT of 141 U/L (>3x ULN), total bilirubin of 2.74 mg/dL (>2x ULN), and normal ALP on Day 7. However, ALT was declining from a baseline of 220 U/L as expected during initial HCV treatment, and total bilirubin was elevated possibly due to acute RBV effects. ALT continued to decline to normal levels where it remained throughout treatment, while bilirubin (including direct bilirubin) remained elevated until FU4. While this case does not appear to be a true Hy's Law case, the persistent elevation of direct bilirubin throughout treatment may indicate some degree of drug-related hepatotoxicity. The event resolved, and though the subject achieved and maintained HCV RNA TND through FU4, he relapsed at FU8 likely due to the presence of baseline NS5A polymorphisms. Subject AN435622 was receiving

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

placebo and met Hy's Law criteria at baseline and throughout the placebo treatment period; laboratory abnormalities were due to underlying HCV infection as the subject was not receiving drug.

Three additional subjects (AN109705, AN480040, and AN680002) fell into or near the Hy's Law quadrant of the e-DISH plot. Although these subjects experienced ALT >3x ULN and total bilirubin >2x ULN, the abnormalities did not occur simultaneously. In all cases, ALT elevations preceded bilirubin elevations, and two of the cases appeared unlikely to be DILI caused by GZR. One case may have been GZR-induced DILI based on the degree and timing of ALT elevations (>5x ULN at TW8) though not a true Hy's Law case.

Miscellaneous Hepatobiliary Events

Clinical AEs (excluding laboratory abnormalities) under the Hepatobiliary Event SOC occurred in 9/1558 (1%) GZR/EBR-treated subjects and 0/105 placebo-treated subjects. PTs were biliary colic, hepatic pain, hepatomegaly, and jaundice, none of which were serious or severe or led to discontinuation of study drug.

Hepatic Safety Conclusions

The pre-specified late ALT/AST elevation event was the predominant hepatic safety finding in the defined hepatic safety population. Specifically, ALT was elevated >5x ULN with or without concomitant AST elevations >5x ULN. The course of the event was similar in all 12 subjects, with swift ALT/AST elevations generally occurring at or after TW8 subsequent to normal ALT/AST levels between TW2 and TW4. Half of the patients experienced bilirubin elevations, which were generally Grade 1 and none >2x ULN. No subject, except one subject with chlonorchiasis, had an elevated absolute eosinophil count, and two subjects had relatively low-level INR elevations (1.3 and 1.8); none of these subjects were symptomatic. The majority of subjects were asymptomatic, and all experienced complete resolution (ALT/AST within normal limits) with continued treatment either by the end of treatment or generally by FU4. Events in subjects who required drug discontinuation also completely resolved. Late ALT/AST elevations did not impact efficacy, as all GT 1 and GT 4 subjects achieved SVR12, even those who discontinued early. One failure occurred in a GT 6 infected subject, and efficacy of GZR/EBR in this population is uncertain.

The exact mechanism of late ALT elevations is unknown, but it appears be a class effect with HCV NS3/4A PIs. The event varies slightly among the HCV PIs; for example, increased ALT elevations usually occur within the first 4 weeks of treatment with Viekira Pak compared to TW8 with GZR/EBR. The reason for this difference is also unknown.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Irrespective of the mechanism, late ALT elevations are related to higher GZR exposures. Several factors associated with increased drug exposure, such as female sex, Asian race, and age \geq 65 years, increase the risk of late ALT/AST elevations. However, cirrhosis does not appear to increase risk based on available clinical trial data even though exposures are increased. Lastly, GT1b infected subjects had a higher incidence of events, which cannot be explained by exposures; it is unclear if this finding is a true association at this time.

Importantly, there were no liver-related deaths or SAEs and no discontinuations due to hepatic events that were not pre-specified. The late ALT/AST elevations that occurred in clinical trials with the proposed dose of GZR/EBR were similar, predictable, and manageable with appropriate monitoring. Overall, the benefit of GZR/EBR 100/50 mg +/- RBV for 12-16 weeks outweighs the risk and implications of hepatic events.

Hepatic Safety Committee

Prior to NDA submission, FDA asked the Applicant to assemble an independent committee of DILI experts and practicing HCV clinicians, preferably including some members not affiliated with Merck or Merck's HCV clinical trials, to formally assess the hepatic safety profile of GZR/EBR. The Applicant's hepatic safety population included subjects in clinical trials who received GZR >100 mg, GZR with PR, and treatment duration <8 weeks. As a result, the Hepatic Safety Committee (HSC) reviewed 25 cases of late ALT/AST elevations, 13 of which were not included in my analysis, and 13 cases of potential Hy's Law based on numerical criteria, 8 of which were not included in my analysis. The consensus of the HSC for the 12 late ALT/AST elevation cases previously discussed was that the majority of events were probable DILI caused by GZR and one event was possible DILI due to confounding chlonorchiasis.

The 13 additional cases reviewed by the HSC included 11 subjects who received GZR >100 mg with PR in P003, one subject who received an 8-week treatment course in C-WORTHY, and one subject who received GZR 100 mg + RBV without EBR. Ten subjects were treated with either GZR 400 mg or 800 mg, which subsequently led to the product being placed on clinical hold and being capped at 100 mg upon releasing the hold. With respect to whether these 13 cases were DILI caused by GZR, the HSC consensus response was probable for 11 cases and unlikely for 2 cases ([GZR 400 mg] and [GZR 100 mg + RBV]) that were more likely muscle-related events. Late ALT/AST elevation events occurring in subjects receiving GZR 100 mg were similar to the events discussed in my review.

The HSC concluded the following key points:

1. A late ALT/AST elevation event, and more specifically late ALT elevation events, is an appropriate marker for assessing hepatic safety of GZR.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

2. No cases clearly fulfilled the accepted criteria for Hy's Law that would indicate significant hepatic injury, although some patients met the numerical criteria.
3. At the recommended dose of GZR/EBR 100mg/50mg, the overall benefit: risk ratio is positive.
4. The overall level of concern regarding hepatic safety findings with GZR/EBR, administered at doses of 100mg/50mg, is low.

8.5.2. **Cardiopulmonary Events**

In October 2014 prior to NDA submission, Merck submitted a safety report describing a case of congestive heart failure (CHF) in a 58-year-old Asian male with ESRD on HD and hypertension enrolled in C-SURFER. A pre-treatment ECHO showed normal cardiac systolic function. Six weeks after completing GZR/EBR treatment, the subject developed new onset CHF with an ECHO showing an EF of 20%. The investigator considered the event related to study drugs. The clinical reviewer at the time, Dr. Adam Sherwat, reviewed cardiac AEs that occurred in any subject who received GZR and/or EBR in Phase 2 or Phase 3 trials. Eleven subjects out of 2642 total subjects (0.4%) experienced a cardiac-related SAE, severe AE, or AE leading to discontinuation). Dr. Sherwat concluded that aside from the index case, no additional cases reviewed raised clinical concern with respect to the ongoing GZR/EBR development program. The index case also occurred in a subject with increased risk of cardiac disease due to underlying ESRD.

