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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 208261 SDN0

Drug Name: ZEPATIER ® (MK-5172/8742) (Grazoprevir 100 mg /Elbasvir 50 mg) fixed dose combination

Indication(s): Treatment of Chronic Hepatitis C genotypes 1, 4 or 6 in adults

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Biometrics Division: Division of Biometrics IV

Statistical Reviewer: LaRee A. Tracy, MA, PhD (DB4)

Concurring Reviewers: Thamban Valappil, PhD (DB4)

Medical Division: Division of Antiviral Products (DAVP)

Clinical Team: Sarita Boyd, MD (DAVP) (Clinical Reviewer)
Prabha Viswanathan, MD (DAVP) (Clinical Reviewer)
Adam Sherwat, MD (CDTL)

Project Manager: Nina Mani, PhD, MPH

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Table of Contents

1	EXECUTIVE SUMMARY	7
2	INTRODUCTION	13
2.1	OVERVIEW	13
2.2	DATA SOURCES	18
3	STATISTICAL EVALUATION	18
3.1	DATA AND ANALYSIS QUALITY	18
3.2	EVALUATION OF EFFICACY	18
3.2.1	<i>Trial Design Characteristics Common to All Included Trials</i>	18
3.2.2	<i>Phase 2 Trials</i>	22
3.2.2.1	Trial 035 (C-WORTHY)	22
3.2.2.2	Trial 047 (C-SCAPE)	31
3.2.2.3	Trial 48 (C-SALVAGE)	35
3.2.3	<i>Phase 2/3 Trial 052 (C-SURFER)</i>	38
3.2.4	<i>Phase 3 Trials</i>	44
3.2.4.1	Trial 060 (C-EDGE TN)	44
3.2.4.2	Trial 061 (C-EDGE CO-INFECTION)	49
3.2.4.3	Trial 068 (C-EDGE TE)	53
3.3	EVALUATION OF SAFETY	60
3.4	BENEFIT-RISK ASSESSMENT	61
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	61
4.1	TRIAL 048	61
4.1.1	<i>Gender, Race, Age, and Geographic Region</i>	61
4.1.2	<i>Other Special/Subgroup Populations</i>	62
4.2	TRIAL 052	62
4.2.1	<i>Gender, Race, Age, and Geographic Region</i>	62
4.2.2	<i>Other Special/Subgroup Populations</i>	63
4.3	TRIAL 060	64
4.3.1	<i>Gender, Race, Age, and Geographic Region</i>	64
4.3.2	<i>Other Special/Subgroup Populations</i>	65
4.4	TRIAL 061	65
4.4.1	<i>Gender, Race, Age, and Geographic Region</i>	65
4.4.2	<i>Other Special/Subgroup Populations</i>	66
4.5	TRIAL 068	67
4.5.1	<i>Gender, Race, Age, and Geographic Region</i>	67
4.5.2	<i>Other Special/Subgroup Populations</i>	68
5	SUMMARY AND CONCLUSIONS	70
5.1	STATISTICAL ISSUES	70
5.2	COLLECTIVE EVIDENCE	71
5.3	CONCLUSIONS AND RECOMMENDATIONS	73
5.4	LABELING RECOMMENDATIONS	74
	REFERENCES	75

NDA 208261 ZEPATIER® (Indication: Treatment of Chronic HCV)
Statistical Review: LaRee A. Tracy, MA, PhD (DB4)

APPENDIX A: SUMMARY OF JUSTIFICATIONS FOR HISTORICAL CONTROL SVR12 BY TRIAL.....76

LIST OF TABLES

Table 1: List of all studies included in analysis.....	8
Table 2: SVR12 (Full Analyses Set) in GT1a Subjects.....	9
Table 3: SVR12 (Full Analyses Set) in GT1b Subjects.....	10
Table 4: SVR12 (Full Analyses Set) in GT4 Subjects.....	11
Table 5: SVR12 (Full Analyses Set) in GT6 Subjects.....	11
Table 6: Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection	14
Table 7: Proposed Dosing and Administration for GZR/EBR.....	15
Table 8: List of all studies included in analysis.....	16
Table 9: Trial 035 Disposition.....	24
Table 10: Trial 035 SVR12 Full Analysis Set (Reviewer’s Analyses) (Missing=Failure).....	27
Table 11: Trial 035 SVR12 in GT1a Subgenotype Subjects	28
Table 12: Trial 035 SVR12 in GT1b Subgenotype Subjects.....	29
Table 13: Trial 035 SVR24 Full Analysis Set (Reviewer’s Analyses) (Missing=Failure).....	30
Table 14: Trial 047 Subject Disposition.....	32
Table 15: Trial 047 Subject Demographics and Characteristics.....	33
Table 16: Trial 047: SVR12 and SVR 24 by Study Part	35
Table 17: Trial 048 Subject Disposition.....	36
Table 18: Trial 048 Subject Demographics and Characteristics.....	37
Table 19: Trial 048: SVR12	38
Table 20: Trial 052 Subject Disposition.....	40
Table 21: Trial 052 Subject Demographics and Characteristics (FAS Population).....	41
Table 22: Trial 052: SVR4 and SVR12 in ITG and IPK Combined (GZR 100 mg/EBR 50 mg x 12)	43
Table 23: Trial 060 Subject Disposition.....	45
Table 24: Trial 060 Subject Demographics and Characteristics (FAS Population).....	46
Table 25: Trial 060: SVR4 and SVR12 (FAS) (Reviewer’s Analyses) in the ITG Combined.....	48
Table 26: Trial 061 Subject Disposition.....	50
Table 27: Trial 061 Baseline Characteristics.....	51
Table 28: Trial 061 SVR4 and SV12 (FAS) (reviewer’s analyses).....	53
Table 29: Trial 068 Subject Disposition.....	55
Table 30: Trial 068 Subject Demographics and Characteristics.....	56
Table 31: Trial 068 SVR 12 Primary Results (FAS) (reviewer’s analyses)	59
Table 32: Trial 068-Sensitivity Analyses of GZR/EBR with and without RBV (pooled 12 and 16 weeks)	60
Table 33: Trial 048 Subgroup Analyses of SVR12	61
Table 34: Trial 052: Reviewer’s Analyses of SVR12 by Age, Gender, Race and Region	62
Table 35: Trial 052: Reviewer’s Analyses of SVR12 by Other Subgroups.....	63
Table 36: Trial 060: Reviewer’s Analyses of SVR12 by Age, Gender, Race and Region	64
Table 37: Trial 060: Reviewer’s Analyses of SVR12 by Subgroup	65
Table 38: Trial 061 SVR12 Subgroup Analyses by Age, Gender, Race and Region	66
Table 39: Trial 061 SVR12 Subgroup Analyses (reviewer’s analyses).....	67
Table 40: Trial 068 SVR12 Subgroup Analyses of Gender, Race and Region (FAS) (reviewer’s analyses).....	68
Table 41: Trial 068 SVR12 Subgroup Analyses (FAS) (reviewer’s analyses).....	69

LIST OF FIGURES

Figure 1: Trial 047 Design.....	31
Figure 2: Trial 052 Treatment Arms and Duration	39
Figure 3: Trial 052: Proportion with HCV RNA ≤ 1.39794 (LLOQ Log10) by Treatment Day (On Treatment) with No Imputation for Missing (missing=failure) in the ITG/IPK Combined Group-Reviewer’s Analyses	43
Figure 4: Trial 060 Design.....	45
Figure 5: Trial 060: Proportion achieving SVR by Treatment Week (FAS) Reviewer’s Analyses.....	49
Figure 6: Trial 060: Mean Change from BL in Log10 HCV RNA (FAS) Reviewer’s Analyses	49
Figure 7: Trial 068 Design.....	54

COMMONLY USED ABBREVIATIONS

SVR	SUSTAINED VIROLOGIC RESPONSE
SVR4	SUSTAINED VIROLOGIC RESPONSE 4 WEEKS AFTER END OF TREATMENT
SVR12	SUSTAINED VIROLOGIC RESPONSE 12 WEEKS AFTER END OF TREATMENT
SVR24	SUSTAINED VIROLOGIC RESPONSE 24 WEEKS AFTER END OF TREATMENT
PP	PER PROTOCOL
FAS	FULL ANALYSIS SET
NC	NON-CIRRHOTIC
C	CIRRHOTIC
TE	TREATMENT EXPERIENCED
TN	TREATMENT NAÏVE
P/R	PEGYLATED INTERFERON/RIBAVIRIN
RBV	RIBAVIRIN
DAA	DIRECTLY ACTING ANTIVIRAL
CHC	CHRONIC HEPATITIS C
HPV	HEPATITIS C VIRUS
GZR	GRAZOPREVIR
EBR	ELBASVIR
PI	PROTEASE INHIBITOR
EOT	END OF TREATMENT
GT	GENOTYPE
CKD	CHRONIC KIDNEY DISEASE
ESRD	END STAGE RENAL DISEASE
ITG	IMMEDIATE TREATMENT GROUP
DTG	DELAYED TREATMENT GROUP
PTF	PRIOR TREATMENT FAILURE
LLOQ	LOWER LIMIT OF QUANTIFICATION
TD (u)	TARGET DETECTED BUT UNQUANTIFIABLE
TND	TARGET NOT DETECTED

1 EXECUTIVE SUMMARY

The applicant (Merck and Co.) submitted New Drug Application (NDA) 208261 for Zepatier (GZR/EBR), which is packaged as a two-drug, fixed dose combination product containing 100 mg grazoprevir (GZR, MK-5172) and 50 mg elbasvir (EBR, MK-8742). Both products are direct-acting antiviral (DAA) agents and specifically, GZR is an HCV NS3/4A protease inhibitor (PI) while EBR is a HCV NS5A inhibitor. The applicant is seeking approval for treatment of chronic hepatitis C (CHC) genotypes (GT) 1, 4 or 6 in adults to include subjects with and without cirrhosis, end-stage renal disease (ESRD), HIV co-infection, and prior pegylated interferon/ribavirin (P/R) failures.

Findings from three Phase 2 clinical trials (035, 047, and 048) and four Phase 2/3 or Phase 3 trials (052, 060, 061 and 068) enrolling a total of 2064 (this includes n=238 subjects assigned to delayed treatment) CHC subjects (as outlined below in Table 1) submitted to support this NDA will be discussed in this review. Five trials (035, 047, 048, 061, 068) were open-label, uncontrolled, and the remaining two trials utilized a double-blind design (through the first 12 weeks of treatment) comparing immediate versus delayed treatment (052 and 060). All trials were designed around the same primary efficacy endpoint, namely sustained virologic response, defined as proportion of subjects achieving a HCV RNA value below the lower limit of quantification, at 12 weeks (SVR12) following end-of-treatment (EOT). The Phase 2/3 and 3 trials were designed to demonstrate that the SVR12 proportion in the GZR/EBR arm is superior to a pre-specified historical rate, which varies according to CHC sub-population and genotype studied. Trial 052 enrolled CHC GT1 subjects with end-stage renal disease including subjects on hemodialysis, a subpopulation of CHC infected subjects for which there is a paucity of data regarding an effective treatment. Trials 052 and 060 both included placebo-controlled arms (delayed treatment for 12 weeks followed by the GZR/EBR treatment) for purposes of comparative safety only.

Table 1: List of all studies included in analysis

Study	Population	GT	Treatment	# of Subjects	Control	Historical Rate*
Phase 2 Trials						
035	TN (+/- C) P/R null-responders (+/-C), HIV co-infection (TN, NC)	1, 3	GZR/EBR +/- R 8, 12, or 18 weeks	573	None	None
047	TN (NC)	2, 4, 5, 6	GZR/EBR +/- R x 12 weeks	98	None	None
048	Prior DAA/P/R failures (+/-C)	1	GZR/EBR + R x 12 weeks	79	None	None
Phase 2/3 or Phase 3						
052	CKD stages 4-5, including dialysis	1	GZR/EBR x 12 weeks, (ITG v. DTG) (randomized)	ITG/PK: 122 DTG: 133	Placebo (DTG)	45%
060	TN (+/-C)	1,4, 6	GZR/EBR x 12 weeks, (ITG v. DTG) (randomized)	ITG: 316 DTG: 105	Placebo (DTG)	73%
061	HIV co-infected (TN +/- C)	1,4, 6	GZR/EBR x 12 weeks	218	None	70%
068	P/R PTF, +/- C, +/- HIV co-infection	1,4, 6	GZR/EBR +/- R x 12 or 16 weeks (randomized)	GZR/EBR 12 w: 105 GZR/EBR/RBV 12w: 104 GZR/EBR 16w: 105 GZR/EBR/RBV 16w: 106	None	58%

GT=Genotype; DAA=Direct-acting Antivirals; TN=Treatment-Naïve; CKD=Chronic Kidney Disease; ITG=Immediate Treatment Group; DTG=Deferred Treatment Group; PK=Intensive PK Group; P/R=Pegylated Interferon/Ribavirin; PTF=Prior Treatment Failure; R=Ribavirin; NC=non-cirrhotic
 *Historical rate used to assess SVR12 in the GZR/EBR treatment group for test of superiority; trials with no historical rate were hypothesis generating only

The applicant is proposing GZR 100 mg/EBR 50 mg for 12 weeks for subjects with CHC genotypes 1, 4, (b) (4) who are either treatment-naïve or had relapsed on prior HCV treatment (b) (4)

The applicant proposes a 16 week treatment regimen of GZR 100 mg/EBR 50 mg given with ribavirin (RBV) for subjects infected with CHC GT1a, 4 (b) (4) who are treatment-experienced or on-treatment virologic failures. Finally, ribavirin (RBV) is recommended for use in combination with GZR 100 mg/EBR 50 mg in subjects with severe renal function or end stage renal disease, including those on hemodialysis. There is no separate treatment recommendation for HCV/HIV1 co-infected subjects from those already described.

Given known variances by genotype in treatment responses to directly acting antiviral agents, this review focuses on efficacy by specific GTs for which the applicant is seeking approval. These are GTs 1a, 1b, 4 (b) (4) discussed below and are presented in Table 2-Table 5, respectively.

Among CHC GT1a subjects (n=519) who were treated with GZR/EBR x 12 weeks in trials 035, 048, 052, 060, 061 and 068, SVR12 point estimates ranged from 86% to 97% (Table 2). When adding RBV to a 12 week GZR/EBR treatment regimen (n=166 subjects), the estimated SVR12 proportions ranged between 89% and 100% with the smallest lower bound of all 95% confidence intervals of 65% and largest upper bound of 100%; however, the sample sizes by trial are relatively small leading to wide confidence intervals around the estimated SVR12. A GZR/EBR+RBV x 16 week regimen was evaluated in 58 GT1a subjects who were prior null-responders resulting in a SVR12 rate of 95% with (95% CI: 86%, 99%), which is a modest improvement over the regimen of GZR/EBR x 16 weeks without RBV.

In trial 052 of TN CHC subjects with chronic kidney disease (CKD), the SVR12 was 97% (95% CI: 89%, 100%) (Table 2). In the same trial, the SVR12 was 98% (95% CI: (88.0%, 100%)) in the subset of GT1a subjects who were also on hemodialysis (n=44) (not shown in table).

Table 2: SVR12 (Full Analyses Set) in GT1a Subjects

% SVR12 (n/N), 95% CI [^]						
Trial	SP	GZR/EBR x 12 w	GZR/EBR +R x 12 w	GZR/EBR x 16 w#	GZR/EBR +R x 16 w	
035*	TN/NC	96.7 (29/30), 82.8, 99.9	100 (14/14), 76.8, 100	Not studied	Not studied	
035*	TN/C	95 (19/20), 75.1, 99.9	90 (18/20), 68.3, 98.8	Not studied	Not studied	
035	P/R	86.4 (19/22), 65.1, 97.1	88.9 (16/18), 65.3, 98.6	Not studied	Not studied	
035	TN/HIV	86.4 (19/22), 65.1, 97.1	91.7 (22/24), 73.0, 99.0	Not studied	Not studied	
048	P/R	Not studied	93.3 (28/30), 77.9, 99.2	Not studied	Not studied	
052	CKD	96.8 (61/63), 89.0, 99.6	Not studied	Not studied	Not studied	
060	TN	91.7 (144/157), 86.3, 95.5	Not studied	Not studied	Not studied	
061	TN/HIV	94.4 (136/144), 89.4, 97.6	Not studied	Not studied	Not studied	
068	P/R	90.2 (55/61), 79.8, 96.3	93.3 (56/60), 83.8, 98.3	93.8 (45/48) 82.8, 98.7	94.8 (55/58) 85.6, 98.9	

SP=subpopulation of HCV infected subjects where TN=treatment naïve, P/R=peg-IFN/ribavirin prior null responders, C=cirrhotic, NC=non-cirrhotic, CKD=chronic kidney disease including subjects on hemodialysis, HIV=HCV/HIV co-infection, w=weeks

[^] Clopper Pearson exact method

GZR/EBR=GZR 100 mg/EBR 50 mg fixed dose, R=ribavirin

*included data only from Part B of the trial

#this regimen is not a proposed regimen for labeling but included here for completeness

Among GT1b CHC subjects (n=295) treated with GZR 100 mg/EBR 50 mg for 12 weeks, the SVR12 point estimates ranged from 88% to 100% with varying confidence intervals widths (across trials 035, 048, 052, 060, 061 and 068) (Table 3). When adding ribavirin to a 12 week GZR 100 mg/EBR 50 mg treatment regimen (n=124), the SVR12 point estimates were slightly higher ranging from 97-100% except

for a single treatment arm studied (Phase 2 trial 035) in treatment naïve (TN) and non-cirrhotic (NC) subjects that resulted in a point estimate of 77%. A GZR 100 mg/EBR 50 mg +RBV x 16 weeks regimen was evaluated in 36 GT1b subjects who were also prior null responders resulting in an SVR12 of 100%, 95% CI (90.3%, 100%).

Findings among G1b subjects studied with CKD (trial 052), the SVR12 was 92% (54/59) (95% CI: 81% to 97%). In the subset of GT1b subjects on hemodialysis at baseline, the SVR12 was 90% (43/48) (95% CI: 77% to 96.5%). This latter estimate is not included in the table below.

An 8-week regimen of GZR 100mg/EBR 50 mg with or without RBV was evaluated in 61 subjects (n=30 RBV, n=31 no RBV) GT1b-infected subjects who were TN and NC (trial 035). SVR12 (95% CI) was 90% (74%, 98%) in both groups (data presented in Table 12).

