

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209394Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 209394/000
Drug Name: **Mavyret™** (fixed dose combination product: Glecaprevir/Pibrentasvir)
Film-coated Tablets, 100 mg/40 mg
Indication(s): Treatment of adult patients with chronic hepatitis C virus (HCV)
genotype 1, 2, 3, 4, 5 or 6 infection
Applicant: AbbVie
Date(s): Received: 12/14/16
Filing Date: 2/12/17
Primary Review Due Date: 5/14/17
PDUFA: 8/14/17
Review Priority: Priority 8-months
Biometrics Division: Division of Biometrics IV
Statistical Reviewers: LaRee A. Tracy, MA, PhD (DB4), Therri Usher, PhD (DB4)
Concurring Reviewers: Thamban Valappil, PhD (DB4), Dionne Price, PhD (DB4)
Medical Division: Division of Antiviral Products (DAVP)
Clinical Team: Larissa Stabinski, MD (Clinical Reviewer)
Wendy Carter, DO (CDTL)
Jeffrey Murray, MD (DAVP Division Lead)
Project Manager: Alicia Moruf, PharmD, MPH (DAVP)
Keywords: HCV, clinical threshold, historical comparison, data pooling

Table of Contents

1	EXECUTIVE SUMMARY	7
2	INTRODUCTION	12
2.1.	OVERVIEW	12
2.2.	DATA SOURCES	18
3	STATISTICAL EVALUATION	18
3.1.	DATA AND ANALYSIS QUALITY	18
3.2.	EVALUATION OF EFFICACY	19
3.2.1.	<i>Trial Design Characteristics Common to Trials</i>	19
3.2.2.	<i>Phase 2 Trials</i>	20
3.2.2.1	Trial M14-867 (SURVEYOR-1)	20
3.2.2.2	Trial M14-868 (SURVEYOR-2)	23
3.2.2.3	Trial M14-172 (EXPEDITION-1)	28
3.2.2.4	Trial M13-583 (ENDURANCE-4)	31
3.2.2.5	Trial M15-410 (MAGELLAN-1)	33
3.2.3.	<i>Phase 3 Trials</i>	39
3.2.3.1	Trial M13-590 (ENDURANCE-1)	39
3.2.3.2	Trial M15-464 (ENDURANCE-2)	43
3.2.3.3	Trial M13-594 (ENDURANCE-3)	46
3.2.3.4	Trial M15-462 (EXPEDITION-4)	52
3.3.	POOLED EFFICACY ANALYSIS	56
3.3.1.	<i>Treatment-Naïve HCV Subjects</i>	56
3.3.2.	<i>Treatment-Experienced</i>	58
3.4.	EVALUATION OF SAFETY	61
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	64
4.1.	GENDER, RACE, AGE, AND GEOGRAPHIC REGION	64
4.2.	OTHER SPECIAL/SUBGROUP POPULATIONS	67
5	SUMMARY AND CONCLUSIONS.....	71
5.1.	STATISTICAL ISSUES	71
5.2.	COLLECTIVE EVIDENCE.....	73
5.3.	CONCLUSIONS AND RECOMMENDATIONS	75
5.4.	LABELING RECOMMENDATIONS.....	76
6	REFERENCES	82
7	APPENDIX A - STUDY DESIGNS	83