This section reviews cardiac AEs reported in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE. The following table includes AEs that occurred in at least 1% of subjects receiving GZR/EBR and that fell under any of the following three SOCs: Cardiac Disorders; Respiratory, Thoracic, and Mediastinal Disorders; and Vascular Disorders. Related AEs cough, dyspnea, and dyspnea on exertion occurred in more subjects receiving RBV (3-6%) compared to those receiving GZR/EBR alone (<1%). Related palpitations occurred at a similar rate regardless of the addition of RBV. Vascular disorders, related or regardless of causality, occurred at a similar rate in subjects treated with GZR/EBR compared to placebo. No related AE was severe in intensity, and no severe AE regardless of causality occurred in more than one subject. Overall, this assessment identified no significant cardiac safety signals.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 37. Cardiac Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE

System Organ Class	GZR/EBR +/- RBV x 12-16w (n=1033)	Placebo x 12w (n=105)
Preferred Term	N (%)	N (%)
Cardiac Disorders	21 (2%)	5 (5%)
Palpitations	10 (1%)	3 (3%)
Respiratory, Thoracic and Mediastinal Disorders	116 (11%)	8 (8%)
Cough	42 (4%)	4 (4%)
Dyspnea	28 (3%)	2 (2%)
Dyspnea exertional	15 (1%)	0
Oropharyngeal pain	15 (1%)	0
Epistaxis	6 (1%)	0
Vascular Disorders	34 (3%)	3 (3%)
Hypertension	17 (2%)	1 (1%)

8.5.3. Psychiatric Events

Psychiatric AEs led to discontinuation of study drug in several subjects in Phase 3 trials (see Section 8.4.3). This section reviews AEs under the Psychiatric SOC reported in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and C-SALVAGE in at least 1% of subjects receiving GZR/EBR. Because AEs leading to discontinuation occurred disproportionately in RBV-treated subjects, AEs were analyzed based on use of RBV. PR-based regimens are associated with significant psychiatric adverse reactions, which have generally been attributed to IFN, though RBV may play a role.

In this analysis, the incidence of overall psychiatric AEs was similar or lower in subjects treated with GZR/EBR without RBV compared to placebo but higher in subjects treated with GZR/EBR + RBV. This finding suggests that RBV may contribute to psychiatric AEs. However, AEs such as depression and anxiety occurred at a similar rate in subjects treated with GZR/EBR with or without RBV and at similar or higher rate in placebo-treated subjects. This finding suggests that untreated HCV infected subjects have an underlying risk of anxiety and depression. None of the events were serious, and the severe events leading to discontinuation of study drug are discussed in Section 8.4.3. Overall, this assessment identified no significant psychiatric safety signals with GZR/EBR, though the data support the prior finding that the addition of RBV may increase the rate of some psychiatric AEs.

Table 38. Psychiatric Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE

System Organ Class	GZR/EBR x 12-16w (n=744)	GZR/EBR + RBV x 12-16w (n=289)	Placebo x 12w (n=105)
Preferred Term	N (%)	N (%)	N (%)
Psychiatric Disorders	95 (13%)	63 (22%)	17 (16%)
Irritability	17 (2%)	14 (5%)	4 (4%)
Sleep disorders ¹	41 (6%)	35 (12%)	7 (7%)
Depression or depressed mood	20 (3%)	9 (3%)	4 (4%)
Anxiety	13 (2%)	5 (2%)	5 (5%)

¹Insomnia, middle insomnia, and sleep disorder

Safety Update Report

One subject completed suicide (see Section 8.4.1) prompting an evaluation of reports of suicidal ideation in the clinical development program. Two additional subjects experienced suicidal ideation in the clinical safety database (n=2704); both cases contain confounding factors as one subject was receiving concomitant PR and one was receiving RBV. Based on available data, there does not appear to be a strong signal for GZR/EBR-associated suicide or suicidal ideation at this time.

8.5.4. Musculoskeletal Events

This section reviews AEs under the Musculoskeletal and Connective Tissue Disorders SOC reported in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE. The table below displays AEs that occurred in at least 1% of subjects receiving GZR/EBR. Overall, more musculoskeletal AEs occurred in subjects receiving placebo compared to GZR/EBR. Most AEs reported in at least 1% of GZR/EBR-treated subjects occurred at a similar or lower rate compared to placebo-treated subjects. Myalgia, musculoskeletal pain, musculoskeletal discomfort, muscular weakness, and muscular tightness as combined terms occurred in 5% of GZR/EBR-treated subjects compared to 7% of placebo-treated subjects. However, investigators deemed none of these events related in placebo-treated subjects but 2% related in GZR/EBR-treated subjects. These events were not related to statins as only two GZR/EBR-treated subjects who experienced any musculoskeletal event were receiving concomitant statin therapy. The majority of AEs were mild, and only one AE, muscular weakness, was severe. No subjects experienced rhabdomyolysis. Overall, this assessment identified no significant musculoskeletal safety signals.

Table 39. Musculoskeletal Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE

System Organ Class	GZR/EBR +/- RBV x 12-16w (n=1033)	Placebo x 12w (n=105)
Preferred Term	N (%)	N (%)
Musculoskeletal and Connective Tissue Disorders	149 (14%)	22 (21%)
Arthralgia	48 (5%)	6 (6%)
Myalgia	38 (4%)	3 (3%)
Back pain	33 (3%)	3 (3%)
Pain in extremity	13 (1%)	3 (3%)
Muscle spasms	11 (1%)	5 (5%)
Musculoskeletal pain	9 (1%)	4 (4%)

8.5.5. Skin and Soft Tissue Events

This section reviews AEs under the Skin and Subcutaneous Tissue Disorder SOC reported in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE in at least 1% of subjects receiving GZR/EBR. Overall, more skin and soft tissue AEs occurred in subjects receiving placebo compared to GZR/EBR. Most AEs reported in at least 1% of GZR/EBR-treated subjects occurred at a similar or lower rate compared to placebo-treated subjects, except rash. A larger percentage of subjects who experienced a rash event were receiving GZR/EBR + RBV (25/289, 9%) compared to GZR/EBR alone (27/744, 4%), and investigators assessed 22 (8%) and 9 (1%) rash events, respectively, as related to study drugs. Most rash events were mild, and none were serious or severe. No subject treated with GZR/EBR (+/- RBV) discontinued study drug due to a rash event, while one subject receiving placebo discontinued drug due to pruritic rash. Overall, this assessment identified no significant skin-related safety signals, particularly in the absence of RBV.

Table 40. Skin and Subcutaneous Tissue Events Occurring in at Least 1% of GZR/EBR-treated Subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE

System Organ Class	GZR/EBR +/- RBV x 12-16w (n=1033)	Placebo x 12w (n=105)
Preferred Term	N (%)	N (%)
Skin and Subcutaneous Tissue Disorders	155 (15%)	18 (17%)
Rash ¹	52 (5%)	2 (2%)
Pruritus ²	46 (4%)	9 (9%)
Alopecia	25 (2%)	4 (4%)
Dry skin	19 (2%)	2 (2%)
Hyperhidrosis	6 (1%)	1 (1%)

¹Rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

pruritic, dermatitis, dermatitis allergic, dermatitis bullous, photosensitivity reaction, skin irritation, urticaria

²Pruritis, pruritis allergic, pruritis generalized

8.5.6. Renal Events

The purpose of this section is to review renal events that occurred in subjects with otherwise normal renal function. As such, this analysis includes subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE, all of which excluded subjects with creatinine clearance <50 mL/min. This analysis does not include subjects in C-SURFER, which enrolled subjects with CKD including those on hemodialysis.

AEs under the Renal and Urinary Disorders SOC occurred in 34/1033 (3%) and 1/105 (1%) subjects receiving GZR/EBR and placebo, respectively. Only dysuria occurred in 1% of GZR/EBR-treated subjects; dysuria also occurred in 1% of placebo-treated subjects. One SAE, renal colic, occurred, but the subject completed treatment, the investigator deemed the event unrelated to study drug, and there were no additional reports. No renal events led to treatment discontinuation, and none were severe in intensity. Furthermore, laboratory analysis of serum creatinine revealed no grade 4 elevations and one grade 2 and one grade 3 elevation, neither of which appears related to GZR/EBR. This assessment identified no significant kidney-related safety signals in subjects with normal baseline kidney function.

8.5.7. Gastrointestinal Events

In C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE, analysis of AEs under the Gastrointestinal Disorders SOC revealed no significant safety concerns. Overall, gastrointestinal AEs occurred at a similar rate in subjects treated with GZR/EBR compared to placebo. Frequently occurring AEs consisted of general symptoms such as abdominal pain, constipation, diarrhea, nausea, and vomiting. All except vomiting occurred at a similar rate in placebo-treated subjects.