Table 3: SVR12 (Full Analyses Set) in GT1b Subjects

Trial	SP	% SVR12 (n/N), 95% CI [^]			
		GZR/EBR x 12 w	GZR/EBR +R x 12 w	GZR/EBR x 16 w#	GZR/EBR +R x 16 w
035*	TN/NC	100 (1/1), 2.5, 100	76.5 (13/17), 50.1, 93.2	Not studied	Not studied
035*	TN/C	100 (7/7), 59.0, 100	100 (10/10), 69.2, 100	Not studied	Not studied
035	P/R	90.9 (10/11), 58.7, 99.8	100 (14/14), 76.8, 100	Not studied	Not studied
035	TN/HIV	87.5 (7/8), 47.3, 99.7	100 (5/5), 47.8, 100	Not studied	Not studied
048	P/R	Not studied	98.0 (48/49), 89.2, 100	Not studied	Not studied
052	ESRD	91.5 (54/59), 81.3, 97.2	Not studied	Not studied	Not studied
060	TN	98.5 (129/131), 94.6, 99.8	Not studied	Not studied	Not studied
061	TN/HIV	95.5 (42/44), 84.5, 99.4	Not studied	Not studied	Not studied
068	P/R	100 (34/34), 89.7, 100	96.6 (28/29), 82.2, 99.9	95.8 (47/48), 85.8, 99.5	100 (36/36), 90.3, 100

SP=subpopulation of HCV infected subjects where TN=treatment naïve, P/R=peg-IFN/ribavirin prior null responders, C=cirrhotic, NC=non-cirrhotic, CKD=chronic kidney disease including subjects on hemodialysis, HIV=HCV/HIV co-infection

[^] Clopper Pearson exact method

GZR/EBR=GZR 100 mg/EBR 50 mg fixed dose, R=ribavirin, w=weeks

*included data only from Part B of the trial

#this regimen is not a proposed regimen for labeling but included here for completeness

Fewer subjects with CHC GT4 were studied in the GZR/EBR clinical development program largely due to the lower US prevalence (approximately 2%) of this subgenotype. Across four trials, among the GT4 subjects who received GZR 100 mg/EBR 50 mg x 12 weeks (n=65) the point estimate based on SVR12 ranged from 78% to 100% but all trial arms were small in sample size, with the associated uncertainties (Table 4). When adding RBV to the 12 week regimen (n=25), the overall SVR12 was improved to 93% and 100% in the two trials but again the individual arm sizes are small. Finally, a 16 week regimen

including RBV was evaluated in trial 068; however, only 8 subjects received this regimen and therefore the evidence is too limited to draw any meaningful conclusions.

Table 4: SVR12 (Full Analyses Set) in GT4 Subjects

Trial	SP	% SVR12 (n/N), 95% CI [^]			
		GZR/EBR x 12 w	GZR/EBR +R x 12 w	GZR/EBR x 16 w#	GZR/EBR +R x 16 w
047	TN	90.0 (9/10), 66.4, 100	100 (10/10), 69.2, 100	Not studied	Not studied
060	TN	100 (18/18), 81.5, 100.0	Not studied	Not studied	Not studied
061	TN/HIV	96.4 (27/28), 81.7, 99.9	Not studied	Not studied	Not studied
068	P/R	77.8 (7/9), 40.0, 97.2	93.3 (14/15), 68.1, 99.8	60.0 (3/5), 14.7, 94.7	100 (8/8), 63.1, 100

SP=subpopulation of HCV infected subjects where TN=treatment naïve, P/R=peg-IFN/ribavirin prior null responders, HIV=HCV/HIV co-infection

[^] Clopper Pearson exact method

GZR/EBR=GZR 100 mg/EBR 50 mg fixed dose, R=ribavirin, w=weeks

#this regimen is not a proposed regimen for labeling but included here for completeness

Among 14 GT6 CHC subjects who received GZR 100 mg/EBR 50 mg for 12 weeks, the SVR12 ranged from 75% to 80%, based on findings from two trials (Table 5). Only one trial each evaluated GZR 100

(b) (4)

(b) (4)

Overall, efficacy was achieved (in terms of SVR12 compared to historical control) with GZR 100 mg/EBR 50 mg given for 12 weeks for treatment of HCV-infected subjects with genotypes 1 and 4. (b) (4)

(b) (4)

Among CHC GT1-infected subjects with end-stage renal disease (an important subgroup of CHC subjects for which there are limited treatment options and no approved regimens in those on hemodialysis), trial 052 provided evidence that the GZR/EBR x 12 weeks regimen is effective in achieving a clinically acceptable SVR12. Specifically, in the primary analysis population, the overall SVR12 achieved was 94% (115/122) and in HCV genotypes, GT1a, the response was (61/63, 97%) and GT1b (54/59, 92%), respectively (Table 22). The SVR12 among those on dialysis was (86/92, 94%) and those not on dialysis was (29/30, 97%) (Table 35). While this trial did not enroll subjects with CHC GT4, it can be assumed that findings in this ESRD population can be extrapolated to this other genotype as there is no evidence of an interaction between HCV genotype and chronic renal dysfunction in terms of treatment response.

Safety was carefully assessed by two clinical reviewers (Drs. Sarita Boyd and Prabha Viswanathan) and the overall conclusion in both reviews is that the safety of the proposed GZR 100 mg/ EBR 50 mg x 12 or 16 weeks with or without RBV (depending on population) is acceptable. General concerns regarding late ALT elevations greater than 5x the upper limit of normal (ULN) with or without AST elevations greater than 5x ULN were expressed; however, it was concluded that these risks could be addressed through appropriate product labeling. Finally, there are some concerns regarding decreased efficacy among GT1a subjects with specific polymorphisms (refer to the clinical virology review by Dr. Takashi Komatsu for details), which will also be addressed in the product label.

There are few key limitations in the reviewed NDA data with the first being that none of the clinical trials were designed to assess compare SVR12 against a concurrent active control consisting of an approved HCV treatment as a control. Majority of the trials are open label and uncontrolled by the design. At the time of development of these clinical trials, there were no DAA-approved/IFN-sparing regimens for treatment of CHC to serve as comparator groups. While regimens containing IFN were available at time of protocol development, these regimens are generally not recommended particularly in TE subjects over concerned of serious toxicities. Therefore, the agreed-upon designs focused on an objective to demonstrate superiority of the GZR/EBR regimen against a pre-specified historical control SVR12 (in the commensurate population of IFN/RBV treated subjects) (Appendix A). Clearly, the use of historical controls suffers from potential confounding associated with lack of patient comparability at baseline with respect to both measured and unmeasured variables that could bias the outcomes. It is important to design trials that are informative using an effective, concurrent control based on drugs that are recently approved. Such a design will make the findings more interpretable for assessing relative efficacy and safety.

The other key limitation to these data is the lack of post-treatment follow up after week 12 in all but two of the seven reviewed clinical trials. While it was agreed upon in advance that these data did not have to be submitted with the NDA (but would be required at a later time) there are limitations in being able to fully assess the sustainability of virologic response at week 24 and longer and evaluate potential virologic failures/relapses among subjects who achieved SVR12. The lack of longer-term data also limits the assessment of long-term safety; however, a larger safety concern pertains to hepatic events that occur while on-treatment.

2 INTRODUCTION

2.1 Overview

Hepatitis C is a complex, rapidly mutating enveloped RNA virus classified into eleven major genotypes (GT) (1-11), several subtypes (a, b, c, etc.). Globally, subgenotypes 1a and 1b are the most common accounting for about 60% of all GTs, followed by GT2. GT3 is most common in parts of Southeast Asia whereas GT4 is often found in part of the Middle East, Egypt and central Africa. GT5 occurs almost exclusively in South Africa and GTs 6-11 in Asia (WHO Global Alert and Response Report).

The World Health Organization estimates that about 3% of the world's population is presently infected with the virus and is therefore viewed as a global public health issue. Data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES 2003-2010) suggest that an estimated 3.6 million people possess antibodies to the hepatitis C virus and of these 2.7 million are infected in the United States (Denniston *et al.*, 2014). Given that the NHANES is a population-based survey that excludes institutionalized and homeless persons-both high at-risk for HCV infection populations-the true prevalence is arguably higher in the United States. The distribution of HCV by genotype is approximately 70% GT1 (of which the majority is of 1a), 20% GT2, 3 and the remainder 4, 5, 6. GT4 accounts for only about 2% of all HCV cases the US.

HCV is typically spread via infected needles, blood and sexual contact leading to an attack of liver cells and subsequent inflammation and multiple chronic conditions in the infected host. Most infected persons fail to clear the virus and therefore become chronic carriers. The definition of chronic hepatitis C (CHC) is continued demonstration of HCV RNA in the blood for at least six months after onset of infection. CHC leads to increased risk of cirrhosis (current estimates of 25% among HCV-infected persons in the United States), hepatocellular carcinoma and end-stage liver disease (about 10-20%) and a slowly progressing lifelong infection leading to need for liver transplantation or death. Among persons with advanced chronic kidney disease (defined as stages 4 or 5); HCV infection is a strong predictor of mortality and also can limit a patient's eligibility for kidney transplantation.

The universal goal in treating HCV infection is to reduce the associated complications and prolong survival. However, given the long period required to evaluate the effect of treatment on reducing end stage liver disease or death an acceptable surrogate endpoint of sustained virologic response (SVR) is used when testing new treatments. The SVR endpoint is typically defined as unquantifiable or undetectable HCV RNA in serum at 24 weeks following the end of treatment (SVR24). More recently SVR at 12 weeks following the end of treatment (SVR12) has been adopted for use as a reliable surrogate endpoint in CHC clinical trial as it has been shown to be highly correlated with SVR24.

There are several FDA approved therapies to treat CHC by specific genotype. Specifically, treatment options for GT1 CHC infection includes IFN-sparing oral DAAs, which are preferred over regimens requiring IFN as these latter regimens are associated with various serious and life-threatening toxicities including bone marrow suppression induced neutropenia and infections. Among the current IFN-sparing regimens, the overall SVR12 rates range from 93-99% (Table 6). For treatment of GT4 CHC infection, fewer options exist but include use of sofosbuvir plus IFN or a more-recently approved (in 2015) regimen of ombitasvir, paritaprevir, and ritonavir (Technivie®) given with RBV for 12 weeks in TN and TE GT4 patients without cirrhosis. Thus, needs remain for other IFN-sparing regimens to treat GT4

subgenotype CHC subjects particularly those with cirrhosis of the liver. In addition, there are no approved DAA or IFN-free regimens to treat HCV GT6 infection or HCV GT 1, 4, or 6 subgenotype infections in patients receiving hemodialysis. Essentially prior to this NDA, there were no completed treatment trials in CHC patients receiving hemodialysis.

Table 6: Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection

Product (s) Name	Product Class	HCV GT	Approval Year	Dosing/ Administration	Efficacy	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

Source: Clinical Review by Dr. Sarita Boyd

The applicant (Merck) submitted the NDA 208261 seeking approval to market a two-drug, fixed dose combination product containing 100 mg grazoprevir (GZR, MK-5172) and 50 mg elbasvir (EBR, MK-8742) packaged into a single tablet hereafter referred to as GZR 100 mg/EBR 50 mg or GZR/EBR. Both drug products are direct-acting antiviral agents and specifically, GZR is an HCV NS3/4A protease inhibitor (PI) while EBR is a HCV NS5A inhibitor. NS5A is a multi-functional RNA binding protein thought to be essential for the replication of the hepatitis C virus. Both products are new drug entities not previously marketed in the United States.

GZR/EBR was evaluated for safety and efficacy in several Phase 2 and Phase 3 clinical trials for treatment of CHC including trials in CHC subgroups of cirrhotic and non-cirrhotic subjects, subgenotypes 1a, 1b, 4 and 6, treatment naïve and experienced (including prior treatment failures), and in subjects with chronic kidney disease including subjects on dialysis at time of treatment. The clinical development program evaluated treatment durations ranging from 8 to 16 weeks with a focus on a 12 week duration regimen. Based on findings from multiple trials/studies, the applicant is proposing the following dosing and administration regimens (Table 7).

Table 7: Proposed Dosing and Administration for GZR/EBR

Subject Population	Treatment Regimen	Duration
<i>Treatment-Naïve or Treatment Experienced* Relapsers</i>		
Genotype 1, 4, (b) (4)	GZR/EBR	12 weeks (b) (4)
	(b) (4)	(b) (4)
<i>Treatment-Experienced</i>		
Genotype 1b [†]	GZR/EBR	12 weeks
Genotype 1a, 4, (b) (4)	GZR/EBR with ribavirin ^{¶, #}	16 weeks

*Patients who have failed treatment with peginterferon alfa + ribavirin or peginterferon alfa + ribavirin + boceprevir, simeprevir, or telaprevir

(b) (4)

In clinical trials, the dose of ribavirin 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. For further information on ribavirin dosing and dose modifications, refer to the ribavirin prescribing information

(b) (4)

The clinical development program for GZR/EBR was quite extensive consisting of 11 Phase 2 clinical trials, one Phase 2/3 trial and 5 Phase 3 clinical trials. At the time of the NDA, two of the Phase 3 trials (062 and 065-both trials in unique subpopulations of CHC subjects) were ongoing without completed 12 week post-treatment follow-up data and therefore not submitted.

This review will focus on findings from three Phase 2 clinical trials (035, 047, and 048) and four Phase 2/3 or Phase 3 trials (052, 060, 061 and 068) enrolling a total of 2064 (this includes n=238 subjects assigned to delayed treatment) CHC subjects. Most trials were open-label and uncontrolled in design and only two trials utilized a double-blind design comparing immediate versus delayed treatment (placebo treatment for first 12 weeks followed by 12 week of GZR/EBR treatment). The phase 2/3 and 3 trials were all designed around a primary objective to demonstrate superiority of SVR12 over a pre-specified historical SVR12 rate in the applicable CHC subpopulation (Table 8). The justification for each SVR12 is provided, by trial, in section 3. The three Phase 2 trials are included in this review as they studied relevant subpopulations to support findings from the Phase 3 trials.

At the time of the NDA, SVR24 data were available for only the two Phase 2 trials 035 and 047 included in this review. During pre-NDA discussion with the applicant, the FDA agreed to review trial data containing data only up to 12 weeks following end of treatment while requiring that the longer-term follow-up data be submitted a later time. Therefore, this review does not include or discuss overall results of the SVR24 endpoint among 5/7 trials reviewed.

Table 8: List of all studies included in analysis

Trial	Study Population	Study Design	# of Subjects per Arm (FAS)	Hypothesis	Data in NDA
035 (C-WORTHY)	TN (+/- C) P/R null-responders (+/-C), HIV co-infection (TN, NC) GT 1, 3	Phase 2, R, MC, parallel-group, blinded (part A only)	A1: (TN, NC): GZR100 mg/EBR 20 mg + RBV x 12 w (n=25) A2: (TN, NC): GZR100 mg/EBR 50 mg + RBV x 12 w (n=27) A3: (TN, NC/ GT1a): GZR 100 mg/EBR 50 mg x 12 w (n=13) B1: (TN, NC/ GT1a): GZR 100 mg/EBR 50 mg + RBV x 8 w (n=30) B2: (TN, NC): GZR 100 mg/EBR 50 mg + RBV x 12 w (n=33) B3: (TN, NC, GT1a): GZR 100 mg/EBR 50 mg x 12 w (n=31) B4: (TN, C): GZR 100 mg/EBR 50 mg + RBV x 12 w (n=31) B5: (TN, C): GZR 100 mg/EBR 50 mg x 12 w (n=29) B6: (TN, C): GZR 100 mg/EBR 50 mg + RBV for 18 weeks (n=32) B7: (TN, C): GZR 100 mg/EBR 50 mg x 18 w (n=31) B8: (NR, C, NC): GZR 100 mg/EBR 50 mg + RBV x 12 w (n=32) B9: (NR, C, NC): GZR 100 mg/EBR 50 mg x 12 w (n=33) B10: (NR, C, NC): GZR 100 mg/EBR 50 mg + RBV x 18 w (n=33) B11: (NR, C, NC): GZR 100 mg/EBR 50 mg x 18 w (n=32) B12: (TN, HIV, NC): GZR 100 mg/EBR 50 mg +RBV x 12 w (n=29) B13: (TN, HIV, NC): GZR 100 mg/EBR 50 mg x 12 w (n=30) C1: (TN, NC, GT1b): GZR 100 mg/EBR 50 mg +RBV x 8 w (n= 30). C2: (TN, NC, GT1b): GZR 100 mg/EBR 50 mg x 8 w (n=31) D1: (TN, NC, GT3): GZR 100 mg/EBR 50 mg + RBV x 12 w (n=20) D2: (TN, NC, GT3): GZR 100 mg/EBR 50 mg + RBV x 18 w (n=21)	None	Through SVR24 (except Part D)
047 (C-SCAPE)	TN (NC) GT 2, 4, 5, 6	Phase 2, Partial R, OL	GT2 : GZR 100 mg/EBR 50 mg + RBV x 12 w (n=30) GT2 : GZR 100 mg/EBR 50 mg x 12 w (n=30) GT4,5,6 : GZR 100 mg/EBR 50 mg + RBV x 12 w (n=19) GT4,5,6 : GZR 100 mg/EBR 50 mg x 12 w (n=19)	None	Through SVR24
048 (C-SALVAGE)	Prior DAA/P/R failures (+/-C), GT1	Phase 2, NR, MC	GZR 100 mg/EBR 50 mg +RBV x 12 w (n=79)	None	SVR12 (trial ongoing)
052 (C-SURFER)	CKD stages 4-5, including dialysis, GT1	Phase 2/3, R, Blinded (first 12 w), parallel, MC	ITG/PK: GZR 100 mg/EBR 50 mg x 12 w (n=122) DTG: Placebo x 12 w, 4 w washout, GZR 100 mg/EBR 50 mg x 12 w (n=113)	SVR12 in ITG superior to 45% HC	SVR12 on ITG, EOT on DTG
060 (C-EDGE TN)	TN (+/-C) GT 1,4,6	Phase 3, R, DB, MC	ITG/PK: GZR 100 mg/EBR 50 mg x 12 w (n=316) DTG: Placebo x 12 w, 4 w washout, GZR 100 mg/EBR 50 mg x 12 w (n=105)	SVR12 in ITG superior to 73% HC	SVR12 on ITG, EOT on DTG (trial ongoing)
061 (C-EDGE CO-INFECTION)	HIV co-infected (TN+/- C) GT 1,4,6	Phase 3, NR, MC	GZR 100 mg/EBR 50 mg x 12 w (n=218)	SVR12 superior to 70% HC	SVR12 (trial ongoing)
068 (C-EDGE TE)	P/R PTF, +/- C, +/- HIV co-infection GT 1,4,6	Phase 3, R, OL, MC, parallel	GZR 100 mg/EBR 50 mg x 12 w (n=105) GZR 100 mg/EBR 50 mg +RBV x 12 w (n=104) GZR 100 mg/EBR 50 mg x 16 w (n=105) GZR 100 mg/EBR 50 mg +RBV x 16 w (n=106)	SVR12 in at least one arm superior to 58% HC	SVR12 (trial ongoing)

NDA 208261 ZEPATIER® (Indication: Treatment of Chronic HCV)
Statistical Review: LaRee A. Tracy, MA, PhD (DB4)

GT=Genotype; DAA=Direct-acting Antivirals; TN=Treatment-Naïve; CKD=Chronic Kidney Disease; ITG=Immediate Treatment Group; DTG=Deferred Treatment Group; PK=Intensive PK Group; HC=historical rate. P/R=Pegylated Interferon/Ribavirin prior null responder; PTF=Prior Treatment Failure; RBV=Ribavirin; NC=non-cirrhotic; N=Number of subjects randomized

Breakthrough Therapy Designation

The applicant applied for Breakthrough Therapy (BT) designations for treatment of HCV GT4 and of HCV GT1, 4 (b) (4) in subjects with (b) (4) including ESRD on hemodialysis. In April 2015, FDA granted the applicant BT designation for HCV GT4 and of HCV GT1 in subjects with ESRD on hemodialysis (HD). (b) (4)

(b) (4) With the BT designations, this NDA falls under a priority review timeline.