LIST OF TABLES

Table 1: SVR12 in GT1-6, TN Subjects by Treatment Duration by Trial	9
Table 2: SVR12 in GT 1-6 TE Subjects by Treatment Duration by Trial	11
Table 3: Summary of Currently Approved Interferon-Free Treatments for Chronic HCV Infection	14
Table 4: Applicant’s Proposed Dosing and Administration for GLE/PIB	15
Table 5: List of Phase 2 Trials Included in Review	16
Table 6: List of Phase 3 Trials Included in Review	17
Table 7: SURVEYOR-1 Subject Disposition	21
Table 8: SURVEYOR-1 Baseline Characteristics/Demographics	22
Table 9: SURVEYOR-1: SVR12 and Other Outcomes for GLE/PIB 8 and 12-week Regimens	23
Table 10: SURVEYOR-2 Disposition (By Genotype)	25
Table 11: SURVEYOR-2 - Baseline Characteristics/Demographics	26
Table 12: SURVEYOR-2: SVR12 and Other Outcomes	28
Table 13: EXPEDITION-1: Subjects Enrolled by Prior Treatment Status.....	30
Table 14: EXPEDITION-1 SVR12 and Relapse Overall and by GT and Treatment Status	30
Table 15: ENDURANCE-4: Subject Disposition.....	31
Table 16: ENDURANCE-4 Baseline Characteristics/Demographics	32
Table 17: ENDURANCE-4 SVR12.....	33
Table 18: MAGELLAN-1 Subject Disposition	34
Table 19: MAGELLAN-1 Baseline Characteristics/Demographics.....	35
Table 20: MAGELLAN-1 SVR12 and Other Outcomes.....	36
Table 21: SVR12 for NS5A and/or NS3/4A PI Experienced Subjects by Treatment Duration.....	37
Table 22: MAGELLAN-1 SVR12 by Subgroup	37
Table 23: ENDURANCE-1 Subject Disposition.....	40
Table 24: ENDURANCE-1 Subject Baseline Characteristics/Demographics	42
Table 25: ENDURANCE-1 SVR12 and Other Outcome, GLE/PIB 8-and 12-week Regimens	43
Table 26: ENDURANCE-2 Subject Disposition.....	44
Table 27: ENDURANCE-2 Subject Baseline Demographics/Characteristics	45
Table 28: ENDURANCE-2 SVR4 and SVR12 and Other Outcomes	46
Table 29: ENDURANCE-3 Subject Disposition.....	47
Table 30: ENDURANCE-3 Subject Demographics/Characteristics	48
Table 31: ENDURANCE-3 SVR12 and Other Outcomes by Treatment Arm.....	49
Table 32: ENDURANCE-3 Statistical Comparisons of SVR12	51
Table 33: ENDURANCE-3 SVR12 by Subgroup	51
Table 34: EXPEDITION-4 Subject Disposition.....	52
Table 35: EXPEDITION-4 Subject Baseline Characteristics/Demographics	53
Table 36: EXPEDITION-4 SVR12 and Other Outcomes	54
Table 37: EXPEDITION-4 SVR12 by Subgroup.....	55
Table 38: Pooled SVR12 by Genotype and Cirrhosis Status in Treatment Naïve GT1-6	58
Table 39: Pooled SVR12 by Genotype and Treatment Duration in DAA- & PR-Experienced, NS5A Naïve, Non-Cirrhotic Subjects.....	60
Table 40: Pooled SVR12 by Genotype in DAA- & PR-Experienced, NS5A Naïve, Cirrhotic Subjects.....	61
Table 41: Incidence of Severe Hypotension/Severe Hypertension across Trials	62
Table 42: Pooled SVR12 by Age, Race, Gender, and Region in TN Subjects, GLE/PIB 12 weeks.....	65
Table 43: Pooled SVR12 by Age, Race, Gender, and Region in TN Subjects, GLE/PIB 8 weeks.....	65
Table 44: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR-Experienced, NS5A Naïve Subjects for 8 Week Treatment Duration.....	66
Table 45: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR-Experienced, NS5A Naïve Subjects for 12 Week Treatment Duration.....	66

Table 46: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR-Experienced, NS5A Naïve Subjects for 16 Week Treatment Duration.....67
Table 47: Pooled SVR12 by Genotype and Subgroup, TN Subjects, GLE/PIB 12 weeks.....68
Table 48: Pooled SVR12 by Genotype and Subgroup, TN Subjects, GLE/PIB 8 weeks.....69
Table 49: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 8 Week Treatment Duration 70
Table 50: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 12 Week Treatment Duration 70
Table 51: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 16 Week Treatment Duration 71