8.5.8. Neurological Events

In C-EDGE TN, C-EDGE COINFECTION, and C-EDGE TE, analysis of AEs under the Nervous System Disorders SOC revealed no significant safety concerns. Overall, neurological AEs occurred at a similar or higher rate in subjects treated with placebo compared to GZR/EBR. Frequently occurring AEs consisted of general symptoms such as headache and dizziness, which also occurred at a similar rate in placebo-treated subjects.

8.6. Specific Safety Studies/Clinical Trials

Safety in Subjects with Renal Impairment

As previously stated, treatment options are severely limited for subjects with advanced CKD.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Hence, breakthrough designation was awarded for the study of GZR/EBR in this population. C-SURFER is an ongoing Phase 2/3 randomized, placebo-controlled clinical trial evaluating the safety and efficacy of GZR/EBR in subjects with HCV infection and chronic kidney disease (CKD). The results of this single trial will be discussed in this section.

Overview of Safety Events

Adverse events occurred more frequently in C-SURFER compared to the other Phase 2 and Phase 3 trials discussed in this review. This was expected, given the multiple co-morbidities that often occur in subjects with advanced CKD, which is why the study was designed with immediate and delayed treatment groups (ITG and DTG) in which subjects were randomized to receive blinded GZR/EBR or placebo, respectively. This safety review will compare key safety data between the ITG and the DTG during the blinded study period, which included the 12 week treatment period plus 14 days of follow-up. Table 41 provides an overview of safety events.

Table 41. C-SURFER Safety Summary

	ITG N=111 N (%)	DTG N=113 N (%)
Adverse Events		
Any AEs	85 (77%)	99 (88%)
Drug-related AEs	39 (35%)	39 (35%)
Discontinuation due to AEs	0 (0%)	5 (4%)
Serious Adverse Events		
Any SAEs	26 (23%)	22 (20%)
Drug-Related SAEs	1 (1%)	1 (1%)
Discontinuation due to SAEs	0 (0%)	3 (3%)
Death	1 (1%)	4 (4%)

The 11 subjects in the intensive PK group were not pooled with the ITG (as was done for the efficacy review) because these subjects received open-label GZR/EBR, which could introduce bias. This cohort of 11 subjects was evaluated separately and found to have a similar AE profile to the ITG population.

As previously mentioned, a safety update was provided which included data for 60 days following the database lock for the initial NDA submission. During this period, subjects in the ITG were being followed to assess safety and durability of antiviral activity, and subjects in the DTG received active treatment with GZR/EBR. Of the original 113 DTG subjects, 102 received treatment, of which 93 had completed treatment at the database lock. Safety events that occurred during this reporting period will be discussed in the following sections.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Deaths

At the time the NDA was filed, 5 deaths had occurred in Study C-SURFER: 1 in the ITG group and 4 in the DTG group. All five subjects were treatment-naïve non-cirrhotics. Death was deemed unrelated to study drug or study procedures in all cases. A brief summary of each case is provided below:

1. Subject 607050 (ITG) was a 66 year old dialysis-dependent white female with diabetes mellitus and hypertension. At treatment week 10, her family reported that she was found unconscious at home following a hemodialysis session earlier in the day. After two weeks of mechanical ventilation in the intensive care unit, care was withdrawn and the subject died from cardiopulmonary arrest.
2. Subject 607037 (DTG) was a 48 year old dialysis-dependent Asian male with diabetes mellitus and hypertension. When the subject failed to arrive for his study visit at follow-up week 2, the study site notified the police. The police found the patient dead at home and the cause of death remains unknown. An autopsy was not performed and no further details are available.
3. Subject 607726 (DTG) was a 58 year old dialysis-dependent white female with a history of coronary artery disease, hypertension, and 2 failed kidney transplants. She presented with severe chest pain and was admitted to the cardiac intensive care unit for management of a suspected myocardial infarction. She underwent angiography and experienced several complications, including post-operative bleeding. The subject died at some point after follow-up week 12 and no further details are available.
4. Subject 607452 (DTG) was a 56 year old white male with diabetes mellitus and hypertension who presented to the emergency department with pneumonia. He was admitted to the hospital and treated with antibiotics but developed multi-system organ failure secondary to septic shock caused by *Klebsiella pneumoniae*. He died at follow-up week 1.
5. Subject 607712 (DTG) was a 67 year old dialysis-dependent black male with hypertension and cerebrovascular disease who presented to emergency department with chest pain during treatment week 9. He was diagnosed with a myocardial infarction, thoracic aortic aneurysm and atrial fibrillation. He underwent cardiac catheterization and was discharged home where he completed study medication. He returned to the hospital at a later date for aneurysm repair and died in the post-operative period.

Reviewer Comment: These events, largely due to cardiovascular disease and dialysis-related complications, highlight the fragility of the advanced CKD population. Details regarding the event that led to Subject 607050's hospitalization and ultimate death remain unclear.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Review of her laboratory results and adverse events during the study period revealed no signs of medication intolerance prior to the event. Hence, while her death was likely related to her underlying medical conditions (hypertension, Stage 5 CKD, diabetes), the possibility of a medication-related event cannot be definitively excluded.

Two additional deaths were reported in the Safety Update Report. Both subjects were initially randomized to the DTG and had received a full 12 weeks of GZR/EBR prior to death.

1. Subject 607761 was a 66 year old non-cirrhotic, treatment-naïve African-American male with Stage 5 CKD who was infected with GT1b HCV. He died from septic shock four months after completing active treatment with GZR/EBR. The illness which led up to his death began 6 weeks after completing a 12 week course of GZR/EBR, at which time he presented to an emergency department with mental status changes and weakness. His work-up included neuroimaging and a brain biopsy, which was suspicious for a brain abscess. He was started on broad-spectrum antibiotics, but six weeks later he experienced septic shock and died three weeks later. The septic shock and death were considered unrelated to study medication by the investigator.
2. Subject 607770 was a 43 year old dialysis-dependent Hispanic male, status-post failed kidney transplant, with GT1a HCV and cirrhosis. He had elevated hepatic transaminases, alkaline phosphatase, and GGT throughout the randomized phase of study, during which time he received placebo. He was also noted to have eosinophilia of unclear etiology. This trend continued during his active treatment period, during which he experienced a late-onset rise in ALT/AST at treatment week 8 (please refer to the Hepatic ECI section of this review for more details). He completed treatment and was undergoing evaluation for hepatocellular carcinoma at the end of the treatment period, the results of which are not available.
Approximately 4 weeks after completing GZR/EBR, he experienced the SAE of “severe sensory impairment” which was manifested as dizziness and disorientation during dialysis. The subject recovered but had a second episode approximately 2 weeks later. The second episode was associated with profound anemia (hematocrit 14%) and hypotension requiring inotropic support. His condition worsened over the next two days despite volume repletion, blood transfusion, and vasoactive medications. He expired on the third hospital day; the cause of death was listed as chronic renal insufficiency and no autopsy was performed.

Reviewer Comment: These two events, like the 5 events that occurred during the randomized study period, are far more likely to be related to underlying CKD and dialysis-related complications than study medication. Hence, I agree with the study investigators that both cases are unrelated to study medication.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Serious Adverse Events

SAEs occurred more frequently in C-SURFER compared to other studies in the GZR/EBR development program. Most events were related to infection, vascular disease, or fluid imbalance, all of which are common in the advanced CKD population (Table 42). All events were considered unrelated to study medication with the exception of 1 case of elevated lipase in the DTG group. The single case of pancreatitis in the ITG occurred in a 65 year old TN, non-cirrhotic man who had elevated amylase and lipase at baseline without clinical symptoms: amylase 492 U/L (Grade 3), lipase 523 U/L (Grade 4). Amylase and lipase values fluctuated on treatment but remained elevated. At treatment week 8, the subject was admitted to the hospital with abdominal pain and was found to have gallstones and biliary sludge. Amylase and lipase at hospital admission were 230 U/L and 104 U/L, respectively. He was diagnosed with gallstone pancreatitis followed by pneumonia two days later. He was treated with antibiotics for pneumonia but no other action was taken. He was discharged from the hospital 4 days after the diagnosis of gallstone pancreatitis was made, at which time the event was resolved. The subject completed GZR/EBR without interruption. He continued to have fluctuating amylase and lipase values through the remainder of the treatment and follow-up period that were asymptomatic.