2.2 Data Sources

The complete submission is located at the EDR Location: <\\CDSESUB1\evsprod\NDA208261\0000>. Trial-level data were provided as analyses legacy files (with relevant programs) and as tabulation (SDTM format) files.

During the filing review, it was noted that the SITEIDs differed between the CLINSITE and legacy datasets. The following link contains updated CLINSITE dataset with corrected SITEIDs.

<\\CDSESUB1\evsprod\NDA208261\0002>

Revisions to the proposed label with justification were submitted during the NDA.

<\\CDSESUB1\evsprod\NDA208261\0035>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical analyses plans for all phase 2/3 or 3 trials were submitted and reviewed in advance. Overall, the data provided in either Study Data Tabulation Model (SDTM) or Analysis Data Model (ADaM) formats are acceptable and organized as per current data standards. The application includes sufficient documentation on variables listed in respective datasets and coding. The reviewer relied on data from both the SDTM and analyses files and was able to replicate the applicant's primary findings. All analyses by the reviewer were performed using the reviewer's SAS programs.

One inconsistency was identified between the applicant's Trial 052 ADaM datasets, ADDEFFOUT.xpt and HCVRV.xpt in terms of the SVR12 variable results. Specifically, the incorrect proportions of negatives and positives were identified in the ADEFFOUT.xpt dataset; however, the correct counts are in the HCVRV.xpt dataset. However, as noted in the applicant's Statistical Review Aid (define.pdf) neither of these two datasets were used to generate the primary results.

3.2 Evaluation of Efficacy

3.2.1 Trial Design Characteristics Common to All Included Trials

Comment: The primary analyses of SVR12 in Trials 052, 060, 061 originally included use of the asymptotic (Wald) method to calculate 95% confidence intervals. However, only a small number of subjects failed to achieve SVR12 in each trial and therefore each protocol was amended to specify that the Clopper-Pearson method (an exact approach) would be the primary approach to calculate 95% CIs. Since these trials were designed to achieve superiority versus a historical control SVR12 estimate, use of an exact method is acceptable and typically yields a wider, thus more conservative, confidence interval than the asymptotic method.

Trial Endpoints

In all clinical trials in CHC, the objective is to achieve SVR as determined by plasma HCV-RNA levels measured using the COBAS™ AmpliPrep/COBAS® Taqman® HCV Test, v2.0. To meet the condition of SVR, the HCV RNA level needed to be less than the lower limit of quantification (LLOQ) defined as 15 IU/mL (target detected but unquantifiable, TD (u)) or not detected (target not detected, TND).

Reviewer's Comment: The LLOQ of 25 IU/mL was used in trial 047, which was a larger cut-off compared to the other six trials.

Primary Efficacy Endpoint

The primary efficacy endpoint was defined as SVR12 (Sustained Virologic Response 12 weeks after the end of all study therapy).

Specific Secondary Endpoints

- SVR4 (Sustained Virologic Response 4 weeks after the end of all study therapy). The subject had HCV RNA < Lower limit of quantification (LLOQ) [either TD (u) or TND] 4 weeks after the end of all study therapy.

- SVR24 (Sustained Virologic Response 24 weeks after the end of all study therapy). The subject had HCV RNA < LLOQ [either TD (u) or TND] 24 weeks after the end of all study therapy.

Reviewer's Comment: SVR24 data were unavailable for all trials except trials 035 and 047. It was agreed upon during the pre-NDA meeting that the applicant would submit complete SVR24 data at a later submission. Therefore, SVR24 findings are not provided in this review.

- Emergence of resistance-associated variants (RAVs) resistant to GZR and EBR. These included NS3/4A and HS5A present at baseline and impact on efficacy as well as emergence of these variants.

Reviewer's Comment: The statistical reviewer did not perform specific analyses of emergence of RAVs due to the small numbers of these outcomes. Refer to the clinical virology review for a breakdown of RAVs by trial.

On treatment virologic failure was defined as follows:

- **Non-response**: Subject with an HCV RNA detected at the end of treatment without HCV RNA < LLOQ while on treatment.

- **Rebound:** Subject with a $>1 \log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.
- **Virologic Breakthrough:** Subject had a confirmed HCV RNA \geq LLOQ [TD (q)] after being $<$ LLOQ previously while on treatment. Confirmation is defined as an HCV RNA \geq LLOQ from a separate blood draw repeated within 2 weeks.

Relapse was defined as a subject with a confirmed HCV RNA \geq LLOQ [TD (q)] following end of all study therapy, after becoming undetectable (TND) at end of treatment. Confirmation of relapse was based on two blood draws within two weeks with an HCV RNA \geq LLOQ.

Primary Analyses Population by Trial

Phase 2 Trials

Trials 035, 047, and 048

The applicant's analyses of SVR12 was performed in the per protocol (PP) population, which used an observed failure (OF) approach for missing data. This approach treated any subject who discontinued treatment early due to lack of efficacy or discontinued study following a confirmed HCV RNA TD (q) during follow-up as failures. Otherwise, subjects with missing values were omitted from the analyses.

Supportive analyses assessed outcomes in the full analyses set, which comprised all randomized/enrolled subjects who received at least one dose of study treatment.

Reviewer's Comment: For consistency and to limit bias associated with PP analyses, the reviewer performed all primary analyses of SVR12 in the full analyses set.

Phase 2/3 or Phase 3 Trials

Trials 060, 061 and 068:

Full Analysis Set (FAS): Defined as all randomized subjects who received at least one dose of study drug.

Trial 052:

Modified Full Analysis Set (mFAS) (applicant's primary analysis population): Defined as all randomized subjects who received at least one dose of study drug excluding those with missing data due to death or early discontinuation from the study with reasons unrelated to their responses to HCV treatment. This later criterion was chosen because the study population of CKD 4/5 subjects, especially those that are HD CKD 5, have a high incidence (~10%) of major cardiovascular events that may lead to death or to study withdrawal.

FAS (applicant's supportive analysis group): All randomized subjects or enrolled but non-randomized (applies to the intensive PK arm of 11 subjects who received immediate treatment and agreed to additional PK assessments) subjects who received at least one dose of study drug.

Statistical Comment: Given that the mFAS population excludes subjects based on a post-randomization factor there is a concern of bias in this population. Therefore, while six subjects in the FAS were omitted from the mFAS, the reviewer used the FAS as the primary efficacy analyses population.

Handling of Missing Values

Trial 035, 047 and 048

Among all Phase 2 trials, one of three approaches was used to treat missing values. These are as follows:

Observed Failure (OF): Subjects were treated as failures if they had one of the following: 1) discontinued treatment early due to lack of efficacy or 2) discontinued from study following a confirmed HCV RNA TD (q) during follow-up. Otherwise, any subject missing an evaluation at any visit was excluded from the analyses at that time point.

Data as Observed (DAO): This approach excluded any subject missing an HCV RNA evaluation at the respective visit.

Missing=Failure (M=F): All missing was treated as failure with the exception of a missing value that is immediately preceded and followed by a TND HCV RNA, where the missing value was imputed to be HCV RNA <25 IU/mL. When a missing value was flanked by a TND RNA and HCV RNA <25 IU/mL, then the missing HCV RNA was imputed as <25 IU/mL.

Reviewer's Comment: The applicant's primary analyses in all three trials used the OF approach to handle missing. The reviewer used the M=F approach as the primary method to handle missing.

Trials 052, 060, 061 and 068

Throughout all Phase 3 protocols and analysis plans, the applicant specified three types of missing data and the different analytic approaches used to account for missing values. These are:

- 1) **Intermittent missing**: If a missing data point that is preceded or followed by a non-missing value, the missing value will be imputed to the worse outcome of the two.
- 2) **Non-Intermittent missing related to study drug**: For missing values associated with premature study discontinuation or treatment-related reasons will be imputed as a treatment failure.
- 3) **Non-Intermittent missing unrelated to study drug**: For data missing due to reasons such as lost to follow-up, protocol violation, withdrawal of consent, administrative reasons, etc. will be handled in the following ways

- a. **Treatment-Related Discontinuation=Failure (TRD=F):** Subjects with treatment-related missing data (type 2 above) are treatment failures; whereas missing that is due to non-treatment related reasons (type 3 above) in subjects who did not have virologic failure during the observed period were excluded from the analyses for all time points following trial withdrawal. Any subject with virologic failure during the treatment or follow-up period-even if there was premature discontinuation-were treated as a failure.
- b. **Missing=Failure (M=F):** Any non-intermittent missing data was treated as failure regardless of reason for missing.

Trials 060, 061, and 068: Missing values were handled as M=F.

Trial 052: A TRD=F approach was used for the primary analyses of the modified FAS.

3.2.2 Phase 2 Trials

3.2.2.1 Trial 035 (C-WORTHY)

Trial Design

This was a multicenter, randomized, parallel-group trial conducted in four separate parts to explore both doses and duration of GZR/EBR (20mg and 50mg) with or without RBV. The protocol mainly focused on GT1 subgenotype infected subjects; however Part D also enrolled GT3-subgenotype CHC-infected subjects. ***NOTE: Part D was ongoing at time of the NDA and the applicant is not presently seeking approval for treatment of this GT. Therefore, results in this part are not discussed in this review.***

The parts were as follows:

Part A: This was a dose response part of GZR/EBR for 12 weeks in TN, NC, GT1b CHC infected subjects. Subjects were randomized in a 2:2:3 fashion to double-blinded treatment of one of the following:

- GZR 100 mg/EBR 20 mg + RBV x 12 weeks (n=24)
- GZR 100 mg/EBR 50 mg + RBV x 12 weeks (n=24)
- GZR 100 mg/EBR 50 mg x 12 weeks (n=12)

Part B: This part was a dose exploration study of GZR 100 mg/EBR 50 +/- RBV for 8, 12 or 18 weeks in 390 (planned) GT1 subjects with or without C, HIV-co-infection, prior null treatment response. Treatment was open-label; however, treatment duration was blinded through weeks 8 or 12. There were a total of thirteen treatment arms with a planned 390 subjects enrolled separately by prior treatment and cirrhosis status as follows:

Treatment-naïve non-cirrhotic subjects: Arms B1-B3

Subjects with HCV GT1 were randomized to 3 treatment arms in a ratio of 2:1:2 (Arms B1, B2, and B3). Subjects with HCV GT1 non-a were all allocated to Arm B2.

- Arm B1: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 weeks (n=30)
- Arm B2: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30)

- Arm B3: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30)

Treatment-naïve cirrhotic subjects: Arms B4-B7

Subjects were randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of treatment.

- Arm B4: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30)
- Arm B5: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30)
- Arm B6: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=30)
- Arm B7: MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=30)

Null responders (cirrhotic and non-cirrhotic): Arms B8-B11

Subjects were randomized in a ratio of 1:1:1:1 to receive 12 or 18 weeks of treatment.

- Arm B8: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30)
- Arm B9: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30)
- Arm B10: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=30)
- Arm B11: MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=30)

Treatment-naïve co-infected with HIV (non-cirrhotic): Arms B12-B13

Subjects were randomized in a ratio of 1:1 to receive 12 weeks of treatment.

- Arm B12: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=30)
- Arm B13: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30)

Part C: This part was open-label intended for dose exploration in 60 (planned), TN, NC, GT1b subjects who were randomized in a 1:1 manner to GZR 100 mg/EBR 50 mg +/- RBV for 8 weeks.

Part D: This final part was open-label with the objective to explore treatment duration in 40 (planned), TN, NC GT3 subjects randomized (1:1) to either 12 or 18 weeks of open-label GZR 100 mg/EBR 50 mg + RBV.

Subject Disposition

A total of 532 CHC GT1 subjects were randomized to trial 035 of which 514 (97%) completed protocol-assigned treatment and protocol visits. Among TN, NC subjects (arms A1, A2, A3, B2 and B3), the overall treatment completion rates were at least 93% and trial completion at least 88%. Four subjects were LTF, 1 withdrew and 1 discontinued due to protocol violations. Among TN, C subjects receiving 12 weeks' therapy (arms B4, B5) all but one completed treatment or trial and among those receiving 18 weeks' therapy (arms B6, 7) all but three completed study therapy. In arms B8 and B9 (NR on 12 weeks treatment), all but two subjects completed treatment or trial due to one AE and one death (not study related). One NR subject receiving the 18 week (arm B11) course failed to complete treatment due to treatment failure. Three subjects in arm B13 failed to complete treatment due to LTF (n=1) and lack of efficacy (n=2). All subjects receiving 8 weeks of therapy (arm B1, C1, C2) completed therapy. These data are shown below in Table 9.

Table 9: Trial 035 Disposition

<i>Population</i>	<i>TN, C, GT1b</i>			<i>TN/NC/GT1a</i>				
Arm	A1	A2	A3	B1	B2	B3		
Duration	12 w	12 w	12 w	8 w	12 w	12 w		
Regimen*	100/20+R	100/50+R	100/50	100/50+R	100/50+R	100/50		
FAS	25	27	13	30	33	31		
Completed Treatment	24 (96)	25 (93)	13 (100)	30 (100)	31 (94)	31 (100)		
Completed Study	22 (88)	26 (96)	13 (100)	28 (93)	31 (94)	31 (100)		
<i>Population</i>	<i>TN/C</i>				<i>Null Responders</i>			
Arm	B4	B5	B6	B7	B8	B9	B10	B11
Duration	12 w	12 w	18 w	18 w	12 w	12 w	18 w	18 w
Regimen*	100/50+R	100/50	100/50+R	100/50	100/50+R	100/50	100/50+R	100/50
FAS	31	29	32	31	32	33	33	32
Completed Treatment	30 (97)	29 (100)	30 (94)	30 (97)	30 (94)	33 (100)	33 (100)	31 (97)
Completed Study	30 (97)	29 (100)	32 (100)	29 (93)	30 (94)	33 (100)	32 (97)	32 (100)
<i>Population</i>	<i>TN, HIV-1</i>		<i>TN, NC, GT1b</i>					
Arm	B12	B13	C1	C2				
Duration	12 w	12 w	8 w	8 w				
Regimen*	100/50+R	100/50	100/50+R	100/50				
FAS	29	30	30	31				
Completed Treatment	29 (100)	27 (90)	30 (100)	31 (100)				
Completed Study	29 (100)	27 (90)	29 (97)	31 (100)				

R=ribavirin, w=weeks of treatment, *GZR/EBR

Subject Demographics and Characteristics

Among TN, NC subjects (arms A1, A2, A3, B1, B2, B3, C1, C2) approximately half were male and most were White race with a median age of 52 years (range 20-73). Per design, all subjects in arms A3, C1, C2 were infected with HCV GT1b subgenotype and all subjects in arms B1 and B3 were infected with GT1a subgenotype except one subject with GT1a who was erroneously enrolled in the B3 arm. In arms A1 and A2, over 70% were GT1a subgenotype.

Among TN, C, HIV co-infected subjects (arms B12 and B13), the majority were males (80%), and mostly of White race with a median age of 47 years (range 22-63), 78% with GT1a subgenotype with mild to moderate levels of fibrosis.

In the cohorts of TN, C subjects (arms B4-B7), 60% were males of mostly White race with a median age of 58 years (range 41 to 82) and 71% infected with HCV GT1a subgenotype.

Among prior null responder subjects (arms B8-B11), 57% were male of mostly White race and a median age of 56 years (range 18-77), 59% of GT1a subgenotype, approximately 49% had mild or moderate levels of fibrosis and 38% were cirrhotic.

A table of demographics is not supplied given the large number of treatment arms and similarity among all arms.

Statistical Methods

This trial was designed to explore varying doses and durations of GZR/EBR with or without RBV and was **not designed around a testable hypothesis**. The primary endpoint of SVR12 was calculated for all treatment arms along with a 95% CI without adjustment. The applicant's primary analysis was in the per-protocol population using the observed failure approach for missing. A secondary analysis was performed in the full analyses set using a data as observed approach (this approach excludes a subjects missing a HCV RNA at any particular visit) for missing. *The reviewer's analysis of SVR12 was performed using the FAS imputing missing as failures.*

Additional secondary analyses included time to first achievement of undetectable (TND) HCV RNA, proportion of subjects TND at weeks 2, 4, 12 and end of treatment visits, SVR4 and SVR24 and emergence of antiviral resistance.

Planned subgroup analyses included SVR12 by gender, GT (part A: 1a v. 1b; part B: 1a vs. 1 non-a), IL28B CC genotype vs. non-CC genotype, HCV RNA at screening (800,000 IU/mL cut-point), and fibrosis stage.

The planned sample size in all four parts of this trial was based on estimation in the per protocol population, which assumes a 10% violation rate. In Part A, among arms including RBV with 22 subjects in the PP population, the lower bound of the 95% CI ranged from 25% to 72% assuming a SVR12 ranging from 10/22 to 20/22. Similarly, in Part A among the arm without RBV assuming an SVR12 ranging from 7/11 to 10/11 led to an estimated lower bound of the 95% CI ranging from 31% to 59%. In Parts B and C, assuming an SVR12 ranging from 17/27 to 27/27, the estimated lower bound of the 95% ranges from 42% to 87%. Finally in Part D, given scenarios of SVR12 of 14/18 to 17/18, the 95% lower bound ranged from 52% to 73%.

Efficacy Results

The SVR12 in all GT1 enrolled subjects in trial 035 are presented below in Table 10.

Among **TN, NC subjects who received 12 weeks of treatment (arms A1, A2, A3, B2 and B3)**, the overall SVR12 ranged from 88% to 100%. Virologic failures included 3 relapses (1 each in arms A2, B2 and B3) and one breakthrough infection in arm B2. The remaining five failures were due to non-virologic causes. Similar efficacy was shown between RBV-containing regimens and non-RBV containing regimens as well as between GT1a and GT1b subgenotypes. Combining results from the A3 and B3 arms

(GZR 100 mg/50 mg x 12 weeks in TN, NC subjects), the SVR12 was 98% (43/44). When including RBV, the combined efficacy (arms A1, A2 and B2) is 93% (79/85).

Among **TN, HIV/HCV co-infected NC subjects (arms B12 and B13)**, the SVR12 was 93% and 87%, respectively with the 12 week treatment duration. The lower SVR12 in the non-RBV containing regimen was driven by 2 subjects who were LTF but who had achieved TND at their last visit thus these two arms do not necessarily suggest that the addition of RBV increases SVR12.

Among **TN, NC subjects who received 8 weeks' treatment (arms B1, C1 and C2)** the SVR12 ranged from 77% (GT1a treated with RBV) to 90% (GT1b with or without RBV). There was one relapse in each of the three arms.

Among **TN, C subjects (arms B4-B7)**, the SVR12 ranged from 90% to 97%. Among those treated with RBV, the longer duration of 18 weeks had a higher SVR12 of 97% compared to those without RBV of 90%; however the reverse was true among those treated with the 12 week duration. Therefore from these limited data there is little evidence suggesting treatment for 18 weeks increases the overall SVR12.

Among **prior null responders (arms B8-B11) who received either 12 or 18 weeks treatment** with GZR 100 mg/EBR 50 mg with or without RBV, the SVR12 ranged from 88% to 100% with some evidence that the increased treatment duration might confer increased SVR12 but the sample sizes are small.