LIST OF FIGURES

Figure 1: Mean Change from Baseline in DBP among subjects (n=28) with DBP ≤ 50 mmHg AND ≥ 15 mmHg decrease from baseline on treatment	62
Figure 2: Mean Change from Baseline in DPB among subjects (n=34) with DBP ≥ 105 mmHg AND ≥ 15 mmHg increase from baseline on treatment	63
Figure 3: Mean Change from Baseline in BBP among subjects (n=36) with a SBP ≤ 90 mmHg AND ≥ 20 mmHg decrease from baseline on treatment	63
Figure 4: Mean Change from Baseline in SBP among subjects (n=24) with a SBP ≥ 180 mmHg AND ≥ 20 mmHg increase from baseline on treatment	64
Figure 5: Applicant's Proposed Dosage and Administration	77
Figure 6: Review Team's Proposed Dosage and Administration	77
Figure 7: Recommended Changes to Applicant's Summary of Clinical Trials	79
Figure 8: Applicant's Results From MAGELLAN-1 Part 2	80
Figure 9: Review Team's Proposed Results From MAGELLAN-1	80
Figure 10: Applicant's Pooled Results for GT1, 2, 4, 5, and 6 With and Without Cirrhosis	81
Figure 11: Review Team's Proposed Pooled Results for GT2, 4, 5, and 6 Without Cirrhosis	81
Figure 12: Recommended Changes to Applicant's Results From ENDURANCE-3	82
Figure 13: ENDURANCE-1 (M13-590) Trial Design	83
Figure 14: ENDURANCE-2 (M15-464) Trial Design	83
Figure 15: ENDURANCE-3 (M14-594) Trial Design	83
Figure 16: ENDURANCE-4 (M13-583) Trial Design	84
Figure 17: EXPEDITION-1 (M14-172) Trial Design	84
Figure 18: MAGELLAN-1 (M15-410) Trial Design	84
Figure 19: SURVEYOR-1 (M14-867) Trial Design	85
Figure 20: SURVEYOR-2 (M14-868) Parts 1 & 2 Trial Design	86
Figure 21: SURVEYOR-2 (M14-868) Parts 3 & 4 Trial Design	86
Figure 22: EXPEDITION-4 (M15-462) Trial Design	87

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
PRS	PEGYLATED INTERFERON/RIBAVIRIN/SOFOSBUVIR
RBV	RIBAVIRIN
DAA	DIRECTLY ACTING ANTIVIRAL
CHC	CHRONIC HEPATITIS C
HPV	HEPATITIS C VIRUS
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
SOF	SOFOSBUVIR
DCV	DACLATASVIR

Trial Names: Trial Numbers: HCV GT, cirrhotic status, treatment history

SURVEYOR-1: M14-867: GT1, 4-6 NC and C, TN or TE-PRS

SURVEYOR-2: M14-868: GT2-6, NC and C, TN or TE-PRS

MAGELLAN-1: M15-410: GT1, GT4-6, NC and C, NS5A- and/or NS3/4A PI-experienced

EXPEDITION-1: M14-172: GT1, G2, GT4-6, C, TN or TE-PRS

ENDURANCE-4: M13-583: GT4-6, NC and C with renal impairment or ESRD, TN or TE-PRS

ENDURANCE-1: M13-590: GT1, NC, TN or TE-PRS

ENDURANCE-2: M15-464: GT2, NC, TN or TE-PRS

ENDURANCE-3: M13-594: GT3, NC, TN

EXPEDITION-4: M15-462: GT1-6, NC or C, chronic kidney disease stages 4, 5 or dialysis, TN or TE-PRS

1 EXECUTIVE SUMMARY

The applicant (AbbVie) submitted a New Drug Application (NDA) 209394 for a New Molecular Entity Mavyret™ (GLE/PIB), which is a fixed two-drug combination tablet comprising 100 mg of glecaprevir (GLE) and 40 mg of pibrentasvir (PIB). Both active products are direct-acting antiviral (DAA) agents and specifically, GLE is a NS3/4A protease inhibitor and PIB is a NS5A inhibitor, each targeting multiple steps involved in the hepatitis C viral replication cycle. The applicant is seeking approval for treatment of chronic hepatitis C genotypes (GT) 1-6 in adults, including patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment to include patients receiving dialysis. Further, the proposed dosing and administration includes an 8-and 12-week GLE/PIB regimen for which duration is driven by HCV GT, cirrhotic status and prior treatment experience. The proposed daily dose is three tablets of GLE/PIB to deliver 300 mg GLE and 120 mg PIB administered once-daily.

Evidence supporting this NDA comes from 4 Phase 3 trials (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3 and EXPEDITION-4) that enrolled 974 HCV-infected adult subjects, of which 759 received GLE/PIB 300 mg/120 mg. ENDURANCE-1 evaluated both 8-and 12-week GLE/PIB regimens in a 1:1 randomized design in GT1, non-cirrhotic (NC) subjects with or without HIV co-infection and either treatment-naïve (TN) or treatment-experienced with PegIFN/ribavirin/sofosbuvir (TE-PRS). ENDURANCE-2 evaluated a 12-week GLE/PIB regimen in GT2, NC, TN or TE-PRS HCV-infected subjects in a double-blind, placebo-controlled design. ENDURANCE-3 evaluated 8-and 12-week GLE/PIB regimens in GT3, NC, TN HCV-infected subjects in an open-label design against a sofosbuvir/daclatasvir active-control. EXPEDITION-4 evaluated a 12-week GLE/PIB regimen in 104 GTs 1-6 infected subjects who were TN or TE with or without cirrhosis with severe renal impairment or end-stage renal disease, among which 85 were on dialysis at time of enrollment. ENDURANCE-1 and ENDURANCE-2 were designed to demonstrate superiority against a pre-specified SVR12 clinical threshold. ENDURANCE-3 was designed to demonstrate non-inferiority of the 12-week GLE/PIB regimen to the active control SOF/DCV. EXPEDITION-4 was a single-arm trial with no testable hypothesis.