Table 42. SAEs Occurring in at least 1 ITG Subject, Trial C-SURFER

Dictionary Derived Term	ITG N=111 N (%)	DTG N=113 N (%)
Pneumonia	2 (2%)	1 (1%)
Hypertension	2 (2%)	1 (1%)
Procedural pain	1 (1%)	0 (0%)
Intervertebral disc protrusion	1 (1%)	0 (0%)
Hypertensive crisis	1 (1%)	0 (0%)
Extremity necrosis	1 (1%)	0 (0%)
Enterobacter sepsis	1 (1%)	0 (0%)
Diarrhoea	1 (1%)	0 (0%)
Osteomyelitis	1 (1%)	0 (0%)
Dehydration	1 (1%)	0 (0%)
Citrobacter sepsis	1 (1%)	0 (0%)
Cardiac arrest	1 (1%)	0 (0%)
Appendicitis	1 (1%)	0 (0%)
Acute respiratory failure	1 (1%)	0 (0%)
Abscess limb	1 (1%)	0 (0%)
Presyncope	1 (1%)	0 (0%)

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Dialysis related complication	1 (1%)	0 (0%)
Prostate cancer	1 (1%)	0 (0%)
Pancreatitis	1 (1%)	0 (0%)
Myocardial infarction	1 (1%)	1 (1%)
Pleural effusion	1 (1%)	1 (1%)
Fluid overload	1 (1%)	1 (1%)

Reviewer Comment: Narratives for each SAE were reviewed and I agree that the events are unrelated to study medication with one exception. An association between study drug and the Dialysis Related Complication that led to death due to Cardiac Arrest for Subject 607050 (discussed in the previous section) cannot be definitively excluded. Causality assessment is difficult in this ill population, but the remainder of cases are more likely related to the subjects' underlying chronic kidney disease (including complications associated with dialysis, co-morbid conditions such as vascular disease, or trauma) than study drug exposure. The case of pancreatitis does not fit the pattern of drug-induced pancreatitis. Elevations in amylase and lipase and not uncommon among CKD 4/5 subjects, and in this case, the onset of symptoms did not correlate with a rise in amylase and lipase. His symptoms were most likely caused by the gallstones, biliary sludge, and possibly referred pain from pneumonia.

Safety Update Report: New SAEs were reported in 11 subjects and follow-up information was provided for subjects who experienced SAEs during the initial blinded period. The types of SAEs were similar to those reported with the initial NDA package, including fever, pneumonia, pleural effusion, and worsening of cardiovascular or cerebrovascular disease. The majority of events occurred weeks to months following completion of GZR/EBR treatment.

Study-drug related events included:

1. A subject with a prior SAE of pleural effusion experienced elevated bilirubin which peaked at Day 7 and trended down below baseline at the last visit. The subject's ALT and AST remained normal throughout the study period.
2. A subject with no prior SAEs experienced rising creatinine one week after beginning open-label GZR/EBR. A biopsy was performed which revealed interstitial nephritis. The investigator considered the interstitial nephritis to be drug-related and discontinued treatment.

Reviewer Comment: The case of interstitial nephritis merits attention. Though renal pathology may have been present in this patient prior to initiation of GZR/EBR, the temporal association with initiation of therapy is concerning. Interstitial nephritis and other types of renal injury will be assessed during post-marketing pharmacovigilance.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Dropouts and Discontinuations due to Adverse Events

There were no discontinuations due to adverse events in the ITG. AEs that resulted in discontinuation of study drug among DTG subjects included acute myocardial infarction, atrial fibrillation, elevated lipase, abdominal pain, and elevated ALT/AST. All events were single occurrences.

Safety Update Report: Two subjects in the DTG who began open-label GZR/EBR discontinued treatment prematurely due to AEs. The first subject is the subject who was diagnosed with interstitial nephritis (discussed in the preceding section describing SAEs). The second subject was hospitalized for headache, nausea, and vomiting; treatment was discontinued due to inability to tolerate oral medications. The subject was subsequently diagnosed with hydrocephalus secondary to intracranial hemorrhage. The SAE was considered unrelated to study medication.

Non-serious Adverse Events

The majority of subjects experienced at least one AE during the blinded study period, with a slightly higher rate of events overall in the DTG compared to the ITG. This difference is primarily driven by a greater number of mild events in the DTG. Table 43 summarizes events that occurred in at least 5% of the ITG population. Events that occurred with at least 3% higher frequency in the ITG include abdominal pain, cough, back pain, night sweats, and flatulence. These events are indicated in red in Table 43.

Table 43. AEs in ≥5% of ITG subjects, all severity and irrespective of causality, C-SURFER

Dictionary Derived Term	ITG N=111 N (%)	DTG N=113 N (%)
Headache	19 (17%)	19 (17%)
Nausea	17 (15%)	18 (16%)
Fatigue	11 (13%)	17 (15%)
Abdominal pain	10 (10%)	3 (3%)
Cough	8 (7%)	2 (2%)
Vomiting	8 (7%)	7 (6%)
Hypertension	7 (6%)	7 (6%)
Insomnia	7 (6%)	12 (11%)
Decreased appetite	6 (5%)	3 (3%)
Asthenia	6 (5%)	5 (5%)
Constipation	6 (5%)	6 (5%)
Pyrexia	6 (5%)	6 (5%)
Diarrhoea	6 (5%)	15 (13%)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Dizziness	6 (5%)	18 (16%)
Back pain	5 (5%)	2 (2%)
Dry mouth	5 (5%)	4 (4%)
Dyspnoea	5 (5%)	4 (4%)
Night sweats	4 (4%)	0 (0%)
Flatulence	4 (4%)	0 (0%)
Accidental overdose	4 (4%)	3 (3%)
Arthralgia	4 (4%)	4 (4%)
Pruritus	4 (4%)	11 (10%)

While a greater number of mild AEs were reported in the DTG group, AEs classified as moderate or severe occurred at similar frequencies between the two study groups (Table 44). Events that occurred more with at least 3% greater frequency in the ITG included fatigue and peripheral edema.

Table 44. Moderate and severe AEs in ≥2 ITG subjects irrespective of causality, C-SURFER

Dictionary Derived Term	ITG N=111 N (%)	DTG N=113 N (%)
Fatigue	5 (5%)	1 (1%)
Peripheral edema*	4 (4%)	1 (1%)
Abdominal pain	3 (3%)	1 (1%)
Hyperkalaemia	2 (2%)	4 (4%)
Headache	2 (2%)	3 (3%)
Pneumonia	2 (2%)	1 (1%)
Pain in extremity	2 (2%)	1 (1%)
Dyspnoea	2 (2%)	1 (1%)
Diarrhoea	2 (2%)	2 (2%)
Back pain	2 (2%)	1 (1%)
Constipation	2 (2%)	1 (1%)

* The dictionary derived terms “peripheral swelling” and “oedema peripheral” were manually combined by the clinical reviewer

Similar to the trend observed for moderate and severe AEs, the overall rate of treatment-related AEs was also comparable between the two study groups. While similar proportions of subjects reported nausea and headache in the trial, a higher proportion of these events were considered treatment-related in the ITG compared to the DTG, as was asthenia. The events are summarized in Table 45.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Table 45. Related AEs in ≥ 2 ITG subjects, all severity, C-SURFER

Dictionary Derived Term	ITG N=111 N (%)	DTG N=113 N (%)
Nausea	14 (13%)	9 (8%)
Headache	13 (12%)	6 (5%)
Fatigue	6 (5%)	9 (8%)
Asthenia	5 (5%)	2 (2%)
Insomnia	4 (4%)	6 (5%)
Decreased appetite	3 (3%)	1 (1%)
Vomiting	3 (3%)	4 (4%)
Dizziness	3 (3%)	4 (4%)
Tinnitus	2 (2%)	0 (0%)
Dyspepsia	2 (2%)	1 (1%)
Dry mouth	2 (2%)	2 (2%)
Pruritus	2 (2%)	3 (3%)
Diarrhoea	2 (2%)	6 (5%)
Flatulence	2 (2%)	0 (0%)
Night sweats	2 (2%)	0 (0%)

Reviewer Comment: Despite the large number of reported AEs, the relative equality of moderate to severe events between study cohorts is reassuring for the safety of GZR/EBR in the CKD population. However, given the small number of subjects in the study cohort, ongoing pharmacovigilance is required to detect low-frequency events that may not be observed with this sample size.