Table 10: Trial 035 SVR12 Full Analysis Set (Reviewer’s Analyses) (Missing=Failure)

Treatment Regimen	SVR12	
	%	95% CI*
PART A: TN NC		
A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks	96.0 (24/25)	79.7, 99.9
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	88.9 (24/27)	70.8, 97.6
A3: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	100.0 (13/13)	75.3, 100
PART B		
TN NC OR C		
B1: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	76.7 (23/30)	57.7, 90.1
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	87.9 (29/33)	71.8, 96.6
B3: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	96.8 (30/31)	83.3, 99.9
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	90.3 (28/31)	74.3, 98.0
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Week	96.6 (28/29)	82.2, 99.9
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	96.9 (31/32)	83.8, 99.9
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	90.3 (28/31)	74.3, 98.0
PRIOR NULL RESPONDERS		
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	93.8 (30/32)	79.2, 99.2
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	87.9 (29/33)	71.8, 96.6
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	100.0 (33/33)	89.4, 100.0
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	96.9 (31/32)	83.9, 99.9
TN HIV CO-INFECTION		
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	93.1 (27/29)	77.2, 99.2
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	86.7 (26/30)	69.3, 96.2
PART C GT1B TN NC		
C1: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	90.0 (27/30)	73.5, 97.9
C2: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 8 Weeks	90.3 (28/31)	74.3, 98.0

*Clopper-Pearson exact method

Similar results were found in the more-restrictive PP population (results are not presented here).

SVR12 by GT1 subgenotype

SVR12 by GT1 subgenotype are presented below in Table 11 and Table 12 by GT1a and GT1b, respectively. Overall, SVR12 among subjects treated for 12 weeks was higher among GT1b subjects compared to GT1a subjects, which is expected given that GT1a subjects are typically more difficult to treat than those with GT1b subgenotype. The 8 week treatment duration evaluated in 30 GT1a-infected subjects resulted in low SVR12 (B1 arm). Among GT1a subjects, there is some evidence that the longer duration of treatment (18 weeks versus 12 weeks) among prior null responders may add to overall SVR12 but the numbers are small. Among GT1b-infected subjects the additional weeks of treatment beyond 12 weeks does not suggest an increase in SVR12 in any subpopulation except perhaps among prior NRs.

Table 11: Trial 035 SVR12 in GT1a Subgenotype Subjects

Treatment Regimen	SVR12	
	%	95% CI*
PART A: TN NC		
A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks	94.7 (18/19)	74.0, 99.9
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	84.2 (16/19)	60.4, 96.6
PART B		
TN NC OR C		
B1: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	76.7 (23/30)	57.7, 90.1
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	100 (14/14)	76.8, 100
B3: TN NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	96.7 (29/30)	82.8, 99.9
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	90 (18/20)	68.3, 98.8
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Week	95 (19/20)	75.1, 99.9
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	95.8 (23/24)	78.9, 99.9
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	87.0 (20/23)	66.4, 97.2
PRIOR NULL RESPONDERS		
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	88.9 (16/18)	65.3, 98.6
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	86.4 (19/22)	65.1, 97.1
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	100 (19/19)	82.3, 100
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	94.1 (16/17)	71.3, 99.9
TN HIV CO-INFECTION		
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	91.7 (22/24)	73.0, 99.0
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	86.4 (19/22)	65.1, 97.1

*Clopper Pearson exact method

Table 12: Trial 035 SVR12 in GT1b Subgenotype Subjects

Treatment Regimen	SVR12	
	%	95% CI*
PART A: TN NC		
A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks	100 (6/6)	54.1, 100
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	100 (8/8)	63.1, 100
A3: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	100.0 (13/13)	75.3, 100
PART B		
TN NC OR C		
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	76.5 (13/17)	50.1, 93.2
B3: TN NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	100 (1/1)	2.5, 100
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	100 (10/10)	69.2, 100
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Week	100 (7/7)	59.0, 100
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	100 (8/8)	63.1, 100
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	100 (8/8)	63.1, 100
PRIOR NULL RESPONDERS		
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	100 (14/14)	76.8, 100
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	90.9 (10/11)	58.7, 99.8
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	100 (14/14)	76.8, 100
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	100 (15/15)	78.2, 100
TN HIV CO-INFECTION		
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	100 (5/5)	47.8, 100
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	87.5 (7/8)	47.3, 99.7
PART C TN NC		
C1: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	90.0 (27/30)	73.5, 97.9
C2: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 8 Weeks	90.3 (28/31)	74.3, 98.0

*Clopper Pearson exact method

Secondary Analyses: SVR24 (FAS)

Results of the reviewer's analyses of SVR24 in the FAS are presented in Table 13 showing that overall subjects achieving a sustained virologic response at week 12 post-treatment maintained suppression through week 24. Between 12 and 24 weeks, there were two additional subjects who experienced virologic failure; one subject (arm B13) was found to have a GT4 infection suggesting a re-infection and another subject (arm B1) with genotype GT1a suggesting relapse.

Reviewer’s Comment: *The applicant’s results (not included here) in the PP population were similar to those reported below with slightly higher SVR12 point estimates due to smaller sample sizes in this restricted population. The higher estimates in the PP analyses are likely biased due to the exclusionary nature of per-protocol populations.*

Table 13: Trial 035 SVR24 Full Analysis Set (Reviewer’s Analyses) (Missing=Failure)

Treatment Regimen	SVR12	
	%	95% CI*
PART A: TN NC		
A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks	92.0 (23/25)	74.0, 99.0
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	88.9 (24/27)	70.8, 97.6
A3: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	100.0 (13/13)	75.3, 100
PART B		
TN NC OR C		
B1: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	73.3 (22/30)	54.1, 87.7
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	90.9 (30/33)	75.7, 98.1
B3: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	96.8 (30/31)	83.3, 99.9
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	90.3 (28/31)	74.3, 98.0
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Week	96.6 (28/29)	82.2, 99.9
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	96.9 (31/32)	83.8, 99.9
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	87.1 (27/31)	70.2, 96.4
PRIOR NULL RESPONDERS		
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	90.6 (29/32)	75.0, 98.0
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	90.9 (30/33)	75.7, 98.1
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks	97.0 (32/33)	84.2, 99.9
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks	96.9 (31/32)	83.9, 99.9
TN HIV CO-INFECTION		
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	96.6 (28/29)	82.2, 99.9
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	80.0 (24/30)	61.4, 92.3
PART C GT1B TN NC		
C1: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks	90.0 (27/30)	73.5, 97.9
C2: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 8 Weeks	93.6 (29/31)	78.6, 99.2

Overall, nine subjects relapses up to follow-up week 12 and two additional between follow-up weeks 12 and 24.

Reviewer’s Comments: *Considering the small number of patients and the associated uncertainties and design limitations, the findings should be interpreted with caution.*

3.2.2.2 Trial 047 (C-SCAPE)

Trial Design

Trial 047 was a Phase 2 multi-site, multi-national, open-label, two-part trial performed in **non-cirrhotic TN** subjects with CHC GT 2, 4, 5 and 6 to evaluate the safety and efficacy of GZR 100 mg with or without EBR 50 mg with or without ribavirin. The trial was conducted in two parts; Part A and Part B, as illustrated in Figure 1 and described below.

Part A: Treated 30 GT2-infected subjects with GZR/EBR/ribavirin for 12 weeks (no control)

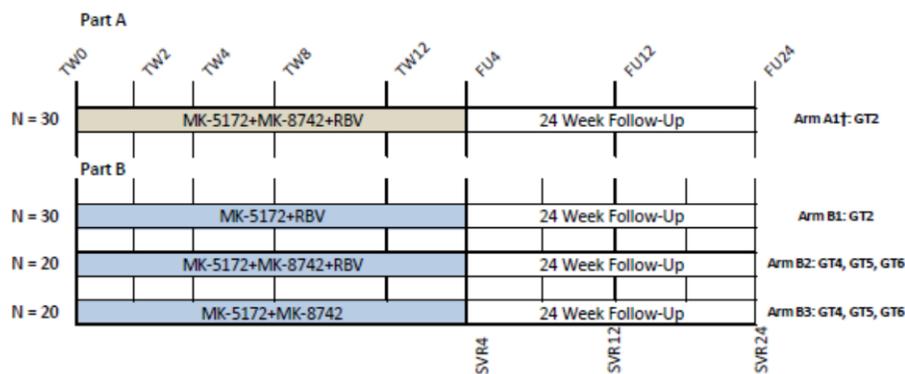
Part B consisted of two sub-parts:

Part B1: This part enrolled 30 GT2-infected subjects who received GZR+RBV (no control) for 12 weeks.

Part B2/B3: This study part randomized 40 GT4, GT5 or GT6 subjects in a 1:1 fashion (stratified by genotype) to 12 weeks of GZR+EBR+RBV or GZR+EBR without RBV. A minimum of 4 subjects with GT4 or GT6 were to be enrolled in both treatment arms and no minimum number of GT5 subjects was specified.

Reviewer’s Comment: The applicant is not seeking approval for treatment of CHC subgenotype GT2 or GT5 therefore all findings from Parts A and B1 are omitted. Findings in the GT5 subgenotypes are presented for Parts B2/B3 for completeness purposes only,

Figure 1: Trial 047 Design



† Arms were identified slightly differently in P047 Protocol (in the protocol Arm A1 was Arm 1; Arm B1 was Arm 2; Arm B2 was Arm 3; and Arm B3 was Arm 4).

Source: Figure 9-1, p047.pdf

Statistical Methods

There were no formal statistical hypotheses and as such the sample sizes were determined based on feasibility. The applicant projected a protocol violation rate of 10% such that the PP population was expected to have 27 subjects in parts A and B1 and 18 in each arm in Part B2/B3.

The primary efficacy analyses included calculation of the proportion of subjects achieving SVR12 with 95% confidence intervals based on the Clopper-Pearson method. The applicant's primary analyses population evaluated SVR12 in the PP population and additional sensitivity analyses in the FAS population treating all missing as failure.

Reviewer's Comment: *The reviewer's primary analyses findings will be presented in the FAS and not the PP.*

Subject Disposition

The overall subject disposition is presented below for study parts B2/B3 only in which 19 subjects were randomized per treatment arm. Few subjects (n=2) in the GZR/EBR group failed to complete assigned treatment due to an AE or lack of efficacy. All randomized subjects in the GZR/EBR/RBV group completed treatment and there was one subject in this group meeting a protocol violation due to having a GT1 CHC infection.

Table 14: Trial 047 Subject Disposition

	Part B2/B3	
	GZR/EBR+RBV	GZR/EBR
Enrolled/Randomized	19	19
Premature Trial D/C	0	1 (5.3)
LTF	0	1
Premature Treatment D/C	0	2 (10.5)
Adverse Event	0	1
Lack of Efficacy	0	1
Per protocol	17 (89.5)	13 (68.4)
Reasons for Exclusion		
Prohibited Medication	0	3
LTF	0	1
Infected w/GT1	1	1
Inclusion criteria not met	1	1

D/C=discontinuation, LTF=lost to follow-up

Subject Demographics and Characteristics

In Part B2/B3, the average subject age was 52 years, over 68% were of White race, and over 79% were enrolled in non-US sites. There is a numerical imbalance in gender with more males in the GZR/EBR group; however, the numbers are small and the difference is not significant. As planned, the trial enrolled 10, 4, and 4 subjects with GT4, 5, and 6 subgenotypes in each group, respectively.

Table 15: Trial 047 Subject Demographics and Characteristics

	Part B2/B3	
	GZR/EBR+RBV	GZR/EBR
Enrolled/Randomized	19	19
Characteristic (%)		
Gender (Male)	8 (42.1)	12 (63.2)
Age (years)		
Mean (+/-se)	52.2 (2.1)	52.8 (2.8)
Range	38-75	34-80
Race		
White	14 (73.7)	13 (68.4)
African American	1 (5.3)	1 (5.3)
Asian	4 (21.1)	5 (26.3)
Region		
US	3 (15.8)	4 (21.1)
Non-US	16 (84.2)	15 (78.9)
IL2B Genotype		
CC	4 (21.1)	6 (31.6)
Non-CC	15 (88.9)	13 (68.4)
Baseline HCV RNA Log10 (IU/mL)**		
Mean (+/-SD)	6.2 (0.7)	6.4 (0.6)
Median	6.2	6.4
HCV Genotype		
1	1 (5.3)	1 (5.3)
4	10 (52.6)	10 (52.6)
5	4 (21.1)	4 (21.1)
6	4 (21.1)	4 (21.1)

Efficacy Findings

In the randomized portion of the study (Part B2/B3), the overall SVR12 in the FAS (95% CI) was 94.7% (74.0, 99.9) and 73.7% (48.8, 90.9) in the GZR/EBR+RBV and GZR/EBR arms, (b) (4)

(b) (4) No additional failures were reported between 12 and 24 weeks after end of therapy.

Although the numbers are small, efficacy by specific genotype (GTs 4 (b) (4)) are presented below given that treatment response (SVR12) is known to vary according by genotype (Table 16).

GT4 (Parts B2 and B3)

The SVR12 achieved among the GT4 subjects randomized to GZR/EBR+RBV and GZR/EBR was 100% (10/10), 95% CI (69.2, 100.0) and 90% (9/10), 95% CI (66.4, 100.0), respectively.

Reviewer's Comments

1) In this trial, the LLoQ was 25 IU/mL (differs from the LLoQ of 15 IU/mL used in the other trials). The overall impact of this higher cut-off is negligible.

2) More subjects were omitted in the PP population in the GZR/EBR arm compared to the GZR/EBR+RBV, which illustrates the issue of use of this population as primary particularly in an open-label trial.

Table 16: Trial 047: SVR12 and SVR 24 by Study Part

	Part B2/B3	
	GZR/EBR+RBV	GZR/EBR
Genotype	GT 4,5 (b) (4)	GT 4,5 (b) (4)
Full Analyses Set	19	19
SVR12 Achieved (%)	18 (94.7)	14 (73.7)
	95% CI [^]	95% CI [^]
	74.0, 99.9	48.8, 90.9
SVR12 Not Achieved	1 (5.3)	5 (26.3)
<i>Futility</i>	0	0
<i>Virologic Breakthrough</i>	0	2
<i>Relapse</i>	1	2
<i>D/C Admin Reasons</i>	0	0
<i>LTF</i>	0	1
SVR12 (n/N) by Genotype*		
4	10/10 (100.0)	9/10 (90.0)
5	4/4 (100.0)	1/4 (25.0)
		(b) (4)
SVR24 (n/N)	18 (94.7)	14 (73.7)
	95% CI [^]	95% CI [^]
	74.0, 99.9	48.8, 90.9
<i>By Genotype</i>		
4	10/10 (100.0)	9/10 (90.0)
5	4/4 (100.0)	1/4 (25.0)
		(b) (4)
Per Protocol	17	13
SVR12 Achieved (%)	16 (94.1)	10 (76.9)
	95% CI [^]	95% CI [^]
	71.3, 99.9	46.2, 95.0
SVR12 Not Achieved	1 (6.3)	3 (30.0)
<i>Virologic Breakthrough</i>	0	2
<i>Relapse</i>	1	1

[^] Clopper Pearson exact method

*Two subjects with HCH GT1 infection were randomized to this trial one in each of the two arms in Part B. Both subjects achieved SVR12.

SVR12 in this trial based on achieving a HCV RNA <25 IU/mL (TD(u) or TND)

The reviewer performed an analysis of SVR24 in the full analyses set and found no additional failures-including non-virologic-occurring between 12 and 24 weeks post-treatment completion.

3.2.2.3 Trial 48 (C-SALVAGE)

Trial Design

Trial 048 was a Phase 2, open-label, single-arm study of GZR 100 mg/EBR 50 mg +RBV for 12 weeks for treatment of CHC GT1 infected subjects who have failed a prior approved DAA regimen of bocepravir, telaprevir, simeprevir or sofosbuvir taken with peginterferon alfa and RBV. A total of 80

subjects who had received at least 4 weeks of treatment with a DAA on the prior treatment regimen and approximately 80% must have met criteria for virologic failure on the prior regimen were planned for enrollment. The proportion of cirrhotic subjects for inclusion was limited to 40%. Treatment was given for 12 weeks followed by a 24 week follow-up period (data collection of 24 week follow-up ongoing at time of the NDA).

Subject Disposition

Among 97 subjects who were screened, 79 were enrolled into the study of which one failed to complete treatment or study. There were no subject deaths. Nine subjects were omitted from the per-protocol population mostly for not having received approved prior DAA regimen as outlined in the inclusion criterion.

Table 17: Trial 048 Subject Disposition

Screened	97
Received Assigned Treatment (FAS)	79
Premature Trial D/C	1
Subject Withdrawal	1
Premature Trt D/C	1
Subject Withdrawal	1
Per-Protocol (% of FAS)	70 (88.6)
Reasons for Exclusion from FAS	
Incorrect dosing*	2
Non Compliance	1
Inclusion criteria not met	6

*Two subjects receiving incorrect dose from the site, i.e. one EBR pill for each day for the first 8 days rather than the required 5.

Subject Demographics and Characteristics

Over 60% of subjects enrolled were males, over 97% were of White race, the mean age was 54 years and most subjects were enrolled in non-US sites. The majority enrolled were GT 1b (62%) versus GT1a and over 57% were non-cirrhotic at screening.

Table 18: Trial 048 Subject Demographics and Characteristics

Characteristic (%)	N (%)
Screened/Enrolled (FAS)	97/79
Gender (Male)	59 (60.8)
Age (years)	
Mean (+/-se)	54.4 (1.1)
Range	23, 75
Race	
White	77 (97.5)
African American	2 (2.5)
Region	
US	18 (22.8)
Non-US	61 (77.2)
IL2B Genotype	
CC	2 (2.5)
Non-CC	77 (97.5)
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)
Fibrosis Stage	
Cirrhotic	34 (43.0)
Non-Cirrhotic	45 (57.0)

Statistical Methods

The primary objective was to evaluate GZR/EBR + RBV by measuring SVR12 in GT1 infected subjects who had failed prior DAA+P/R. **This was a hypothesis-generating study therefore it lacked a testable hypothesis.** The applicant's analysis included estimation of the SVR12 with a 95% CI based on the Clopper-Pearson method, in the per-protocol population imputing missing using the OF approach. Secondary analyses included estimation of SVR12 by prior DAA class and by prior DAA, SVR12 in the FAS and SVR24. Note: Data on SVR24 were incomplete at time of the NDA. Therefore, SVR24 will be reported in a future clinical study report.

Reviewer's Comment: The FAS will serve as primary in the reviewer's analyses whereas the per-protocol is viewed as a secondary.

Reviewer’s Comment: A subgroup analyses by prior failed DAA was not performed since most enrolled subjects had received bocepravir, telaprevir or simeprevir (all are NS3/4A PIs) and none failed prior therapy with sofosbuvir (an NS5B PI).

The planned samples size of 80 subjects was based on an assumed protocol violation rate of 10% in the per-protocol population leading to 72 subjects. If the observed SVR12 was 83% (60 out of 72), then the exact 95% CI would range from 72.7% to 91.1%.

Efficacy Findings

In this non-randomized, uncontrolled study the overall SVR12 (FAS population) among CHC GT1 prior DAA failure subjects was 96.2% with a 95% CI from 89.3% to 99.2% and all failures were due to relapse. A slightly lower SVR12 was observed among subjects with GT 1a versus GT 1b subgenotypes. Findings in the per-protocol population were similar to those achieved in the FAS.