In addition, supportive data were reviewed from 5 Phase 2 trials (SURVEYOR-1, SURVEYOR-2, EXPEDITION-1, MAGELLAN-1, and ENDURANCE-4) enrolling a total of 1273 HCV-infected adult subjects, of which, 970 received the proposed GLE/PIB 300 mg/120 mg dosage. SURVEYOR-1 evaluated 8- and 12-week GLE/PIB regimens in GT1, 4-6 infected subjects, TN or TE-PRS with or without cirrhosis. SURVEYOR-2 was a multi-arm, dose and duration finding trial evaluating 8- 12- and 16-week regimens of GLE/PIB in GT2-6 infected, NC or cirrhotic (C), TN or TE-PRS adult subjects. EXPEDITION-1 was a single-arm trial evaluating a 12-week GLE/PIB regimen in GT1, 2, 4-6 infected adults who were cirrhotic and either TN or TE-PRS. MAGELLAN-1 was a multi-part trial of 12-and 16-week GLE/PIB regimens in GT1, GT4-6, NS5A and/or NS3/4A PI-experienced, NC or C subjects. Finally, ENDURANCE-4 was a single arm trial evaluating GLE/PIB 12 weeks in less-prevalent GT4-6, NC subjects. All nine trials were designed around the same primary efficacy endpoint of sustained virologic response, defined as proportion of subjects achieving a HCV RNA value below the lower limit of quantification, at 12 weeks following the end-of-treatment (SVR12).

The applicant's proposed treatment durations are based upon prior HCV treatment, and cirrhosis, status. Specifically, for all six GTs, the proposed duration is 8-weeks for TN, NC subjects and 12-weeks for TN, C subjects. Among TE, (b) (4)

(b) (4)

Evidence supporting the 8-week regimen in GT1, NC subjects largely comes from ENDURANCE-1 achieving a SVR12 (95% CI) of 99% (97, 100) demonstrating superiority against a 91% pre-specified clinical threshold. Supportive data from an additional 29 GT1, NC subjects comes from SURVEYOR-1 in which all but one subject achieved SVR12. Evidence for the 8-week regimen in GT2 and GT4, NC subjects comes from SURVEYOR-2 for which the SVR12 (95% CI) was 99% (96, 100) for GT2 and 92% (80, 97) for GT4.

Evidence supporting treatment for GT3, TN, NC subjects largely comes from ENDURANCE-3 for which the SVR12 (95% CI) in the 8-week and 12-week arms were 95% (90, 97) and 95% (92, 97), respectively. The trial was successful in demonstrating efficacy of the 12-week regimen based on showing non-inferiority (NI) to the active-control. The 8-week arm was non-randomized and therefore comparisons of NI are statistically inappropriate. Instead, the regimen was compared against the pre-specified 92% clinical threshold and findings suggest that the arm failed to achieve superiority against this rate. Supportive data for the 8-week regimen in 29 GT3, TN, NC subjects come from SURVEYOR-2 yielding a SVR12 (95% CI) of 96% (83, 99).

The available data are too limited and do not support an 8-week GLE/PIB regimen in TN, GT5 (n=2 studied) or GT6 (n=8 studied) infected non-cirrhotic subjects. However, more data exist in subjects treated with the 12-week regimen; 22 GT5 and 28 for GT6 specifically, for these less-prevalent genotypes and the overall SVR12 was 100%.

EXPEDITION-1 provides evidence to support a 12-week GLE/PIB regimen in TN and TE-PRS, cirrhotic subjects infected with GT 1, 2, 4-6. SVR12 (95% CI) rates were 98.9% (94, 100) for GT1 and 100% for GT2 (89, 100), GT4 (81, 100), GT5 (34, 100), and GT6 (65, 100) with one post-treatment relapse in a GT1-infected subject.

Evidence supporting a 16-week GLE/PIB regimen in GT3, TE subjects with and without cirrhosis comes from SURVEYOR-2 from which the pooled SVR12 (95% CI) was 94.5% (87, 98).