As discussed in the efficacy review, there may be situations that merit consideration of prolonging the total treatment course from 12 to 16 weeks. However, treatment beyond 12 weeks was not evaluated in the CKD 4/5 population. In order to gauge the probability of late-onset AEs, the timing of AE onset (all severity) was assessed. The majority of events began during the first 8 weeks of treatment. AEs occurring later in the treatment course (8-12 weeks) were primarily gastrointestinal events, such as nausea and abdominal pain, which were primarily mild but occasionally moderate in intensity. While such an analysis cannot predict treatment tolerance beyond 12 weeks, this limited analysis did not identify a trend toward late-onset events that were severe.

Safety Update Report: DTG subjects experienced fewer AEs during the active treatment phase than the placebo phase of the trial. The rate of events was lower in all categories than those reported among ITG or DTG subjects during the blinded study period. As found during the

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

primary safety analysis, the most frequent drug-related AEs were nausea, headache, and fatigue.

Laboratory Abnormalities

Chemistry and hematology parameters were closely monitored in C-SURFER. A summary of laboratory trends is presented in Tables 46 and 47 using a format similar to that used to present the pooled analyses (Section 8.4.6). Subjects who had abnormal results for the same laboratory test on more than one occasion are counted only once at the highest toxicity grade.

Certain laboratory abnormalities are common among CKD 4/5 subjects due to their underlying disease, such as low hemoglobin and elevated creatinine and alkaline phosphatase. This was the case for the C-SURFER population; the proportions of Grade 2-4 abnormalities was similar in the two treatment groups with the exception of a numerically higher occurrence of Grade 3 low hemoglobin in the ITG group than the DTG group (10% versus 5%, respectively).

Chemistry abnormalities were generally similar between treatment groups, or more common in the DTG than the ITG. Neither group experienced Grade 4 elevations in hepatic transaminases or bilirubin. Elevated amylase was common but no cases of clinical pancreatitis were reported (with the exception of the case of gallstone pancreatitis which was not consistent with drug-induced pancreatitis). Elevated CK was noted in more ITG subjects than DTG subjects but was not associated with clinical musculoskeletal symptoms.

With the exception of anemia, moderate and severe hematologic abnormalities were uncommon. Grade 1 and 2 low platelet count occurred more frequently in C-SURFER than the pooled analysis presented in Section 8.4.6, but this could be related to dialysis; this hypothesis is supported by the observation that Grade 2 low platelets was more common in the DTG than the ITG.

Table 46. Abnormalities in key chemistry parameters by highest toxicity grade, C-SURFER

Laboratory Parameter	Highest Toxicity Grade*	ITG N=111 N (%)	DTG N=113 N (%)
Alanine Aminotransferase (IU/L)	1	3 (2%)	25 (22%)
	2	1 (1%)	3 (3%)
	3	0 (0%)	2 (2%)
Alkaline Phosphatase (IU/L)	1	27 (22%)	23 (20%)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Laboratory Parameter	Highest Toxicity Grade*	ITG N=111 N (%)	DTG N=113 N (%)
	2	2 (2%)	4 (4%)
	3	0 (0%)	3 (3%)
Amylase (IU/L)			
	1	34 (28%)	29 (26%)
	2	24 (20%)	17 (15%)
	3	25 (20%)	22 (19%)
	4	0 (0%)	4 (4%)
Aspartate Aminotransferase (IU/L)			
	1	2 (2%)	21 (19%)
	2	0 (0%)	2 (2%)
	3	0 (0%)	2 (2%)
Bilirubin (mg/dL)			
	1	1 (1%)	2 (2%)
	2	0 (0%)	2 (2%)
Creatine Kinase (IU/L)			
	1	7 (6%)	2 (2%)
	2	2 (2%)	1 (1%)
	3	1 (1%)	1 (1%)
	4	0 (0%)	1 (1%)
Creatinine (mg/dL)			
	1	0 (0%)	1 (1%)
	2	3 (2%)	3 (3%)
	3	18 (15%)	19 (17%)
	4	78 (64%)	76 (67%)
Direct Bilirubin (mg/dL)			
	1	1 (1%)	3 (3%)
	2	0 (0%)	3 (3%)
	3	0 (0%)	1 (1%)
Gamma Glutamyl Transferase (IU/L)			
	1	8 (7%)	3 (29%)
	2	3 (2%)	8 (7%)
	3	1 (1%)	13 (12%)
	4	0 (0%)	4 (4%)
Prothrombin Intl. Normalized Ratio			
	1	17 (14%)	7 (6%)
	2	2 (2%)	1 (1%)

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Laboratory Parameter	Highest Toxicity Grade*	ITG N=111 N (%)	DTG N=113 N (%)
	3	2 (2%)	2 (2%)
	4	0 (0%)	2 (2%)

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

Table 47. Abnormalities in hematology parameters by highest toxicity grade, C-SURFER

Laboratory Parameter	Highest Toxicity Grade*	ITG N=111 N (%)	DTG N=113 N (%)
Hemoglobin (g/dL)			
	1	26 (21%)	26 (23%)
	2	23 (19%)	16 (14%)
	3	12 (10%)	6 (5%)
	4	1 (1%)	2 (2%)
Leukocytes (10³/μL)			
	1	0 (0%)	1 (1%)
	2	0 (0%)	1 (1%)
Lymphocytes (10³/μL)			
	1	5 (4%)	4 (4%)
	2	2 (2%)	4 (4%)
Neutrophils (10³/μL)			
	1	1 (1%)	2 (2%)
	2	1 (1%)	1 (1%)
	3	0 (0%)	1 (1%)
Platelet (10³/μL)			
	1	12 (10%)	15 (13%)
	2	8 (7%)	12 (11%)

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

Hepatic Events of Clinical Interest

As noted in the discussion of pooled Phase 3 safety data, hepatic events were closely scrutinized to characterize the population at highest risk for GZR-associated hepatic injury. Please refer to Section 8.5.1 for definitions of hepatic ECI.

Three subjects in the ITG met criteria for hepatic ECIs in C-SURFER, all due to elevations in alkaline phosphatase. No subjects experienced late ALT or AST elevations beyond nadir. In one case, the subject had a normal alkaline phosphatase at baseline which trended up upon

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

initiation of GZR/EBR and remained elevated until treatment completion, at which point it trended down to normal. The initial rise was accompanied by a rise in ALT and AST, which peaked at Treatment Week 4 and trended down despite ongoing treatment and returned to normal by Treatment Week 6. No subjects in the intensive PK group experienced hepatic ECIs.