Table 19: Trial 048: SVR12

GZR 100 mg/EBR 50 mg + RBV for 12 weeks	SVR12	
	% (n/N)	95% CI*
Full Analyses Set	96.2 (76/79) ^	89.3, 99.2
By Genotype (FAS)		
1a	93.3 (28/30)	77.9, 99.2
1b	98.0 (48/49)	89.2, 100.0
Per Protocol	97.1 (68/70)	90.1, 99.6

^ Three subjects failed to achieve SVR12 due to relapse

* Clopper Pearson exact method

3.2.3 Phase 2/3 Trial 052 (C-SURFER)

(Initiated in March 2014 and is ongoing at time of the NDA submission) (n=68 clinical sites)

Trial Design

This was a randomized, parallel-group, multi-site, multi-national, placebo-controlled trial in cirrhotic and non-cirrhotic GT1 TE and TN CHC subjects with CKD. This trial is also referred to as the **C-SURFER** trial. The trial enrolled adult subjects 18 years of age or older with CKD stages 4 and 5, including subjects on hemodialysis. The majority of subjects to be enrolled were to be on maintenance hemodialysis and at least 20% of enrolled subjects were to have stage 4-5 CKD, but not on hemodialysis.

Subjects were randomized in a 1:1 ratio to either:

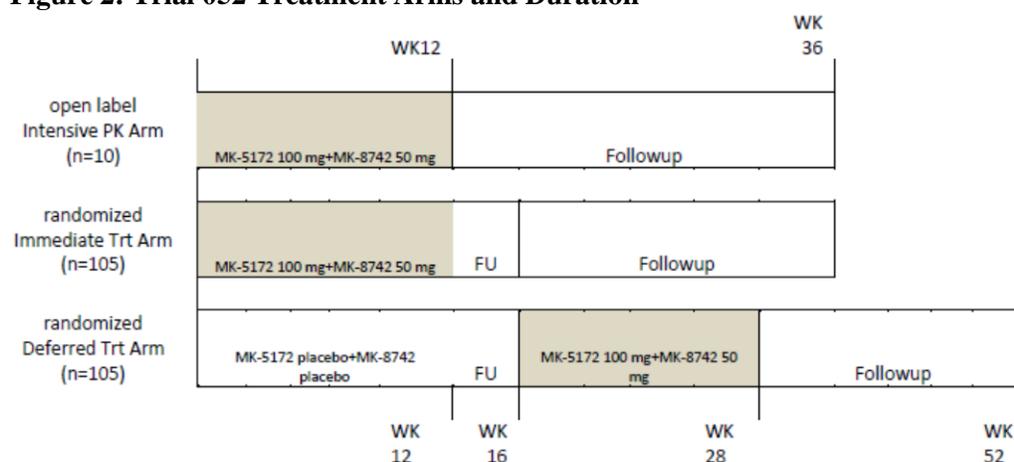
- Immediate treatment group (ITG): GZR 100 mg QD + EBR 50 mg QD for 12 weeks

- Delayed treatment group (DTG): matching placebo for 12 weeks, followed by a 4-week unblinding period followed by a 12 week period of open-label fixed dose combination study treatment (GZR 100 mg +EBR 50 mg QD)

An additional 11 subjects were enrolled to ITG and underwent intensive PK monitoring. *Note: This group was combined with ITG for analyses purposes.*

Randomization was stratified according to baseline dialysis status (y/n) and diabetic status (y/n). In all treatment arms, subjects were followed for 24 week following the end of treatment (Figure 2).

Figure 2: Trial 052 Treatment Arms and Duration



Source: Figure 9-1 of p052v01.pdf

Primary hypothesis: The proportion of HCV GT1 infected CKD 4-5 subjects achieving SVR 12 weeks after the end of study therapy is superior to the historical rate (defined as 45%) in the GT1 CHC population with CKD.

Secondary endpoints included the following:

- SVR24 in the ITG
- SVR4 in the ITG
- SVR12 in the DTG
- SVR12 for all active treatment arms combined
- Emergence of resistance-associated variants (RAVs) resistant to GZR and EBR

Note: *Analyses of the emergence of RAVs secondary endpoint is included in the current CSR. Results of the other secondary endpoints are to be provided in a future submission as per an agreement between DAVP and the applicant during the pre-NDA negotiations.*

Subject Disposition

Across 74 clinical sites, 328 subjects were screened of which 237 subjects were randomized (across 68 clinical sites) to one of the three arms: ITG, DTG or intensive PK/ITG. Of the 237 randomized, 235

subjects received treatment (FAS population) and n=229 were included in the modified FAS population (67 clinical sites). The six subjects omitted from the mFAS population were all in the ITG group and reasons for exclusion due to missing were: subject withdrawal due to transportation issues (n=1), LTF unrelated to study medication (n=2), death due to cardiorespiratory arrest (n=1), non-compliance due to hospitalization of acute appendicitis surgery (n=1), and withdrawn by investigator due to violent behavior (n=1) (Table 20).

Table 20: Trial 052 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 (99.1)	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

^Reasons listed for exclusion: 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

Over 70% of enrolled subjects were male, among all subjects the average age was 55-58 years and less than 20% were 65 years of age or older. The racial breakdown was approximately split between White and African American subjects, with the latter having a greater representation in this trial compared to other trials in CHC. This is due to the targeted inclusion of subjects with ESRD, which is more prevalent among persons of Black race compared to persons of non-Black race. The distribution of GTs 1a and 1b was approximately one-half in both the ITG and DTG arms and the majority of subjects were non-cirrhotic at baseline. One-third of the study subjects were diabetic, over 77% were on dialysis and approximately 25% were both diabetic and on dialysis. This trial was largely conducted in sites located in the US (40 out of 67 total sites) enrolling over 60% (151/235) of the trial subjects.

Table 21: Trial 052 Subject Demographics and Characteristics (FAS Population)

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
IL2B 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
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

Statistical Methods

Primary Analysis: A two-sided, one-sample exact test was used to test the proportion of subjects achieving SVR12 against the historical rate of 45%. The 95% CI was constructed using the Clopper-Pearson exact method.

The choice of 45% as the historical rate from which to compare the SVR12 was based on the following:

- Findings from a meta-analysis of IFN mono-therapy among HCV-infected subjects with CKD stages 3-5 produced a summary SVR24 of 39% (95% CI 32-46%)
 - Bayesian random-effect modeling predicting that if all available trials included in the meta-analysis (Fabrizi *et al.*, 2012) enrolled GT1 that the estimated overall population mean for SVR rate would be 45% with a 90% posterior probability or confidence.
- An SVR of approximately 40% was estimated in a large study of peg-IFN/RBV in 3,070 HCV GT1 subjects without CKD in the United States. Therefore, it is not expected that the SVR12 in subjects with CKD 4/5 would be any higher than that estimated in the general population.

Power/Sample Size: The trial was designed to enroll 105 subjects each in the ITG and DTG arms along with 10 additional subjects planned for enrollment into 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.

Efficacy Findings

The overall proportion of SVR12 in the mFAS (applicant's primary population) was 99.1% (115/116), 95% CI (95.3, 100.0). Only one subject failed to achieve SVR12 due to relapse. This subject was a 59 year old, Caucasian male, non-cirrhotic with GT1b on dialysis for 2 years who achieved TND at treatment week 3 but became detectable at follow-up week 12 (refer to the clinical and virologic reviews for more specifics on this case). In addition, there were three subjects with missing HCVRNA at week 12; however, both SVR4 and SVR24 were negative for each subject therefore SVR12 was imputed as negative as per the applicant's approach for handling missing values flanked by non-missing values (Table 22).

The proportion achieving SVR12 in the FAS (reviewer's primary analyses population) was 94.3% (115/122), 95% CI (88.5, 97.7) due to one subject who relapsed and six other subject outcomes imputed as failures due to missing HCV RNA values at the follow-up week 12 time point. SVR12 was achieved in almost all subjects in the combined ITG/IPK group by treatment week 12 as shown below in Figure 3. The proportion of subjects achieving SVR at follow-up week 4 (secondary endpoint) was 95.9% in the FAS population resulting in a 95% CI of 90.7% to 98.7%. By genotype, the SVR12 proportion was numerically higher in subtype 1a (96.8%) compared to GT1b (91.5%). This finding differs from the other trials in non-CKD subjects discussed in which overall the SVR12 among subjects with G1b infection was numerically (not statistically) higher than among those subjects with G1a infection (by trial). Note; however, that among the subjects failing to achieve SVR12, only one was a true virologic failure and the remainder were imputed failures due to missing from LTF, death, or other reasons as noted above.

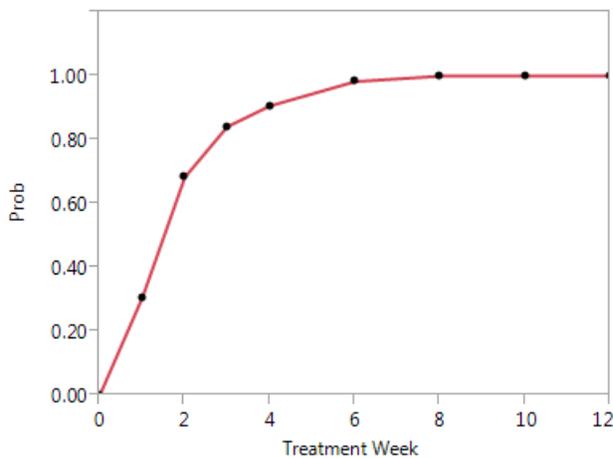
Table 22: Trial 052: SVR4 and SVR12 in ITG and IPK Combined (GZR 100 mg/EBR 50 mg x 12)

GZR 100 mg QD/EBR 50 mg QD for 12 weeks	SVR4 (FAS) (n=122) (reviewer)	SVR12 (mFAS) (n=116) (applicant)	SVR12 (FAS) (n=122) (reviewer)
SVR Achieved (%)	117 (95.9)	115 (99.1)	115 (94.3)
95% CI [^]	90.7, 98.7	95.3, 100.0	88.5, 97.7
p-value*	<0.0001	<0.0001	<0.0001
SVR Not Achieved	5	1 (0.9)	7 (5.7)
Relapse	0	1 (0.9)	1 (0.8)
Missing unrelated to treatment	5 (4.1)	NA	6 (4.9)
SVR by HCV genotype			
1a	60/63 (95.2)	61/61 (100)	61/63 (96.8)
95% CI [^]	86.7, 99.0	94.1, 100	89.0, 99.6
1b	57/59 (96.6)	54/55 (98.2)	54/59 (91.5)
95% CI [^]	88.3, 99.6	90.3, 100	81.3, 97.2

[^]Clopper-Pearson exact method

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

Figure 3: Trial 052: Proportion with HCV RNA ≤ 1.39794 (LLOQ Log10) by Treatment Day (On Treatment) with No Imputation for Missing (missing=failure) in the ITG/IPK Combined Group-Reviewer’s Analyses



Analyses of post-treatment relapse rates is limited due to lack of complete SVR24 data in the submission; however there were two subjects (one in the ITG and one in the IPK group) who achieved SVR12 but relapsed by follow-up week 24. Further analyses of 24 weeks post-therapy follow-up data will be performed once these data are submitted by the applicant.

3.2.4 Phase 3 Trials

3.2.4.1 Trial 060 (C-EDGE TN)

(This trial was initiated in June 2014 and was ongoing at the time of the NDA submission)

Trial Design

Trial 060 (also referred to as the **C-EDGE TN** trial) was a randomized, double-blind, placebo-controlled, multi-site, multi-national, trial conducted in TN (to all anti-HCV treatment including the DAAs) GT 1, 4, and 6 HCV mono-infected subjects with or without cirrhosis. The trial enrolled adults (≥ 18 years) with an HCV RNA $\geq 10,000$ IU/mL at the time of screening and without decompensated liver disease.

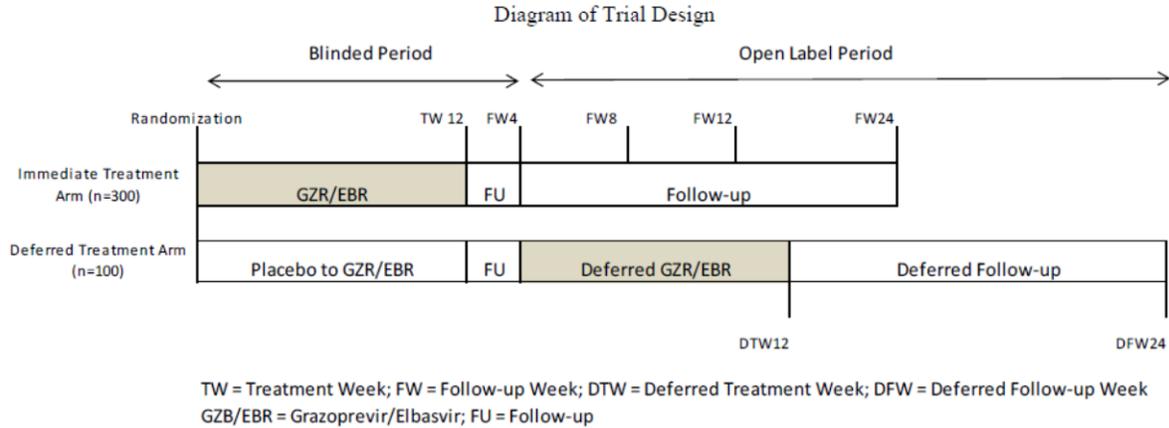
Subjects were randomized to blinded treatment following a 3:1 ratio to either (Figure 4):

- Immediate treatment group (ITG): GZR 100 mg QD + EBR 50 mg QD for 12 weeks with 24 weeks follow-up once dosing was complete
- Delayed treatment group (DTG): placebo for 12 weeks, followed by a 4-week un-blinding period followed by a 12 week period of open-label fixed dose combination study treatment (GZR 100 mg +EBR 50 mg QD) and an additional 24 weeks of follow-up once medication was complete.

Randomization was stratified by fibrosis stage (C vs. NC) and HCV subtype (GT1a vs. GT1 non-a. vs. GT4/GT6). Cirrhotic status was defined as having a liver biopsy prior to day 1 with a fibrosis score of F4 (Fibroscan result >12.5 kPa or a FirboSure (Fibrotest®) score of ≤ 0.48 AND an aspartate aminotransferase to platelet ratio index of ≤ 1 during screening). All subjects were followed for 24 weeks after end of randomized treatment as illustrated in Figure 4. Enrollment was managed to ensure that at least 20% of subjects had compensated cirrhosis at baseline and that roughly 15% had GT4 or GT6 CHC infection.

Reviewer's Comment: The cut-off of 12.5 kPa chosen by the applicant to define cirrhosis is viewed as too low by the clinical reviewer. Therefore, a sensitivity analyses using a Fibroscan cut-off score of 14.5 kPa was performed and findings are given below.

Figure 4: Trial 060 Design



Source: Figure 9-1, p060v01.pdf

Reviewer’s Comment: *The primary purpose of the blinded 12-week treatment period was to allow for a comparative safety assessment between the ITG and DTG treatment arms and was not intended for comparative efficacy. Note also that SVR12 results in the DTG were ongoing at time of the submission and will be submitted at a later time.*

Subject Disposition

There were 469 subjects screened for inclusion of which 421 were randomized to treatment: n=316 ITG and n=105 to DTG. All randomized subjects received at least one dose of study drug and therefore the n=421 subjects comprise the full analyses set (FAS). Overall few subjects (less than 2%) failed to complete assigned treatment or study follow-up (Table 23).

Table 23: Trial 060 Subject Disposition

GZR 100 mg + EBR 50 mg for 12 weeks	ITG	DTG
Randomized	316	105
Received Assigned Treatment (FAS)	316	105
Premature Trial Discontinuation	3 (0.9)	2 (1.9)
Death	2 (0.6)	0
LTF	1 (0.3)	0
Subject withdrawal	0	2 (1.9)
Premature Treatment Discontinuation	5 (1.6)	1 (0.01)
Adverse Event	3 (0.9)	1 (0.01)
Death	1 (0.3)	0
LTF	1 (0.3)	0

Subject Demographics and Characteristics

More than half of subjects (approximately 53%) enrolled in both arms were males with an average age of 52-53 years. The majority of subjects enrolled were of White race (60-70%); however, there were approximately 17% enrolled who were of Black or African American race and between 12-17% of Asian race. Approximately 50% enrolled were GT1a, 38- 41% were GT 1b, 6-8% GT4 and the remainder GT6. The majority of subjects (more than 77%) were non-cirrhotic at baseline corresponding to fibrosis scores of zero to two. The distribution of sites in the US versus outside the US was approximately split and balanced between treatment arms (Table 24). Enrollment across the 60 sites ranged from 3-18 subjects.

Table 24: Trial 060 Subject Demographics and Characteristics (FAS Population)

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)
IL2B 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-F02	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

Statistical Methods

The primary trial objective was to evaluate the safety and efficacy of GZR 100 mg / EBR 50 mg given for 12 weeks as determined by the proportion achieving SVR12. The overall goal was to demonstrate superiority compared to a historical rate of 73%, which was derived based on findings from two prior Phase 3 trials of simeprevir/P/R in TN, HCV mono-infected subjects (QUEST 1 and 2). Specifically, the proportion of subjects achieving SVR12 in Quest 1 and 2 was approximately 80%; however, neither trial enrolled a large number of subjects with cirrhosis (approximately 9% in both trials). Among subjects with compensated cirrhosis, the SVR12 was 60% compared to 82% in non-cirrhotic subjects. Therefore, given the planned proportion (~20%) of subjects with compensated cirrhosis in trial 060 and an estimated 5% decrease due to an expected improved safety profile due to an IFN-free regimen, the applicant calculated a 73% historical rate for comparison.

Reviewer's Comment: The applicant's justification for a 73% HC rate was evaluated during the protocol review and deemed acceptable. The division concluded that any new treatment regimen found to be statistically superior to this rate would be also convincingly superior to P/R. Accounting for a 5% loss in SVR12 with improved safety was not considered relevant by the division.

Primary Hypothesis: A two-sided, one-sample exact test was used to test the proportion of subjects achieving SVR12 against the historical rate of 73%. The 95% CI was constructed using the Clopper-Pearson exact method. .

The key secondary endpoints included SVR4, SVR24 (data collection ongoing at time of NDA), and RAVs. The analysis windows are presented below.

Power/Sample Size

The trial was designed to enroll 400 subjects overall with 300 planned in the ITG group and 100 in the DTG group. The sample size was based on an assumed response rate of 85% in the ITG, and greater than 99% power to demonstrate superiority of the GZR/EBR ITG compared to the historical 73% SVR12 HC rate with a one-sided 2.5% alpha level.

Efficacy Findings

The trial demonstrated a high proportion of SVR12 among subjects randomized to the ITG group. Specifically, SVR12 was 94.6% with a lower bound of the 95% CI of 91.5%, which was statistically superior to the 73% historical rate (Table 25). Among the 17 subjects failing to achieve SVR12, 4 (1.3% of overall FAS) failed due to non-virologic reasons including 2 deaths (1 due to incarcerated hernia and 1 cardiac arrhythmia), 1 LTF and 1 AE discontinuation. Virologic failures (n=13) was largely driven by relapses (n=12) for which the majority (n=9) were among subjects with GT1a subgenotype.