Data supporting treatment in HCV-infected patients with CKD disease come from EXPEDITION-4, which enrolled 104 subjects of which 53%, 15%, 11%, 19%, 1% and 1% were GT1, 2, 3, 4, 5 and 6; respectively. Subjects in the trial achieved a SVR12 (95% CI) of 98.1% (93, 99) with two non-virologic failures in two GT1-infected subjects. Refer to the clinical review for a deeper assessment of this trial and the underlying level of kidney disease among the enrolled subjects.

Finally, data supporting the proposed treatment among NS5A- and/or NS3/4A PI-experienced come from MAGELLAN-1 for which all but four subjects were infected with GT1 HCV. (b) (4)
GT1-infected subjects who were NS3/4A PI-experienced achieved a SVR12 (95% CI) rate of 92.0% (75, 98) with two non-virologic failures in the 12-week treatment duration. GT1-infected subjects who are NS5A-experienced achieved a SVR12 rate of 94.1% (73, 99) with one on-treatment virologic failure. Among GT1-infected subjects that are NS3/4A PI- and

NS5A-experienced, SVR12 (95% CI) rates were 80% in both 12-week (58, 92) and 16-week (55, 93) GLE/PIB regimens. In addition, there were 3 relapses and 1 on treatment virologic failure (OTVF) in the 12-week regimen and 3 OTVFs in the 16-week regimen. The lower SVR12 rate and higher number of virologic failures indicated that GLE/PIB did not achieve an acceptable threshold of efficacy for this subgroup.

Table 1 and Table 2 present SVR12 (95% CI) rates by genotype, trial, cirrhotic status, and treatment duration among TN and TE subjects, respectively. In addition, pooled SVR12 rates are displayed by GT, cirrhotic status and treatment duration when data were collected from more than one trial. The data supporting respective regimens are shown in bolded red font.

Table 1: SVR12 in GT1-6, TN Subjects by Treatment Duration by Trial
 % SVR12 (n/N), 95% CI*

GT	Trial	Cirrhotic Status	GLE/PIB x 8 w	GLE/PIB x 12 w
1	590	NC	99.1 (217/219)	99.5 (216/217)
	(ENDUR1)		96.7, 99.7	97.4, 99.9
1	867	NC	96.5 (28/29)	NS
	(SURV1)		82.8, 99.4	
1	462	NC	NS	100 (43/43)
	(EXPED4)			91.8, 100
1	Pooled	NC	98.8 (245/248)	99.6 (259/260)
			96.5, 99.6	97.8, 99.9
1	172	C	NS	100 (66/66)
	(EXPED1)			94.5, 100
1	462	C	NS	81.8 (9/11)
	(EXPED4)			52.3, 94.9
1	Pooled	C	NS	97.4 (75/77)
				91, 99.3
2	868	NC	98.8 (172/174)	95.5 (21/22)
	(SURVY2)		95.9, 99.7	78.2, 99.2
2	464	NC	NS	99.3 (140/141)
	(ENDUR2)			96.1, 99.9
2	462	NC	NS	100 (13/13)
	(EXPED4)			77.2, 100
2	Pooled	NC	98.8 (172/174)	98.9 (174/176)
			95.9, 99.7	95.9, 99.7
2	172	C	NS	100 (24/24)
	(EXPED1)			86.2, 100
2	462	C	NS	100 (4/4)
	(EXPED4)			51.0, 100
2	Pooled	C	NS	100 (28/28)
				87.9, 100
3	594	NC	94.9 (149/157)	95.3 (222/233)
	(ENDUR3)		90.3, 97.4	91.7, 97.3
3	868	NC	96.5 (28/29)	96.3 (26/27)
	(SURVY2)		82.8, 99.4	81.7, 99.3
3	462	NC	NS	100 (10/10)
	(EXPED4)			
3	Pooled	NC	95.2 (177/186)	95.5 (258/270)

NDA 209394 Mavyret™ (Indication: Treatment of Chronic HCV GT1-6 Infection)
 Statistical Review: LaRee A. Tracy, MA, PhD (DB4) & Therri Usher, PhD (DB4)