Safety Update Report: One hepatic ECI occurred in a subject initially randomized to the DTG who began open-label GZR/EBR following the blinded phase of the trial. Subject 607770 was a 43 year old Hispanic male with GT1a HCV and cirrhosis. He was noted to have elevated alkaline phosphatase (700-800 U/L) throughout the randomized phase of the study, accompanied by elevated ALT, AST, GGT, and direct bilirubin (55-80 U/L, 60-120 U/L, 1300-2120 U/L, and 0.5-1.9 mg/dL, respectively). He was also noted to have eosinophilia (peak of 12.4%) with no clear etiology. His alkaline phosphatase, GGT, and hepatic transaminases trended down after starting open-label GZR/EBR while direct bilirubin remained relatively unchanged. All parameters had nadired at treatment week 6 but subsequently spiked at treatment week 8 (ALT 182 U/L and AST 208 U/L, up from 40 and 59 U/L, respectively, two weeks prior) and then trended back down to baseline by follow-up week 4. Direct bilirubin remained elevated at > 2 mg/dL for the remainder of the treatment period but trended down by follow up week 4 to 0.95 mg/dL. Alkaline phosphate and GGT continued to trend down and were below baseline values by follow-up week 4.

Reviewer Comment: This case was discussed in an earlier section summarizing deaths that occurred in C-SURFER. The rise in hepatic transaminases at treatment week 8 is similar to hepatic events observed in the other phase 3 trials reviewed in this application. The trend toward normalization in all parameters despite ongoing treatment with GZR/EBR provides reassurance that the subject did not sustain lasting hepatic injury related to study drug exposure. I agree with the investigators that the subject's death at follow-up week 6 is most likely associated with complications of long-standing Stage 5 CKD and unrelated to this hepatic event.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

The relatively short duration of GZR/EBR treatment in clinical trials (majority 12-18 weeks) generally with 24 additional weeks of follow-up limits the assessment for oncologic events. Based on the available data from Phase 2 and Phase 3 trials, there is no clinical evidence of carcinogenicity for the GZR/EBR combination regimen. Thirteen subjects in C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SALVAGE experienced an event within the SOC of Neoplasms, Benign, Malignant, and Unspecified, and no clustering of any particular neoplasm was noted. Hepatocellular carcinoma occurred in one subject and is a malignancy consistent with the patient population.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

8.7.2. Human Reproduction and Pregnancy

A total of five pregnancies were reported across the Phase 2 and Phase 3 trials for the GZR/EBR development program: three were among female trial participants, and two were among partners of male trial participants. The cases are summarized below by trial:

Protocol 035

1. A female subject had a positive pregnancy test during the screening period and was therefore a screen failure. The subject never received or was exposed to GZR/EBR.
2. A female subject reported being pregnant approximately 5 months after her last dose of treatment, which included ribavirin. No information is available regarding the outcome of the pregnancy.
3. The female partner of a male subject conceived approximately 3 weeks after his last dose of treatment, which included ribavirin. No information is available regarding the outcome of the pregnancy.

Protocol 038

4. Approximately 5 months after the last dose of study medication, a female subject terminated pregnancy at 8 gestational weeks. Details regarding her decision to terminate (e.g. fetal malformation) are not available.

Protocol 039

5. After receiving his first dose of GZR/EBR, a male subject reported that his wife was 24 weeks pregnant. Medication was discontinued and he withdrew from the study. The outcome of the pregnancy was a healthy baby.

Given the lack of data to support safe use during pregnancy, treatment should not be initiated in pregnant or lactating women or their male partners, and patients should not conceive a child while undergoing treatment.

8.7.3. Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial Pediatric Study Plan (iPSP) for GZR/EBR on July 17, 2014. The document was reviewed and found to be generally satisfactory by both the review division as well as the Pediatric Review Committee (PeRC). The Agency's recommendations were conveyed to the Applicant who, in turn, revised the iPSP and returned the document for review. Both the Division and the PeRC approved of the Applicant's Agreed PSP, and the Division issued a notice of Agreed PSP on February 10, 2015.

In brief, the proposed pediatric development plan includes a (b) (4) study to evaluate the safety and efficacy of GZR/EBR in children ages 3 to < 18 years of age. (b) (4)

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Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

(b) (4)

The Applicant has requested a deferral of pediatric studies until data from Phase 3 studies are complete and have been reviewed by the Agency. The Division is in agreement with this proposal, as we felt that a thorough analysis of the safety data, particularly dose-related hepatic events, is necessary to inform dose selection for pediatric studies. The Applicant has also requested a waiver for studying children < 3 years of age. The Division agrees with this proposal as well, given the high rate of spontaneous viral clearance and lack of significant disease progression in this age group. The deferral and waiver requests will be presented to the PeRC, and final actions regarding these requests will be made pursuant to the PeRC's recommendations.

In addition, the Applicant submitted a Request for Pediatric Exclusivity on April 10, 2015. The Division felt that it was premature to issue a Written Request prior to Agency review of Phase 3 safety data in adults. Hence, the Applicant was advised to resubmit a request after completion of the NDA review.

8.7.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Overdose was a pre-specified event of clinical interest defined as any excess intake of the prescribed dose of GZR or EBR per calendar day, not associated with clinical symptoms or laboratory abnormalities. Overdose associated with an AE was considered an SAE.

Analysis of the PTs overdose, accidental overdose, and intentional overdose in Phase 3 trials revealed no significant concerns regarding excess intake of GZR/EBR. Overall, 47/954 (5%) subjects experienced an overdose event, and 45 of these subjects experienced no associated clinical events or laboratory abnormalities. Two subjects experienced an associated AE, but both subjects took excess doses of a concomitant medication rather than GZR/EBR; one subject took excess clonidine and one subject took excess RBV.

The potential for drug abuse, withdrawal, or rebound for GZR or EBR was not evaluated but is not anticipated.

8.8. **Safety in the Postmarket Setting**

8.8.1. **Safety Concerns Identified Through Postmarket Experience**

There is no postmarket experience with either GZR or EBR as neither is available on the U.S.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

market or any foreign market.

8.8.2. **Expectations on Safety in the Postmarket Setting**

Safety in the postmarket setting can be managed by routine pharmacovigilance activities. While increased ALT elevation was the hallmark hepatic event, more serious hepatic events, such as hepatic failure, may occur in the postmarket setting as it has occurred with other approved HCV NS3/4 PIs. Furthermore, when a larger number of patients likely to experience higher exposures, such as females, Asians, and elderly, receive this drug in the postmarket setting, additional safety signals may be identified.

8.9. **Additional Safety Issues From Other Disciplines**

There are no additional safety issues from other disciplines that are not presented elsewhere in this review.

8.10. **Integrated Assessment of Safety**

The safety database for GZR/EBR includes C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, C-SALVAGE, and C-SURFER and is considered adequate. The hepatic safety pool included additional subjects who received GZR 100 mg and EBR 50 mg for at least 12 weeks in other clinical trials. The trials included adequate numbers of subjects with cirrhosis and subjects on hemodialysis to assess safety in these subpopulations, respectively.

The pre-specified late ALT/AST elevation event was the major safety issue identified in this review. More specifically, the event consisted of ALT elevations >5x ULN with or without concomitant AST elevation >5x ULN. The event was infrequent, occurring in 12/1558 (0.8%) subjects in the hepatic safety population. ALT levels increased swiftly, usually at or after TW8, and generally were not associated with symptoms. Half of the subjects experienced bilirubin elevations but none >2x ULN. ALT levels normalized for all subjects generally by FU4, whether treatment was continued or not; all discontinuations were according to pre-specified criteria. All GT 1 or 4 infected subjects who experienced a late ALT elevation event achieved SVR12.

Based on this review, hepatic events can be adequately managed through appropriate labeling as a Warning and Precaution with specific monitoring recommendations. Hepatic events were a known safety issue with GZR from an early Phase 2 trial (P003) and were associated with higher drug exposures (e.g., GZR 400 mg or 800 mg). This review characterizes the event in a larger safety database of 1558 subjects who received GZR 100 mg and EBR 50 mg with or without RBV for at least 12 weeks. Overall, the late ALT elevation event in Phase 2 and Phase 3 trials at the proposed marketed dose was a laboratory event, not associated with clinical hepatic AEs. Higher rates of ALT elevations occurred in the following subpopulations: female

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

sex (2%), Asian race (3%), and age > 65 years (2%); these populations were also shown to experience higher GZR exposures. However, the increased exposures are well below the equivalent of 200 mg of GZR. Additionally, drug-drug interactions may increase GZR exposures but can be managed through labeling, specifically through designation of relevant concomitant drugs as contraindicated or not recommended.