By subgenotype, SVR12 was numerically higher among GT1b (98.5%) compared to GT1a (91.7%) subgenotypes. The SVR12 was 100% (n=18) and (b) (4) in the GT4 (b) (4) subgenotype infected subjects, respectively; however, these numbers are small and therefore difficult to make any valid inferences on efficacy, given all the uncertainties.

The reviewer's analyses using the applicant's legacy data set (adefout.xpt) arrived at a SVR4 of 96.2% (304/316); however, the applicant reports a SVR4 of 97.2% (307/316) in table 11-7 of the clinical study

report (p060v01.pdf). The reviewer is unable to verify the applicant's SVR4 using this dataset but replication was achieved using SDTM data. SVR12 was replicated using the same data set.

Table 25: Trial 060: SVR4 and SVR12 (FAS) (Reviewer's Analyses) in the ITG Combined

Treatment Regimen	SVR4 (FAS)	SVR12 (FAS)
	(n=316) (reviewer)	(n=316) (reviewer)
	GZR/EBR x 12 weeks	GZR/EBR x 12 weeks
SVR Achieved (%)	304 (96.2)	299 (94.6)
<i>95% CI[^], p-value*</i>	<i>93.5, 98.0</i> <i><0.0001</i>	<i>91.5, 96.8</i> <i><0.0001</i>
SVR Not Achieved	12 (3.8)	17 (5.4)
Non-virologic failure	7 (2.2)	4 (1.3)
Death	1 (0.3)	2 (0.6)
LTF/Missing Value	4 (1.3)	1 (0.3)
Adverse Event Discontinuation	2 (0.6)	1 (0.3)
Virologic failure	5 (1.6)	13 (4.1)
Breakthrough	1 (0.3)	1 (0.3)
Relapse	4 (1.3)	12 (3.8)
<i>1a</i>	<i>2 (0.6)</i>	<i>9 (2.8)</i>
<i>1b</i>	<i>0</i>	<i>1 (0.3)</i>
		(b) (4)
%SVR by Genotypes (95% CI)		
1a (n=157)	94.9 (90.2, 97.8)	91.7 (86.3, 95.5)
1b (n=131)	98.5 (94.6, 99.8)	98.5 (94.6, 99.8)
4 (n=18)	100.0 (81.5, 100.0)	100.0 (81.5, 100.0)
		(b) (4)

[^]C

*One-sided Exact test, alpha=0.025 based on test for true proportion=0.73.
 SVR4 and SVR12=sustained virologic response at follow-up week 4 and 12, respectively

As illustrated in Figure 5, SVR12 was achieved by overall 90% of subjects by week 6 of treatment. Mean change from baseline in HCV RNA (on the log10 scale) is shown in Figure 6 illustrating a rapid decline in viral load in the first 4 weeks of treatment and leveling off by week 8.

Figure 5: Trial 060: Proportion achieving SVR by Treatment Week (FAS) Reviewer’s Analyses

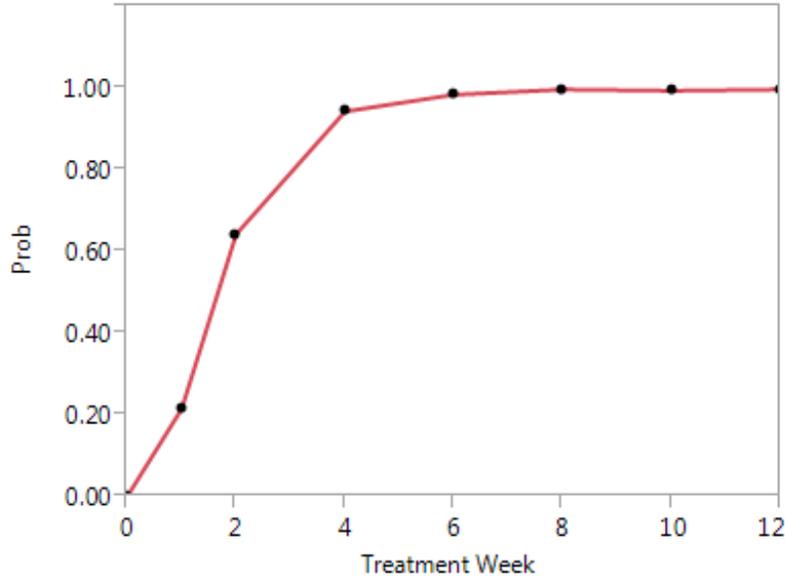
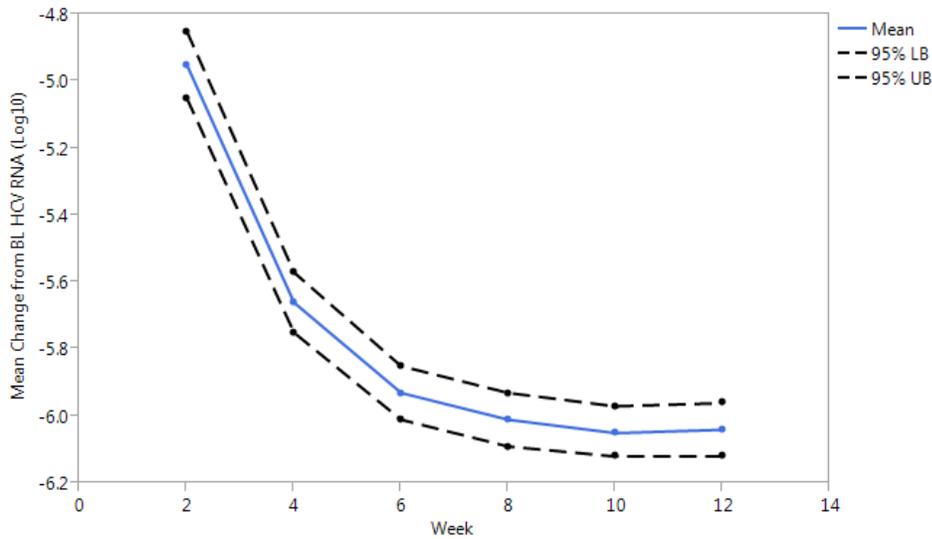


Figure 6: Trial 060: Mean Change from BL in Log10 HCV RNA (FAS) Reviewer’s Analyses



3.2.4.2 Trial 061 (C-EDGE CO-INFECTION)

(Trial was conducted from June 2014 through April 2015)

Trial Design

This trial (also referred to as the **C-EDGE CO-INFECTION** trial) was a non-randomized, uncontrolled, multi-center trial to assess the safety, tolerability and efficacy of GZR 100 mg/EBR 50 mg in CHC GT 1, 4, and 6-infected TN (to all anti-HCV treatments including DAAs), adult subjects (≥ 18 years), with or without cirrhosis and who were also co-infected with HIV. All enrolled subjects were treated with GZR/EBR for 12 weeks with a 24-week follow-up following completion of all study treatment.

HCV RNA was assessed on day 1, every two weeks through TW12, and then at FW4, FW8, FW12 and FW24.

Reviewer's Comment: The trial was classified as phase 3 trial in applicant's development program mainly due to the large sample size and lack of dose finding. In general, this trial lacks in several criteria germane to phase 3 trials; however, at the time of the protocol development there were no available IFN-free regimens from which to directly compare the GZR/EBR treatment regimen and hence the applicant chose a non-comparative design.

Subject Disposition

Overall, 261 TN CHC GT1, 4 and 6 subgenotype infected subjects were screened of which 218 were enrolled to the study and received treatment. Among the 43 subjects not receiving treatment, the majority (n=41) failed to meet entry criteria and the remaining two subjects withdrew consent prior to treatment receipt. All enrolled subjects completed study medication except for one subject who stopped treatment at treatment week two (TW2) due violating the protocol by receiving a prohibited (by protocol) concomitant medication nevirapine. Two subjects were lost to follow-up and therefore failed to complete trial follow-up.

Table 26: Trial 061 Subject Disposition

	Subjects (%)
Screened	261
Received Assigned Treatment (FAS)	218
Premature Trial D/C (all randomized)	2 (0.9)
LTF	2 (0.9)
Premature Trt D/C-protocol violation	1 (0.4)

The study enrolled mostly male subjects (84%), subjects of White race (77%) having a mean age of 49 years with a baseline HCV RNA log₁₀ of 6 IU/mL and the majority of subjects (84%) were non-cirrhotic at baseline. By subgenotype, GT1a was the most common (66%), followed by GT1b (20%). Only 13% of enrolled subjects were infected with GT4 subgenotype and less than 1% with GT6 subgenotype. A total of 37 sites enrolled at least one subject (range 6-18 subjects) and 62% of subjects were enrolled in sites outside the United States. All subjects were co-infected with HIV-1.

Table 27: Trial 061 Baseline Characteristics

Characteristic	GZR/EBR x 12 weeks (N=218)	
	n	%
Gender (Male)	183	83.9
Age (years)		
Mean (+/-se)	48.7 (0.6)	-
Range	21-71	-
% ≥ 65 years	6	2.8
Race		
White	167	76.6
Black/African American	38	17.4
Asian	6	2.8
Other	7	3.2
IL2B Genotype		
CC	77	35.3
Non-CC	141	64.7
Baseline HCV RNA Log10 (IU/mL)**		
Mean (+/-SD)	6.0 (0.6)	-
Median	6.1	-
Range	3.8-7.2	-
HCV Genotype		
1a	144	66.1
1b	44	20.2
1 other	1	0.5
4	28	12.8
6	1	0.5
Hepatic Stage		
Cirrhotic	35	16.1
Non-Cirrhotic	183	83.9
Fibrosis Stage^		
F0-F02	160	73.4
F3	23	10.6
F4	35	16.1
Fibroscan® Hepatitis Score (kPa)^	147	-
Mean (SE)	9.8 (0.9)	-
Median	6.6	-
Range	0.07-69	-
Region		
US	83	38.1
Non-US	135	61.9
Country		
Australia	13	6.0
Canada	9	4.1
Denmark	18	8.3
France	26	11.9
Germany	16	7.3
Israel	6	2.8
Spain	28	12.8
United Kingdom	19	8.7
United States	83	38.1

ARV Therapy

Abacavir containing regimen	47	22.3
w/Rilpivirine	4	8.7
w/Raltegravir	23	50.0
w/Dolutegravir	19	41.3
Tenofovir containing regimen	164	77.7
w/Rilpivirine	34	20.7
w/Raltegravir	90	54.9
w/Dolutegravir	40	24.4

Statistical Methods

The primary study objective was to evaluate the safety and efficacy GZR 100 mg/EBR 50 mg as determined by SVR12 with a superiority objective comparing against a historical rate of 70%. The SVR12 historical control was derived based on findings from a Phase 2 trial of sofosbuvir in HCV GT1 subjects co-infected with HIV (PHOTON-1) in which the overall SVR12 was 76% and 60% in cirrhotic subjects (accounted for only 4% of all trial subjects). Therefore, after accounting for a greater proportion of subjects with cirrhosis planned in trial 061 (20%) versus the 4% observed in PHOTON-1 and for a 5% decrease in response rate due an expected improved safety profile of GZR/EBR as an IFN-free regimen, the estimated historical rate was 70%.

Reviewer's Comment: The justification for the HC rate of 70% was previously reviewed by another OB reviewer. Overall, a 70% historical rate for SVR12 in a TN was deemed reasonable and that new drug found superior to this rate would be also convincingly superior to P/R. Accounting for a loss of 5% in SVR12 with improved safety was not considered relevant at the time of the protocol review.

Primary Analysis: A two-sided, one-sample exact test was used to test the proportion of subjects achieving SVR12 against the historical rate of 70%. The 95% CI was constructed using the Clopper-Pearson method.

Power/Sample Size: The trial was designed to enrolled 200 subjects in a single treatment group based on an assumed response rate of 85% on treatment, and greater than 99% power to demonstrate superiority of the GZR/EBR compared to the estimated historical 70% reference, one-sided 2.5% alpha level.

Efficacy Findings

The proportion of subjects in the FAS who achieved SVR12 was 95% (207/218) with a 95% CI ranging from 91.2% to 97.5% demonstrating statistical significance compared to the target 70% historical rate (Table 28). Virologic failure due to relapse occurred in 3.2% of all subjects of which the majority (5/7) were among GT1a subgenotype infected subjects. SVR12 was similar among the three subgenotypes; however, few subjects were enrolled with GT4 or GT6 subgenotype (b) (4)

Table 28: Trial 061 SVR4 and SV12 (FAS) (reviewer’s analyses)

Treatment Regimen	SVR4 (FAS)	SVR12 (FAS)
	(n=218) (reviewer)	(n=218) (reviewer)
	GZR/EBR 12 weeks	GZR/EBR 12 weeks
SVR Achieved (%)	207 (95.0)	207 (95.0)
<i>95% CI[^], p-value*</i>	<i>91.5, 97.5</i>	<i>91.2, 97.5, <0.0001</i>
SVR Not Achieved	11 (5)	11 (5)
Non-virologic failure	9 (4.1)	4 (1.8)
LTF/Missing Value	8	3
Early Discontinuation [^]	1	1
Virologic failure	2 (0.9)	7 (3.2)
Relapse	2 (0.9)	7 (3.2)
1a	2	5
1b	0	1
4	0	1
HCV genotype**		
1a (n=144)	94.4 (89.4, 97.6)	94.4 (89.4, 97.6)
1b (n=44)	93.2 (81.3, 98.6)	95.5 (84.5, 99.4)
4 (n=28)	100 (87.7, 100)	96.4 (81.7, 99.9)

[^]Clopper-Pearson exact method

*One-sided exact test, true p=0.70 based on historical estimate

**One subject with GT 1 other and one with GT6-both achieved SVR4 and SVR12

3.2.4.3 Trial 068 (C-EDGE TE)

(Trial conducted from June 2014-March 2015)

Trial Design

This trial (also referred to as the **C-EDGE TE** trial) was randomized, parallel-group, multi-site, and open-label in design performed in a diverse CHC-infected adult population with GT 1, 4, or 6 subgenotype who had previously failed pegylated interferon or ribavirin treatment. The trial aimed to enroll approximately 400 subjects of which approximately 30% were required to have evidence of compensated cirrhosis at time of screening along with at least 20% who were co-infected with HIV and no more than 20% of subjects who had relapsed on a prior P/R.

Note: Originally the trial was designed to include GT5 subjects; however, preliminary data from another trial demonstrated virologic failure in a small number of GT5 subjects. Therefore, in August 2014, the protocol was amendment (Amendment 3) to excluded subjects with CHC GT6 subgenotype from trial.

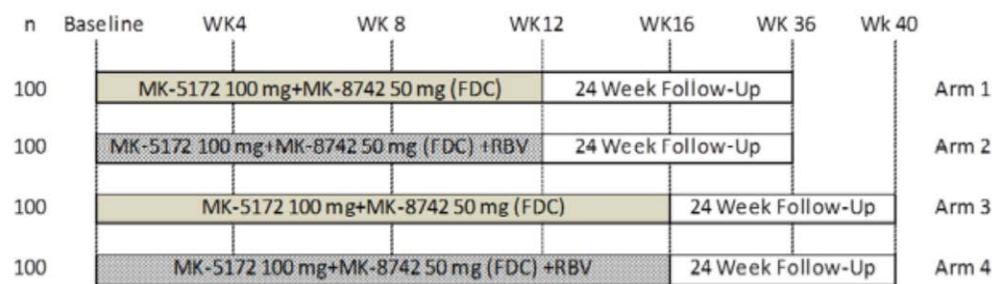
Previous failed HCV treatment was defined as one of following: peg-IFN/RBV (P/R) null responder (<2log 10 IU/mL reduction in HCV RNA at week 12 or <1 log 10 IU/mL decline from baseline as week 4 and discontinued therapy by week 12), P/R partial responder (> 2 log 10 IU/mL reduction in HCV RNA

by week 12 of treatment, but with HCV RNA quantifiable at end of treatment, or prior P/R treatment relapse (relapse after completion of prior course of treatment including a dual regimen of peg-IFN with RBV).

Subjects were randomized in a 1:1:1:1 fashion to receive GZR/EBR daily for 12 weeks with or without (+/-) RBV or for 16 weeks +/- RBV and was stratified by presence or absence of cirrhosis and by prior P/R treatment response (responders, partial responders, or null responder). Investigators and study participants were blinded to treatment assignment during the first 12 weeks of treatment. All subjects were followed for 24 weeks following the end of treatment (Figure 7).

Reviewer’s Comment: Genotype was not accounted for the randomization schema. Therefore, there is unbalance among treatment arms among those with GT4 and GT6 albeit smaller counts.

Figure 7: Trial 068 Design



FDC=Fixed Dose Combination

Source: Figure 9-1, p068v01.pdf

Subject Disposition

There were 420 subjects randomized to one of four treatment arms and all randomized received at least one dose of treatment (FAS). Few subjects prematurely discontinued from the trial (1-3%) and 2.6% overall prematurely discontinued from treatment with more discontinuing in the 16 week duration regimens versus the 12 week duration regimens. There was one death (day 22 days after end of treatment) attributed to cancer, which was a subject randomized to the GZR/EBR 12 week regimen and considered unlikely due to treatment (refer to the clinical review for details on this subject) (Table 29).

Table 29: Trial 068 Subject 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)

Baseline characteristics and demographics were mostly balanced across the four treatment arms with the exception of race for which there was an imbalance in the distribution of African American/Black and Asian races by treatment arm. Fewer subjects of AA/Black race were enrolled in the two 16-week treatment arms compared to the two 12-week treatment arms. Over 60% of subjects in all four arms were male subjects, the mean age was approximately 55 years, and the majority (over 63%) of subjects was of White race. Between 46% and 58% of subjects were infected with GT1a subgenotype, 28-46% GT1b subgenotype and the remainder infected with GT4 or GT6 subgenotype. No subjects infected with GT6 subgenotype were enrolled to the 12-week treatment regimens. This trial included a large (over 30%) proportion of subjects with fibrosis (stage 4) and this was balanced across arms as it was a factor included in randomization. Over 40% of the sample included P/R null responders, approximately 20% were P/R partial responders and the remaining subjects were subjects who had relapsed on prior P/R therapy. Overall there were 420 participating clinical sites of which 195 were located in the United States accounting for over 40% of subjects enrolled. The minimum and maximum number of subjects enrolled per site was 2-20 (Table 30).

Table 30: Trial 068 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)
IL2B Genotype[^]				
CC	20 (19.2)	16 (15.7)	28 (26.7)	21 (19.8)
TC	63 (60.6)	59 (57.8)	50 (47.6)	60 (56.6)
TT	21 (20.2)	27 (26.5)	27 (25.7)	25 (23.6)
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-F02	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)
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

Statistical Methods

The primary trial objective was to evaluate the efficacy of GZR/EBR with or without RBV in a CHC population who had failed prior P/R therapy. The primary hypothesis was that that SVR12 proportion in at least one of the four randomized arms is superior to a historical SVR12 rate of 58%, which was derived from a prior Phase 2b trial of simeprevir given for 12, 24, or 48 weeks in combination with P/R for 48 weeks in TE CHC subjects. Findings from this prior trial demonstrated a 70% SVR overall and 40% SVR among prior relapsers (accounted for only 20% of the trial sample). Similarly, the SVR was 70% in prior partial responders and 45% in prior null responders (accounting for 35% and 25% subjects, respectively). The applicant assumed that trial 068 would enroll 40% prior null responders and 40% prior partial responders and therefore estimated a SVR to be 63%. Also, assuming a 5% decrease in this response rate because of an expected improved safety profile given the absence of IFN, the applicant arrived at a 58% SVR historical rate.

Reviewer’s Comment: There is copious evidence supporting a lower than 45% SVR for prior P/R treatment failures. Therefore, the proposed HC rate of 58% was deemed acceptable during the protocol review and any drug that is shown to be statistically significantly superior to this target would be viewed as superior to P/R therapy. Certainly, use of a historical control is not void of limitations due to potential bias from unmeasured confounders; however, at the time of the protocol development there were no IFN-free approved regimens and it is generally not recommended to re-treat prior P/R failures with subsequent course of P/R.

Primary Analyses

The overall trial objective was to show that at least one of the four treatment arms is superior to the historical reference rate of 58% with two planned tests. The first set of tests compared each of the 12-week treatment arms against the 58% reference rate using a closed test procedure such that the 12-week + RBV arm was tested first at a one-sided alpha level of 0.0125. If superiority was achieved, then the 12-week – RBV arm was then compared against the historical rate also with an alpha of 0.0125. The second set of tests compared the 16-week treatment arms (+RBV and –RBV) against the historical reference using a 1-sided, type-I error of 0.0125 using the same closed testing procedure as described for the 12-week group. A one-sided exact test for binomial proportion was used for hypothesis testing. The 95% CI was calculated via the Clopper-Pearson exact method.

Power/Sample Size

The trial was designed to enrolled 400 subjects into one of four treatment arms (n=100 each). With this sample size, the trial would have more than 99% power to demonstrate superiority of each of the four arms over the historical reference rate of 58% when assuming a treated SVR12 of at least 80%.

Efficacy Findings

Overall SVR12 in the FAS was 92.4%, 94.2%, 92.4% and 97.2% in the GZR/EBR x 12 w, GZR/EBR+RBV x 12 w, GZR/EBR x 16 w and GZR/EBR+RBV x 16 w regimens, respectively, and all arms achieved statistical superiority compared to the 58% HC rate using the pre-specified closed testing approach. In all arms except the GZR/EBR+RBV x 16 w arm, the main cause for failure was virologic failure due to relapse and the majority of these relapses were among patients of GT1a subgenotype. No subjects in the GZR/EBR+RBV x 16 weeks arm failed due to virologic failure but instead failed to achieve SVR12 due to missing values or early discontinuation due to an adverse event (Table 31).

Among the 6, 6, and 4 virologic relapses at week 12 post treatment follow-up in the GZR/EBR x 12 w, GZR/EBR+RBV x 12 w, and GZR/EBR x 16 w, respectively 67%, 50% and 25% of subjects were cirrhotic at baseline and all but one subject in the 16 week arm were HCV-mono-infected.

By subgenotype, the SVR12 was numerically lower in the GT1a subgroup compared to the GT1b subgenotype in all four arms, which is expected as the 1a subtype is often more difficult to treat. Among the GT1a subgenotype-infected subjects who suffered a virologic relapse, 10/12 had a baseline NS5A RAV. Few subjects of GT4 or GT6 subgenotype were enrolled to assess SVR12, (b) (4)

Table 31: Trial 068 SVR 12 Primary Results (FAS) (reviewer’s analyses)

	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
p-value*	<0.0001	<0.0001	<0.0001	<0.0001
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)
Relapse	6	6	4	0
1a	5	4	3	0
1b	0	1	1	0
4	1	1	0	0
Breakthrough	0	0	1	0
Rebound	0	0	2	0
%SVR12 By Genotype (95% CI)#				
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)

[^]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

#GT 1 other omitted due to small counts

Finally, among GT1a subgenotype subjects who were prior null or partial responders (n=150), SVR12 was 89.5% (34/38), 97.1% (34/35), 88.1% (37/42) and 94.3% (33/35) in the GZR/EBR 12 week, GZR/EBR+RBV x 12 week, GZR/EBR 16 week, GZR/EBR+RBV x 16 week arms, respectively. These findings suggest a longer duration of treatment in this subpopulation of GT1a infected subjects may confer higher SVR12.

Exploratory Analyses: Pooled 12 and 16 weeks with and without RBV

To better understand the added contribution of RBV, if any, to a regimen of GZR/EBR of at least 12 weeks in duration, the reviewer performed an exploratory analysis where regimens containing RBV were pooled and those lacking RBV were pooled separately, although there are limitations in its interpretations due to potential confounding by genotypes. As shown below in Table 32, the pooled SVR12 in non-RBV regimen was 92.4% with a 95% CI of 87.2% to 95.9%. The estimated SVR12 in the pooled regimen containing RBV was 95.7%, 95% CI of 91.4% to 98.3% suggesting a slight increase in SVR12 with the addition of RBV. However, the assessment is most meaningful when assessing pooled estimates by

subgenotypes as it is well understood that response to treat varies by subgenotype. Therefore, the pooled non-RBV estimate in subjects with GT1a subgenotype was slightly lower (91.7%) compared to the pooled RBV containing regimen (94.1%) though there is no evidence of a difference given overlapping CIs. Among subjects with GT1b subgenotype, the pooled estimates by inclusion of RBV are similar and among those with GT4 subgenotype infection the estimates are difficult to interpret given the small and imbalanced samples sizes. SVR12 was numerically lower in the pooled non-RBV group in both cirrhotic and non-cirrhotic subjects compared to the RBV containing group with no evidence of an interaction.

Table 32: Trial 068-Sensitivity Analyses of GZR/EBR with and without RBV (pooled 12 and 16 weeks)

SVR12	n	GZR/EBR (12+16 Weeks)		
		<u>Without RBV</u> % (95% CI)	n	<u>With RBV</u> % (95% CI)
Overall	210	92.4 (87.2, 95.9)	210	95.7 (91.4, 98.3)
By Subgroup				
Genotype				
1a	109	91.7 (84.9, 96.1)	118	94.1 (88.2, 97.6)
1b	82	97.6 (91.5, 99.7)	65	98.5 (91.7, 100.0)
4	14	71.4 (41.9, 91.6)	23	95.6 (78.1, 99.9)
Baseline cirrhosis				
Yes	75	90.7 (81.7, 96.2)	72	94.4 (86.4, 98.5)
No	135	93.3 (87.7, 96.9)	138	96.4 (91.7, 98.9)

3.3 Evaluation of Safety

A detailed safety review of trials 060, 061 and 068 individually and pooled was performed by the medical officer, Dr. Sarita Boyd. A separate analysis of trial 052 was performed by medical officer, Dr. Prabha Viswanathan. Please refer to each review for a detailed assessment of the clinical safety. Individual analyses of trials 060 and 052 are important given that each trial was designed with a placebo control primarily for safety comparisons. Trial 068 is useful to compare safety profiles across multiple regimens containing GZR 100 mg/EBR 50 mg with or without RBV.

The major safety issue identified during the drug development program for GZR/EBR was late ALT elevations > 5x ULN with or without AST elevations > 5x ULN and therefore this was a focused area in both clinical reviews. Overall, this event was infrequent, occurring in 12/1558 (0.8%) subjects comprising the hepatic safety population and not associated with clinical events. As per the clinical review by Dr. Sarita Boyd, these events can be managed via appropriate product labeling with specific monitoring guidelines. This issue was also assessed in detail by the clinical pharmacology reviewers, Drs. Su-Young Choi and Luning (Ada) Zhuang (see reviews for complete details) who concluded that risk of ALT/AST elevation increases with increased exposure to GZR. The risk of ALT/AST elevation is low at the GZR dose proposed. There were no other major safety issues or concerns identified related to the GZR 100 mg/EBR 50 mg regimen identified in Drs. Boyd or Viswanathan's review. Therefore, a targeted statistical review of safety was not performed.

3.4 Benefit-Risk Assessment

The overall benefit of treatment of chronic hepatitis C infection leading to sustained virologic response is essential to reduce or potentially prevent long-term negative outcomes including end-stage liver failure and subsequent liver transplantation. GZR 100 mg/EBR 50 mg given for 12 weeks to CHC subjects with HCV genotypes 1 and 4 demonstrated high proportions of SVR12 across multiple trials in different populations. The overall safety concerns of late elevated ALT/AST are manageable and not considered to result in clinical events. Therefore, the overall benefit/risk of this GZR 100 mg/EBR 50 is favorable.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Given the variations in population studied across the eight included clinical trials, results of subgroup analyses are all presented below by trial. Note that findings by subgenotype are presented above in section 3 as efficacy by HCV subgenotype is more informative than overall (combined subgenotype) findings in this therapeutic area. The Phase 2 trials 035 (arms size ranged from 13-33) and 047 (arms size 19 subjects each) included too few subjects per treatment arm to allow for any meaningful subgroup analyses and therefore are omitted here.

4.1 Trial 048

4.1.1 Gender, Race, Age, and Geographic Region

Numerically, the proportion achieving SVR12 was higher among females versus males, among those less than 65 years at baseline versus those 65 years or older but due to small sample sizes and a lack of a comparator arm no tests were performed. Given the overlap in confidence intervals it can be concluded; however that there is no evidence of a by-treatment interaction. Ninety-seven percent of the trial population was of White race preventing any meaningful subgroup analyses by race (Table 33).

Table 33: Trial 048 Subgroup Analyses of SVR12

Characteristic	SVR12	
	% (n/N)	95% CI*
Gender		
Male	93.5 (43/46)	82.1, 98.6
Female	100 (33/33)	89.4, 100.0
Age		
<65	97.1 (66/68)	89.9, 99.6
>=65	90.9 (10/11)	58.7, 99.8

* Clopper Pearson exact method

4.1.2 Other Special/Subgroup Populations

The only other baseline variable with sufficient distribution between levels was baseline fibrosis stage. Findings from this subgroup analyses suggested no difference in SVR12 (95% CI) between cirrhotic subjects 94.1% (80.3%, 99.3%) and non-cirrhotic subjects, 97.8% (88.2%, 99.9%).

4.2 Trial 052

4.2.1 Gender, Race, Age, and Geographic Region

Findings from the reviewer’s subgroup analyses of SVR12 in the FAS population are presented below in Table 34 and Table 35. Overall there were no discernible differences between specific subgroup levels on proportion achieving SVR12. In several analyses, the proportions of subjects in each subgroup were imbalanced preventing meaningful comparisons. SVR12 was slightly higher in male subjects compared to female subject with overlapping CIs. Similarly, a numerically higher SVR12 was shown in the subgroup of subjects less than 65 years of age compared to older subjects but the overall number of older subjects is small (n=22) preventing any further assessment by age and other factors. In addition, there does not appear to be a numerical difference in SVR12 by region (US vs. non-US). Overall there is no evidence of a qualitative interaction by subgroup.

Table 34: Trial 052: Reviewer’s Analyses of SVR12 by Age, Gender, Race and Region

	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

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

4.2.2 Other Special/Subgroup Populations

The proportion of SVR12 between arms when dichotomizing baseline HCV RNA at 800,000 IU/mL appears to be similar suggesting high baseline viral load does not impact the ability to achieve SVR12 when treated with GZR/EBR. Too few subjects with cirrhosis at baseline were enrolled preventing a meaningful comparison by this subgroup. Finally, subjects with diabetes or baseline CKD stage 5 had a numerically lower SVR12 compared to non-diabetic or CKD stage 4 subjects, respectively, yet overall point estimates of SVR12 in all subgroups were above 93%.

Among the subset of subjects on hemodialysis, the SVR12 was 97.7% (43/44) and 89.6% (43/48) in GT1a and 1b-infected subjects, respectively. Similarly, among subjects not on HD, the SVR12 was 100% (19/19), 95% CI (82.4%, 100%) and 90.9% (10/11), 95% CI (58.7%, 99.8%) (data not shown in table).

Table 35: Trial 052: Reviewer’s Analyses of SVR12 by Other Subgroups

	Immediate + Intensive PK GZR/EBR Arms (n=122)	
SVR12	% (n/N)	95% CI*
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
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		
Naïve	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

*Clopper-Pearson exact method

4.3 Trial 060

4.3.1 Gender, Race, Age, and Geographic Region

The reviewer's results of subgroup analyses of SVR12 data in the ITG are presented below in Table 36 and Table 37. By age, SVR12 was achieved among all subjects greater than or equal to 65 years versus 94% among those less than 65 years but fewer subjects were enrolled in the greater age category and CIs overlap. SVR12 was numerically higher among female subjects and in the non-US sites compared to male subjects and non-US sites, respectively. None of these findings showed a treatment-by-factor interaction.

Table 36: Trial 060: Reviewer's Analyses of SVR12 by Age, Gender, Race and Region

SVR12	Immediate Treatment Group (n=316)	
	% (n/N)	95% CI*
Age (years)		
< 65	94.1 (270/287)	90.7, 96.5
≥ 65	100.0 (29/29)	88.1, 100.0
Gender		
Male	93.0 (159/171)	88.1, 96.3
Female	96.6 (140/145)	92.1, 98.9
Race		
Caucasian	94.2 (180/191)	89.9, 97.1
Non-Caucasian	95.2 (119/125)	89.9, 98.2
Region		
US	91.8 (135/147)	86.2, 95.7
Non-US	97.0 (164/169)	93.2, 99.0

*Clopper-Pearson exact method

4.3.2 Other Special/Subgroup Populations

The SVR12 achieved across all subgroups was above 90% with no apparent subgroup differences. The analyses by cirrhosis status based on the FDA cut point (14.5 kPa) did not yield findings that differed greater from those based on the applicant’s 12.5 kPa cut point.

Table 37: Trial 060: Reviewer’s Analyses of SVR12 by Subgroup

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
IL28 Genotype**		
CC	93.4 (99/106)	86.9, 97.3
TC	94.4 (153/162)	89.7, 97.4
TT	100.0 (46/46)	92.3, 100.0
Cirrhosis		
Yes	97.2 (68/70)	90.1, 99.7
No	93.9 (231/246)	90.1, 96.6
Cirrhosis (FDA)#		
Yes	96.8 (60/62)	88.8, 99.6
No	94.1 (239/254)	90.4, 96.7
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

**Missing for 2 subjects

#Cirrhosis redefined as per a Fibroscan score >14.5kPa (among those with Fibroscan scores) (Fibroscan score >12.5 kPa used by the applicant). This re-classification results in n=8 subjects’ status changing from cirrhotic to non-cirrhotic.

4.4 Trial 061

4.4.1 Gender, Race, Age, and Geographic Region

Results of the reviewer’s subgroup analyses of SVR12 in the FAS as provided below in Table 38 and Table 39. There were no discernible subgroup differences on SVR12 and all subgroups achieved a SVR12 above 90%. Due to small numbers of subjects greater than 65 years of age it is difficult to conclude efficacy in this older age category. SVR12 was similar by gender though the point estimate was higher among female subjects versus males.

Table 38: Trial 061 SVR12 Subgroup Analyses by Age, Gender, Race and Region

SVR12	GZR/EBR (n=218)	
	% (n/N)	95% CI*
Age (years)		
< 65	94.8 (201/212)	90.9, 97.4
≥ 65	100 (6/6)	54.1, 100.0
Gender		
Male	94.0 (172/183)	89.5, 97.0
Female	100 (35/35)	90.0, 100.0
Race		
Caucasian	94.6 (158/167)	90.0, 97.5
Non-Caucasian	96.1 (49/51)	86.5, 99.5
Region		
US	95.2 (79/83)	88.1, 98.7
Non-US*	94.8 (128/135)	89.6, 97.9

*Clopper-Pearson exact method

4.4.2 Other Special/Subgroup Populations

All subjects with cirrhosis at baseline (n=35) achieved SVR12 compared to 94% among the larger subgroup of non-cirrhotic subjects. There is no evidence that using a higher cut-off score (14.5 kPa v. 12.5 kPa) to identify cirrhotic subjects led to any differences in SVR12 by cirrhosis.

Table 39: Trial 061 SVR12 Subgroup Analyses (reviewer’s analyses)

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
IL28 Genotype		
CC	96.1 (74/77)	89.0, 99.2
TC	94.4 (102/108)	88.3, 97.9
TT	93.9 (31/33)	79.8, 99.3
Cirrhosis		
Yes	100 (35/35)	90.0, 100.0
No	94.0 (172/183)	89.5, 97.0
Cirrhosis (FDA)#		
Yes	100.0 (30/30)	88.4, 100.0
No	94.1 (177/188)	89.8, 97.0
Fibrosis Stage		
F0-F02	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

#Cirrhosis redefined as per a Fibroscan score >14.5kPa (among those with Fibroscan scores) (Fibroscan score >12.5 kPa used by the applicant). This re-classification results in n=5 subjects’ status changing from cirrhotic to non-cirrhotic. *Clopper-Pearson exact method

4.5 Trial 068

4.5.1 Gender, Race, Age, and Geographic Region

Analyses of SVR12 by age category revealed inconsistent results across treatment arms such that among subjects less than 65 years of age, SVR12 was higher in the GZR/EBR x 12 week and 16 weeks treatment arms but less in the other two arms including RBV. A test for interaction was performed using a generalized linear model (PROC GLIMMIX) in SAS revealing a p-value=0.9471 suggesting no interaction.

Across all four treatment arms, female subjects achieved a higher SVR12 compared to male subjects though the 95% CIs all overlap suggesting no differences. There appears to be no differences overall by race while noting that the majority of subjects (over 63%) were of White race thus leading to challenges in assessing for subgroup effects. Finally, there is no evidence of a treatment interaction by location (US versus non-US). An assessment of outcome by site is difficult given the large number of clinical sites (n=420); however, numerically there were no sites with an unusual number of failures (Table 40).

Table 40: Trial 068 SVR12 Subgroup Analyses of Gender, Race and Region (FAS) (reviewer’s analyses)

% SVR12 (95% CI)	GZR/EBR	GZR/EBR+ RBV	GZR/EBR	GZR/EBR + RBV
	(N=105)	(N=104)	(N=105)	(N=106)
Treatment Duration	12 Weeks		16 Weeks	
Age (years)				
< 65	93.2 (85.8, 97.5)	93.5 (86.3, 97.6)	93.3 (85.9, 97.5)	96.8 (91.0, 99.3)
≥ 65	88.2 (63.6, 98.5)	100.0 (73.5, 100.0)	87.5 (61.7, 98.5)	100.0 (73.5, 100.0)
Gender				
Male	90.9 (81.3, 96.6)	91.7 (82.7, 96.9)	91.3 (82.0, 96.7)	96.9 (89.2, 99.6)
Female	94.9 (82.7, 99.4)	100.0 (89.1, 100.0)	94.4 (81.3, 99.3)	97.6 (87.4, 99.9)
Race[^]				
Caucasian	89.4 (79.4, 95.6)	92.9 (84.1, 97.6)	93.1 (84.5, 97.7)	97.4 (91.0, 99.7)
Asian	100.0 (78.2, 100.0)	100.0 (66.4, 100.0)	86.4 (65.1, 97.1)	100.0 (69.2, 100.0)
Black/AA	95.6 (78.1, 100.0)	100.0 (85.8, 100.0)	100.0 (66.4, 100.0)	100.0 (78.2, 100.0)
Region				
US	92.6 (82.1, 97.9)	94.2 (84.1, 98.8)	92.9 (80.5, 98.5)	93.6 (82.5, 98.7)
Non-US	92.2 (81.1, 97.8)	94.2 (84.1, 98.8)	92.1 (82.4, 97.4)	100.0 (93.9, 100.0)

[^]other race omitted due to small counts, 95% CI via Clopper-Pearson exact method

4.5.2 Other Special/Subgroup Populations

As expected, the SVR12 was higher among subjects with a baseline HCV RNA less than or equal to 800,000 versus those with a baseline value greater than 800,000 IU/mL and this was consistent across all four treatment arms. In the two arms of 12 weeks’ duration, non-cirrhotic subjects achieved a higher SVR12; however, this difference was less obvious in the two 16 week regimens. Overall there was no interaction by baseline cirrhotic status. SVR12 by prior treatment response varied slightly across the four arms with no evidence of an interaction. Among GT1a subgenotype subjects who were prior null or partial responders (n=150), SVR12 was 89.5% (34/38), 97.1% (34/35), 88.1% (37/42) and 94.3% (33/35) in the GZR/EBR 12 week, GZR/EBR+RBV x 12 week, GZR/EBR 16 week, GZR/EBR+RBV x 16 week arms, respectively. These findings suggest a longer duration of treatment in this subpopulation of GT1a infected subjects may confer higher SVR12 (Table 41).