No additional major safety issues or concerns specifically related to GZR or EBR were identified in this review. Fatigue, headache, nausea, and asthenia were the most common AEs reported across major clinical trials in which subjects received GZR/EBR without RBV for 12 or 16 weeks, and all occurred at comparable rates compared to placebo. No notable differences appeared with increased duration of GZR/EBR without RBV from 12 to 16 weeks, with the exception of asthenia. Subjects treated with GZR/EBR with RBV had a notably higher rate of most AEs compared to GZR/EBR without RBV and to placebo, whether the regimen was administered for 12 or 16 weeks. Fatigue, anemia, dyspnea, nausea, rash, and pruritis were most commonly reported with GZR/EBR with RBV, all of which are known RBV-related side effects.

In addition to common adverse reactions, RBV is associated with serious risks, but these safety issues are well known. None of the RBV-related effects were exacerbated by the addition of GZR/EBR. The safety profile of GZR/EBR was more favorable without RBV compared to with RBV in terms of discontinuations due to psychiatric disorders and occurrence of common AEs.

9 Advisory Committee Meeting and Other External Consultations

Not applicable

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

Indications and Usage

- Remove (b) (4) from the indication (b) (4)

(b) (4)

(b) (4)

Dosage and Administration

- Edit all current recommendations to include the following:
 - TN and PR-experienced GT 1a infected patients without baseline NS5A polymorphisms: GZR/EBR for 12 weeks (treatment regimen and duration is unknown for patients with baseline NS5A polymorphisms)
 - PI/PR-experienced GT 1a infected patients without baseline NS5A polymorphisms: GZR/EBR + RBV for 12 weeks (treatment regimen and duration is unknown for patients with baseline NS5A polymorphisms)
 - TN and PR-experienced GT 1b infected subjects: GZR/EBR for 12 weeks
 - PI/PR-experienced GT 1b infected patients: GZR/RBV + RBV for 12 weeks
 - TN GT 4 infected subjects: GZR/EBR for 12 weeks
 - PR-experienced GT 4 infected subjects: GZR/EBR + RBV for 16 weeks

(b) (4)

- R [REDACTED]
- Combine TE relapsers and on-treatment virologic failures
- Split TE patients based on PR experience vs. PI/PR experience.

Contraindications

- Revise the recommendation for use in patients with moderate hepatic impairment from [REDACTED] (b) (4) to “contraindicated.”

Warning and Precautions: Increased Risk of ALT Elevations

- Add rates of elevations in subpopulations of female sex, Asian race, and age > 65 years.
- Add specific monitoring recommendations, such as performance of hepatic laboratory testing every [REDACTED] (b) (4) weeks on therapy and as clinically indicated.

Adverse Reactions: Clinical Trials Experience

- Remove [REDACTED] (b) (4) except C-SALVAGE and C-SURFER.
- Revise depending on the final agreed upon treatment regimens.
- Split adverse reactions into TN and TE based on clinical trial designs.

Clinical Review
Sarita Boyd, PharmD
Prabha Viswanathan, MD
NDA 208261
Zepatier (elbasvir and grazoprevir)

Clinical Studies

- Present GT 1 and GT 4 data separately. Subdivide GT 1 into TN (non-CKD), TE, and CKD patients, such as:
 - 14.2 Genotype 1: Treatment-Naïve Subjects (include C-EDGE TN and C-EDGE COINFECTION, not pooled)
 - 14.3 Genotype 1: Treatment-Experienced Subjects (include C-EDGE TE and C-SALVAGE, not pooled)
 - 14.4 Genotype 1: Chronic Kidney Disease (include C-SURFER)
 - 14.5 Genotype 4 (brief section with relevant data from C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE, and C-SCAPE)
- Include descriptions of each trial within each subsection of GT 1.
- Display the impact of baseline NS5A polymorphisms on SVR12 rates within each subsection.

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. Non-Prescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

No identified safety issues warrant consideration of REMS.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were still under discussion at the time this review was completed.

13 Appendices

13.1. References

1. Gower E, Estes C, Blach, S, Razavi-Shearer K, Razavi H. Globalepidemiology and genotype distribution of hepatitis C infection. *Journal of Hepatology*, 2014; 61:S45-S57.
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Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of GZR/EBR.

Covered Clinical Study (Name and/or Number): C-EDGE TN 060

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>291</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>1</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>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

One investigator holds financial interests and/or arrangements requiring disclosure. (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$40,000 for consulting, promotional speaking, and promotional educational lecturing.

Clinical Review
 Sarita Boyd, PharmD
 Prabha Viswanathan, MD
 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Covered Clinical Study (Name and/or Number): C-EDGE COINFECTION 061

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>198</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>2</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>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Two investigators hold financial interests and/or arrangements requiring disclosure. (b) (6) (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$54,116 for consulting and Advisory Board fees. (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$120,000 to the (b) (6) over a four-year period for an investigator-initiated research grant.

Clinical Review
 Sarita Boyd, PharmD
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 NDA 208261
 Zepatier (elbasvir and grazoprevir)

Covered Clinical Study (Name and/or Number): C-EDGE TE 068

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>286</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>2</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>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Two investigators hold financial interests and/or arrangements requiring disclosure. (b) (6)
 at Site (b) (6) disclosed significant payments of other sorts (b) (6)
 at Site (b) (6) disclosed significant payments of other sorts in the amount of \$108,165 over five years for Advisory Board fees and non-CME speaking.

Clinical Review
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Covered Clinical Study (Name and/or Number): C-SURFER 052

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>74</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>2</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>4</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Four investigators hold financial interests and/or arrangements requiring disclosure. (b) (6) (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$85, 574 for honoraria, consulting, speaking, and Advisory Board fees. (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$54,116 for consulting and Advisory Board fees. (b) (6) at Site (b) (6) disclosed significant payments of other sorts in the amount of \$108,165 over five years for Advisory Board fees and non-CME speaking. (b) (6) at Site (b) (6) disclosed significant payment of other sorts in the amount of \$40,000 for promotional speaking and educational lecturing.

Clinical Review
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13.3. Pre-Specified Hepatic Safety Events in the Hepatic Safety Population

The following table describes hepatic safety events of concern in Phase 3 (C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE) and Phase 2 (C-WORTHY, C-SCAPE, C-SALVAGE) trials in which the planned treatment was GZR 100 mg and EBR 50 mg +/- RBV for at least 12 weeks (i.e., hepatic safety population). See Section 8.5.1 for additional details.

Table 48. Pre-specified Late ALT Elevation, Hepatic ECI, and Hepatic-Related Treatment Discontinuation

Subject ID	PN	Age Sex Race	Country	Regimen GZR/EBR 100 mg/ 50 mg	GT	C/ NC	BL: ALT/AST Tbili EOS/%	Nadir: ALT/AST Tbili EOS/%	Nadir: Week	Peak: ALT/AST Tbili/Dbili EOS/%	Peak: Week	EOT: ALT/AST Tbili EOS/%	D/C Study Drug	Resolution and Timeframe	Liver SXS	SVR/ Other Info/ Comment
Late ALT/AST Elevation (> 5x ULN after TW4 with an occurrence of ALT/AST ≤ ULN between TW2 and TW4) [n=12]																
040900004 AN436026	060	67 F Black	US	12w	1b	NC	94/99 0.57 0.1/1.1	18/26 0.69 0.1/1.8	TW8	474/352 0.83 0.3/6.0	TW10	Same at TW10	Y	Complete FU4	N	SVR12
033200001 AN436615	060	52 F Asian	Korea	12w	1b	C	80/70 0.59 0/0.8	22/26 0.56 0.1/1.9	TW2	702/459 1.31/0.46 0.2/4.9	TW10 (1 st ↑ TW8)	Same as TW10	Y	Complete FU4	N	SVR12 EOS/% 0.4/8.8% at TW8
010100001 AN436088	060	62 F White	Czech Rep	12w	1b	NC	46/47 0.67 0.1 /1.4	18/22 0.75 0.1/1.4	TW2	376/198 0.74 0.4/5.3	TW6	127/85 1.04 0.2/2.6	N	Complete FU4	N	SVR12 Tbili/Dbili 1.31/0.63 at TW7
040800006 AN437030	060	61 F Asian	US	12w	6a	NC	45/53 0.51 0.1/2.1	18/29 0.51 0.1/1.9	TW6	170/133 0.39 0.1/2.6	TW12	Same as TW12	N	Complete FU8	N	Relapse FU4 BL VL 15 million
072200001 AN191539	061	58 M White	Spain	12w	1b	C	109/89 0.51 0/0.2	17/20 0.76 0/0.2	TW2	204/180 1.13 0.1/1.4	TW10	134/69 1.24/0.65 0.1/1.9 INR 1.8	N	Complete FU4	N	SVR12 Met criteria for d/c at TW12
072300006 AN191542	061	49 F White	Spain	12w	1a	NC	31/36 0.53 0.1/2.5	27/30 0.46 0.1/3.1	TW2	212/127 0.41 0.1/2.3	TW8 (1 st ↑ TW6)	40/37 0.36 0/1.2	N	Complete FU4	N	SVR12 INR peak 1.3 Abd u/s normal

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Subject ID	PN	Age Sex Race	Country	Regimen GZR/EBR 100 mg/50 mg	GT	C/ NC	BL: ALT/AST	Nadir: ALT/AST	Nadir: Week	Peak: ALT/AST	Peak: Week	EOT: ALT/AST	D/C Study Drug	Resolution and Timeframe	Liver SXS	SVR/ Other Info/ Comment
							Tbili EOS/%	Tbili EOS/%		Tbili/Dbili EOS/%		Tbili EOS/%				
148100014 AN681288	068	64 F Asian	Taiwan	12w/RBV	1b	NC	60/44 0.61 0.2/3.1	24/22 1.29 0.2/2.0	TW6	216/128 1.23/0.32 0.1/1.1	TW12	Same as TW12	N	Complete FU4	N	SVR12
Late ALT/AST Elevation (> 5x ULN after TW4 with an occurrence of ALT/AST ≤ ULN between TW2 and TW4) [n=12]																
166800006 AN682069	068	73 F White	France	16w	1b	NC	32/32 0.51 0.1/0.9	11/16 0.57 0.1/1.3	TW2	232/105 0.71 0.1/2.1	TW10	21/20 0.96 0.1/2.2	N	Complete TW12	N	SVR12 SXS: headache, asthenia, vertigo
156000001 AN680815	068	72 F White	Israel	16w	1b	C	104/91 1.03 0.2/4.0	19/26 1.0 0.1/0.9	TW4	260/198 1.13 0.3/4.1	TW10	27/30 0.98 0.1/1.2	N	Complete TW16	N	SVR12 Tbili/Dbili 1.26/0.61 at TW12
150300004 AN681211	068	64 M Asian	Korea	16w	1b	NC	33/25 0.49 0.7/14.6	16/17 0.5 0.6/12.7	TW4	416/178 1.0 0.7/15.8 ALP 405	TW10	49/32 0.84 0.5/9.4	N	Complete FU4	N	SVR12 PMH: chronic chlonorchiasis and eosinophilia
032200003 AN150805	035	58 F White	Australia	18w/RBV	1a	C	114/158 0.6 NA	22/34 0.91 0.1/1.4	TW4	170/149 1.28 0.4/8.8	TW12	20/34 0.78 0.1/4.4	N	Complete TW16	N	SVR12 Repeat Tbili/Dbili 2.0/0.61 at TW12
016300003 AN109711	047	57 F White	France	12w	4a	NC	62/34 0.32 NA/3.4	25/20 0.41 NA/3.3	TW2	1012/431 0.55 NA/5.8	TW8	Same as TW8	Y	Complete FU12	Y abd pain	SVR12 Confounders: EtOH, etifoxine, Kudzu root, herbal tea
Hepatic ECI or Protocol-Specified Treatment Discontinuation without Late ALT/AST Elevation (n=6)																
039500008 AN435082	060	64 F Black	US	12w	1a	NC	26/34 0.16 0/0.4	10/17 0.15 0/0.8	TW2	129/97 0.22 0/0.8	TW12	Same as TW12	N	Complete FU2	N	SVR12 Rash on R upper arm TW9-TW11
078200005 AN191604	061	32 M Black	US	12w	1a	NC	119/49 0.84 0.1/2.1	18/20 0.96 0.1/2.4	TW4	104/174 1.27/0.27 0.1/3.6	TW6	20/20 1.34/0.24 0.1/1.7	N	Complete TW6 (within 5d)	N	SVR12 Associated with strenuous

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Subject ID	PN	Age Sex Race	Country	Regimen GZR/EBR 100 mg/50 mg	GT	C/ NC	BL: ALT/AST	Nadir: ALT/AST	Nadir: Week	Peak: ALT/AST	Peak: Week	EOT: ALT/AST	D/C Study Drug	Resolution and Timeframe	Liver SXS	SVR/ Other Info/ Comment
							Tbili EOS/%	Tbili EOS/%		Tbili/Dbili EOS/%		Tbili EOS/%				
058500004 AN191637	061	31 M White	Germany	12w	1a	NC	242/136 0.68 0.3/4.9	48/29 0.37 0.5/4.7	TW2	168/143 0.46 0.6/8.8	TW12	Same as TW12	N	Unresolved but < BL	N	workout SVR12 Met d/c criteria at TW12; FU12 ALT/AST/EOS/EOS% 183/108/0.6/6.8%
050000004 AN191517	061	46 M White	Australia	12w	1a	NC	90/49 0.27 0.1/2.0	N/A	N/A	696/392 1.37/0.83 0.1/1.5 ALP 182	TW2	20/17 0.27 0.1/2.1	N Temp d/c x 3d	Complete TW6 (after drug resumed)	Y acute nausea, pruritis	SVR12 Abd u/s: biliary stent blockage; endoscopic intervention
151100004 AN681270	068	58 M Asian	New Zealand	12w/RBV	1b	NC	45/36 0.4 0.6/6.3	19/22 0.32 0.5/5.0	TW6	41/113 0.53 0.2/1.2	TW10	28/23 0.16 0.2/1.6	N	Complete TW12	Y pruritis	SVR12
141200008 AN681642	068	57 F White	US	16w	1a	NC	67/71 0.36 0.1/2.7	37/33 0.35 0.1/2.7	TW4	257/175 0.49 0.2/4.1	TW8	30/28 0.51 0.2/2.6	N	Complete TW14	N	SVR12

PN = protocol number, GT = HCV genotype, C = cirrhotic, N= non-cirrhotic, BL = baseline, EOT = end of treatment, D/C = discontinued, SXS = symptoms, TW = treatment week, FU = follow-up week

Note: ALP values are not shown for subjects who had normal values, which was the case in the majority of subjects. Direct bilirubin is shown if total bilirubin is elevated. Other relevant lab parameters are shown only if abnormal.

Units: ALT (U/L), AST (U/L), Total bilirubin (mg/dL), Eosinophil count (K/mm³)/%, ALP (U/L), Direct bilirubin (mg/dL)

Normal range (Central lab): ALT (10-33/40 U/L), AST (10-36/43), Total bilirubin (0.10-1.10 mg/dL), Direct bilirubin (0.10-0.40 mg dL), Eosinophil absolute count (0.0-0.8 K/mm³), Eosinophil % (0.0-7.0%), ALP (30-115 U/L), Direct bilirubin (0.00-0.40 mg/dL)

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

/s/

SARITA D BOYD
10/28/2015

PRABHA VISWANATHAN
10/28/2015

ADAM I SHERWAT
10/28/2015