Finally, this trial included few HIV co-infected subjects preventing a meaningful comparison by HIV status.

Table 41: Trial 068 SVR12 Subgroup Analyses (FAS) (reviewer's analyses)

% SVR12 (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	
Baseline HCV RNA (IU/mL)				
≤ 800,000	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	91.4 (83.0, 96.5)	93.9 (86.3, 98.0)	90.7 (82.5, 95.9)	96.2 (89.2, 99.2)
IL28 Genotype				
CC	95.0 (75.1, 99.9)	93.8 (69.8, 99.8)	96.4 (81.7, 99.9)	100.0 (83.9, 100.0)
TC	92.1 (82.4, 97.4)	93.2 (83.5, 98.1)	92.0 (80.8, 97.8)	96.7 (88.5, 99.6)
TT	90.5 (69.6, 98.8)	96.3 (81.0, 99.9)	88.9 (70.8, 97.7)	96.0 (79.7, 99.9)
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)
Cirrhosis (FDA)#				
Yes	87.9 (71.8, 96.6)	87.5 (71.0, 96.5)	90.9 (75.7, 98.1)	100.0 (89.4, 100.0)
No	94.4 (86.4, 98.5)	97.2 (90.3, 99.7)	93.1 (84.5, 97.7)	96.9 (88.5, 99.1)
Prior HCV Treatment 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)
HIV Co-Infection				
Positive	100.0 (54.1, 100.0)	100.0 (47.8, 100.0)	83.3 (35.9, 99.6)	100.0 (47.8, 100.0)
Negative	91.9 (84.7, 96.5)	93.9 (87.3, 97.7)	92.9 (86.0, 97.1)	97.0 (91.6, 99.4)

#Cirrhosis redefined as per a Fibroscan score >14.5kPa (among those with Fibroscan scores) (Fibroscan score >12.5 kPa used by the applicant). This re-classification results in n=16 (n=3 GZR/EBR 12w; n=4 GZR/EBR 16w; n=4 GZR/EBV/RBV 12 w; n=5 GZR/EBR/RBV 16w) subjects' status changing from cirrhotic to non-cirrhotic. 95% CI via Clopper-Pearson exact method

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

- 1) The main statistical issue is that all of the primary analyses in the hypothesis-based trials 052, 060, 061 and 068 were of comparisons of SVR12 in the GZR/EBR regimen against a historical control SVR12 rather than against an active control arm. The lack of a concurrent comparator group complicates the overall interpretation of efficacy given the inability to control for measured and unmeasured variables that might influence the treatment effect. Given that at the time of protocol development of these trials, there were no approved IFN-sparring DAA regimens available for comparison, and that IFN-based regimens are known to be associated with serious toxicities and complicated dosing thereby not serving as ideal comparisons, the historical-controlled design was agreed upon between the FDA and the applicant. Two trials in this submission included a placebo group, which was a delayed treatment arm where subjects received a matching placebo for the first 12 weeks of treatment followed by GZR 100 mg/EBR 50 mg for 12 weeks. This design was not chosen for purposes of comparative efficacy but rather for comparative safety. While much consideration was taken in determining appropriate historical control SVR12 proportions to set as thresholds for superiority, there are general concerns that populations used to derive historical control estimates differ from current trial populations on demographics and other baseline factors. Findings based on comparisons against a historical control can be seriously biased if subject comparability is not established at baseline with respect to disease characteristics and prognostic factors. This is often difficult to achieve given lack of data among the historical control populations.
- 2) While agreed upon in advance between the applicant and FDA, data on SVR24 were incomplete for the Phase 2/3 and 3 trials. As such, the reviewer is unable to assess the proportion achieving SVR24 and perform correlation analyses of SVR12 versus SVR24 across trials. These analyses will be performed once the SVR24 data are complete to verify that there is sustained virologic response in targeted CHC groups at specified GZR 100 mg/EBR 50 mg durations.
- 3) The applicant's primary analysis population (mFAS) for trial 052 excluded subjects with missing data due to death or early discontinuation from the study with reasons unrelated to their responses to HCV treatment. This later criterion was chosen because the study population of CKD 4/5 subjects, especially those that are HD CKD5, have a high incidence (~10%) of major cardiovascular events that may lead to death or to study withdrawal. The reviewer's primary analyses (FAS) included these subjects (n=6) as failures over concerns of using post-randomization factors to exclude subjects from the primary analysis. The difference in SVR12 between the applicant and the reviewer was 99.1% versus 94.3% suggesting little impact of the six subjects with missing HCV RNA. The product label will present the SVR12 based on the FAS.
- 4) In the two Phase 2 trials included in this review (trial 047 and 048), the per-protocol population served as the primary in the applicant's analyses. Despite these trials being hypothesis-generating only, the reviewer still considers the FAS population as more reliable as it does not omit treated subjects based on post-randomization factors. Nevertheless, there were minor differences between the PP and FAS findings.

5.2 Collective Evidence

This NDA contained efficacy and safety data from seven clinical trials evaluating 8, 12, 16 and 18 weeks treatment with GZR/EBR with or without RBV in various CHC-infected adult (≥ 18 years) populations. All trials evaluated sustained virologic response at 12 weeks following end of treatment as the primary efficacy endpoint. Only two trials-both Phase 2-submitted included follow-up data at 24 weeks following end of treatment.

Among TE-prior relapsers and TN CHC subjects infected with GT1, GT4 (b) (4) subgenotypes, the applicant is proposing a treatment regimen of GZR 100 mg/EBR 50 mg administered daily for 12 weeks. Among TE on-treatment virologic failure CHC GT1b-subgenotype infected subjects, the applicant is proposing a 12 week course of daily GZR 100 mg/EBR 50 mg and a 16-week course with RBV for persons with CHC GT1a, GT4 (b) (4) subgenotype infection. These proposed treatment regimens were considered in the following assessment of the data provided from the eight clinical trials. Overall, there were few subjects in all trials who failed to achieve SVR12 and in most trials; HCV RNA was undetectable as early as week 4 of treatment in the majority of enrolled subjects. Relapse rates up to week 12 following treatment were similarly low. Data out to week 24 following end of treatment were limited as most trials were ongoing at time of the NDA submission. Overall findings by trials are summarized below.

Trial 035

Trial 035 was a large, complex, dose duration and dosing exploration Phase 2 trial in **GT1**-infected subjects including several cohorts by prior treatment experience, presence of cirrhosis at baseline, HIV co-infection and prior null responders. Overall, results of this trial do not support duration of treatment with GZR 100 mg/50 mg for less than 12 weeks among GT1a-subgenotype infected subjects due to high failure rates. In addition, while data suggest a high SVR12 among GT1b-infected subjects receiving less than 12 weeks, the numbers are small. Among prior null responders, this trial does provide some evidence-albeit the numbers are small, to support a longer (more than 12 weeks) treatment with GZR 100 mg/EBR 50 mg regardless of RBV addition.

Trial 047

This Phase 2 trial was conducted to explore efficacy in **non-GT1 and non-GT3, TN, NC, CHC subjects** of two different regimens: GZR/EBR+RBV and GZR+RBV. Although this was a small, proof-of-concept, Phase 2 trial, it was included in this review because this trial included subjects with GT 4 (b) (4) subgenotypes, which are subgenotypes in the applicant's proposed indication (along with GT1).

Overall, efficacy based on SVR12 was high among GT4 (b) (4) CHC receiving GZR/EBR with RBV; however, there were only few subjects in each group with considerable uncertainties in interpreting SVR12 rates. The results also suggest that addition of RBV to the GZR/EBR regimen for treatment of GT4 (b) (4) CHC does not increase overall SVR12 numerically compared to a regimen without RBV; however, the sample sizes per arm are small.

Trial 048

Trial 048 was a small hypothesis-generating study of 79 (FAS population) **CHC GT1-infected subjects with prior DAA treatment failure**. Overall, the SVR12 ranged from 89% to 99% and SVR12 by GT1 subgenotype was slightly higher among GT1b subjects compared to GT1a subjects. There were no clear differences in SVR12 by specific subgroup. These findings suggest that a regimen of GZR/EBR+RBV in

GT1 CHC subjects who had failed a prior DAA regimen may achieve a high SVR12 but given the small sample size findings should not be viewed as conclusive.

Trial 052

Trial 052 was a Phase 2/3, randomized, double-blind (during the first 12 weeks) trial performed in a targeted CHC population of 122 (FAS population) **subjects with GT1 subgenotype with CKD including those on dialysis**. Overall trial (up to 12 weeks post-treatment completion) and treatment completion was greater than 93% and only two subjects were lost to follow-up. This trial demonstrated that a regimen of GZR 100 mg/EBR 50 mg given for 12 weeks led to an SVR12 of 94% with a 95% CI of 88.5% to 97.7% demonstrating statistical significance in terms of superiority over a pre-specified historical rate of 53%. Only one subject failed to achieve SVR due to experiencing a relapse by week 12 post-treatment follow-up. SVR12 was numerically higher among GT1a-subgenotype subjects (96.8%) compared to GT1b-infected subjects (91.5%); however the 95% CIs greatly overlap suggesting no difference and the majority of failures were for non-virologic reasons. No differences were noted in SVR12 by baseline factors including having diabetes or requiring dialysis at baseline. While data are incomplete for 24 week follow-up outcome, there were two subjects reported to have experienced a virologic relapse. Further analyses of week 24 follow-up will be performed when the complete dataset is available.

Trial 060

This randomized, blinded (during the first 12 weeks) trial that enrolled 316 (FAS population) **TN GT 1, 4, and 6 HCV mono-infected subjects with or without cirrhosis**. Overall, achieved a 94.6% SVR12 with a 95% CI of 91.5% to 96.8% thus achieving the primary goal to demonstrate superiority over a historical rate of 73% ($p < 0.0001$). By subgenotype, GT1a-infected subjects ($n=157$) achieved a slightly lower SVR12 (91.7% CI 86.3-95.5%) compared to GT1b-infected subjects ($n=131$) (98.5%, 94.6-99.8%) with confidence intervals barely overlapping. SVR12 was 100% in the small ($n=18$) subset of GT4-infected subjects and much lower among the GT6-infected subjects (80%) but that subtype comprised only 10 subjects thus leading to challenges in determining efficacy in this subtype. Among the subjects failing to achieve SVR12, 3.8% ($n=12$) suffered a relapse with the majority (9/12) occurring in GT1a-infected subjects. There were no apparent differences in SVR12 by targeted subgroup. Findings on SVR24 and SVR12 in subjects randomized to the DTG will be presented in a future submission as data at this time point were incomplete at time of the NDA.

Trial 061

This non-randomized, uncontrolled clinical trial in 218 (FAS population) **HCV/HIV co-infected GT 1, 4, and 6-subgenotype infected TN, with or without cirrhosis** subjects resulted in a superior SVR12 (b) (4)

(b) (4) Less than 1% of subjects failed to complete treatment or complete the study follow-up. Overall, there were no differences in SVR12 by targeted subgroup including subgenotype. Despite the lack of randomization or control group, these findings suggest a high SVR12 among a subgroup of co-infected HCV/HIV TN subjects treated with GZR 100 mg/EBR 50 mg for 12 weeks.

Trial 068

This large trial ($n=420$, FAS) randomized, parallel-group, multi-site, and open-label was performed in a **diverse (C or NC, few HIV co-infected subjects) CHC-infected adult population with GT 1, 4, or 6 who had previously failed P/R treatment** achieving high SVR12 rates across all four treatment arms. (b) (4)

GZR/EBR+RBV x 12 weeks, GZR/EBR+RBV x 16 weeks, GZR/EBR+RBV x 16 weeks arms, respectively. The primary objective to achieve superiority over a historical control SVR12 proportion of 58% in the TE population was achieved in all four arms.

By subgenotype, SVR12 was higher (ranged from 96% to 100%) in all four arms among the GT1b-infected subjects compared to the GT1a-infected subjects (ranged from 90% to 95%). Few subjects were enrolled with GT4; however, among these subjects a regimen including RBV for 12 weeks led to an SVR12 (95% CI) of 93.3% (68.1%, 99.8%) compared to 100% (63.1% to 100%) in the RBV-containing regimen given for 16 weeks. Among GT4-infected subjects treated for either 12 or 16 weeks without RBV, the SVR12 was unacceptably low (60-78%) suggesting that in TE GT4 subgenotype infected subjects, the addition of RBV may be necessary to achieve a clinically acceptable SVR12 (b) (4)

(b) (4). Subgroup analyses did not reveal any obvious interactions; however, treatment response varied as a function of baseline cirrhotic status. Too few subjects were enrolled with HCV/HIV co-infection to allow for a meaningful subgroup analyses by HIV status.

5.3 Conclusions and Recommendations

Given the totality of data provided from seven clinical trials evaluating a regimen of GZR 100 mg/EBR 50mg for treatment of CHC infection, the reviewer's conclusions are as follows:

- 1) A regimen of GZR 100 mg/EBR 50 given daily for 12 weeks achieved a clinically acceptable SVR12 among treatment naïve CHC subjects with GT 1a, 1b or 4 subgenotype. The data suggest a small increase in SVR12 with the addition of RBV to this regimen; however, given known RBV toxicities its use in the TN population may not be warranted.
- 2) Among TE subjects with CHC GT 1a subgenotype, the applicant is proposing a GZR 100 mg/EBR 50 mg regimen of 16 weeks with RBV. Given the available data from trials 035, 048 and 068 that enrolled TE subjects, there is some suggestion that a longer duration with RBV confers a greater SVR12; however, the overall trends are modest. Specifically, in two trials that evaluated 12 weeks with or without RBV (trial 035 and 068) there was a numerical increase in SVR12 of approximately 2-3% with overlapping confidence intervals. Only one trial compared 16 weeks with or without RBV (trial 068) for which there was little gain in SVR12. Comparing the 12 weeks with RBV arm to the 16 weeks with RBV arm (trial 068 only), the gain in SVR12 again was modest.
- 3) Although the numbers of enrolled treatment experienced subjects with GT4 subgenotype was small, treatment for 16 weeks with GZR 100 mg/EBR 50 mg plus RBV appeared to confer higher SVR12 compared treatment for 12 weeks with RBV. Regimens of GZR 100 mg/EBR 50 mg for 12 or 16 weeks without RBV in the TE GT4 subgenotype resulted in clinically unacceptable (less than 80%) proportions of SVR12. (b) (4)

- 5) The four trials (trials 052, 060, 061 and 068) designed around a testable hypothesis of superiority versus a historical control were successful despite the noted limitations of historical controls. Each trial was designed with a historical control commensurate to the population studied and all planned

comparison achieved statistical significance of the GZR 100 mg/EBR 50 mg arm over the historical control, with the limitations in its interpretations.

5.4 Labeling Recommendations

Labeling negotiations with the applicant are ongoing; however, the following is a summary of key changes recommend by the reviewer (in collaboration with the clinical reviewers) to Section 14. Clinical Studies of the proposed product label.

- 1) Omit all [REDACTED] (b) (4)
Instead, present SVR12 and baseline characteristics/demographics by trial.
- 2) Removal of [REDACTED] (b) (4)
- 3) Present results for GT1 and GT4 separately in the clinical studies section. Further subdivide findings in the GT1 subgenotype into TN (non-CKD), TE and CKD subjects.
- 4) Omit [REDACTED] (b) (4)

References

- 1) World Health Organization Global Alert and Response Report on Hepatitis C
<http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index2.html>
- 2) Denniston MM, Jiles RB, Drobeniuc J et al. Chronic hepatitis C virus infection in the United States National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med.*, 2014; 160 (5): 293-300.
- 3) Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality? *J Viral Hepat*, 2012; 19:601-7.

Appendix A: Summary of Justifications for Historical Control SVR12 by Trial

Trial	Historical SVR12	Justification
052	45%	<p>Meta-analyses of IFN mono-therapy among HCV-infected subjects with CKD stages 3-5 produced a summary SVR24 of 39% (95% CI 32-46%)</p> <p>Bayesian random-effect modeling predicting that if all available trials included in the meta-analyses enrolled GT1 that the estimated overall population mean for SVR rate would be 45% with a 90% posterior probability or confidence</p>
060	73%	<p>The SVR12 historical control was derived based on findings from a Phase 2 trial of sofosbuvir in HCV GT1 subjects co-infected with HIV (PHOTON-1) in which the overall SVR12 was 76% and 60% in cirrhotic subjects (accounted for only 4% of all trial subjects). Therefore, after accounting for a greater proportion of subjects with cirrhosis planned in trial 061 (20%) versus the 4% observed in PHOTON-1 and for a 5% decrease in response rate due an expected improved safety profile of GZR/EBR as an IFN-free regimen, the estimated historical rate was 70%.</p>
601	70%	<p>The SVR12 historical control was derived based on findings from a Phase 2 trial of sofosbuvir in HCV GT1 subjects co-infected with HIV (PHOTON-1) in which the overall SVR12 was 76% and 60% in cirrhotic subjects (accounted for only 4% of all trial subjects). Therefore, after accounting for a greater proportion of subjects with cirrhosis planned in trial 061 (20%) versus the 4% observed in PHOTON-1 and for a 5% decrease in response rate due an expected improved safety profile of GZR/EBR as an IFN-free regimen, the estimated historical rate was 70%.</p>
068	58%	<p>HC of 58% derived from a prior Phase 2b trial of simeprevir given for 12, 24, or 48 weeks in combination with P/R for 48 weeks in TE CHC subjects. Findings from this prior trial demonstrated a 70% SVR overall and 40% SVR among prior relapsers (accounted for only 20% of the trial sample). Similarly, the SVR was 70% in prior partial responders and 45% in prior null responders (accounting for 35% and 25% subjects, respectively). The applicant assumed that trial 068 would enroll 40% prior null responders and 40% prior partial responders and therefore estimated a SVR to be 63%. Also, assuming a 5% decrease in this response rate because of an expected improved safety profile given the absence of IFN, the applicant arrived at a 58% SVR historical rate.</p>

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/s/

LAREE A TRACY
10/28/2015

THAMBAN I VALAPPIL
10/28/2015

DIONNE L PRICE
10/28/2015
Concur