			91.1, 97.4	92.4, 97.4
3	868 (SURVY2)	C	NS	98.4 (63/64) 91.7, 99.7
3	462 (EXPED4)	C	NS	100 (1/1)
3	Pooled	C	NS	98.5 (64/65) 91.8, 99.7
4	583 (ENDUR4)	NC	NS	100 (45/45) 92.1, 100
4	867 (SURV1)	NC	NS	100 (18/18) 82.4, 100
4	868 (SURVY2)	NC	92.3 (36/39) 79.7, 97.3	NS
4	462 (EXPED4)	NC	NS	100 (16/16) 80.6, 100
4	Pooled	NC	92.3 (36/39) 79.7, 97.3	100 (79/79) 95.4, 100
4	172 (EXPED1)	C	NS	100 (12/12) 75.7, 100
4	462 (EXPED4)	C	NS	100 (4/4) 51, 100
4	Pooled	C	NS	100 (16/16) 80.6, 100
5	583 (ENDUR4)	NC	NS	100 (20/20) 83.9, 100
5	867 (SURVY1)	NC	NS	100 (1/1)
5	868 (SURVY2)	NC	100 (2/2)	NS
5	462 (EXPED4)	NC	NS	1/1 (100)
5	Pooled	NC	100 (2/2)	100 (22/22) 85.1, 100 100 (2/2)
5	172 (EXPED1)	C	NS	100 (2/2)
6	583 (ENDUR4)	NC	NS	100 (17/17) 81.6, 100
6	867 (SURVY1)	NC	NS	100 (10/10) 72.2, 100
6	868 (SURVY2)	NC	87.5 (7/8) 61, 100	NS
6	462 (EXPED4)	NC	NS	100 (1/1)
6	Pooled	NC	87.5 (7/8) 61, 100	100 (28/28) 87.9, 100
6	172 (EXPED1)	C	NS	100 (6/6) 61, 100

NC=non-cirrhotic; C=cirrhotic; NS=not studied

* Confidence intervals were calculated using the Wilson score method, no CI calculated for group sizes less than 5

Source: reviewer created

ENDUR1=ENDURANCE-1; ENDUR2=ENDURANCE-2; ENDUR3=ENDURANCE-3,
 ENDUR4=ENDURANCE-4; SURV1=SURVEYOR-1; SURV2=SURVEYOR-2; EXPED1=EXPEDITION-1;
 EXPED4=EXPEDITION-4

Table 2: SVR12 in GT 1-6 TE Subjects by Treatment Duration by Trial

GT	Trial	SP	Prior Treatment Experience	% SVR12 (n/N), 95% CI*		
				GLE/PIB x 8 w	GLE/PIB x 12 w	GLE/PIB x 16 w
1	590 (ENDUR1)	NC	TE-PRS	99.2 (131/132) 95.8, 100.0	100 (135/135) 97.2, 100	NS
1	867 (SURVY1)	NC	TE-PRS	100 (5/5) 56.6, 100	NS	NS
1	868 (SURVY2)	NC	TE-PRS	100 (2/2)	NS	NS
1	464 (ENDUR2)	NC	TE-PRS	NS	100 (3/3)	NS
1	Pooled	NC	TE-PRS	99.3 (137/138) 96.0, 100.0	100 (138/138) 97.3, 100	NS
1	172 (EXPED1)	C	TE-PRS	NS	95.8 (23/24) 79.8, 99.3	NS
1	410 (MAGEL1)	NC/C	NS3/4A PI (NS5A inhibitor naïve)	NS	92.0 (23/25) 75.0, 97.8	100 (12/12) 75.8, 100
1	410 (MAGEL1)	NC/C	NS5A inhibitor (NS3/4A PI naïve)	NS	90.0 (18/20) 69.9, 97.2	94.1 (16/17) 73.0, 99.0
1	410 (MAGEL1)	NC/C	NS5A inhibitor & NS3/4 PI	NS	80.0 (16/20) 58.4, 91.9	80.0 (12/15) 54.8, 93.0
2	464 (ENDUR2)	NC	TE-PRS	NS	100 (58/58) 93.8, 100	NS
2	868 (SURVY2)	NC	TE-PRS	91.3 (21/23) 73.2, 97.6	100 (3/3)	NS
2	Pooled	NC	TE-PRS	91.3 (21/23) 73.2, 97.6	100 (61/61) 94.1, 100	NS
2	172 (EXPED1)	C	TE-PRS	NS	100 (7/7) 64.6, 100	NS
3	868 (SURVY2)	NC	TE-PRS	NS	87.8 (36/41) 74.5, 94.7	95.5 (21/22) 78.2, 99.2
3	868 (SURVY2)	C	TE-PRS	NS	NS	94.1 (48/51) 84.1, 98.0
4	583 (ENDUR4)	NC	TE-PRS	NS	96.8 (30/31) 83.8, 99.4	NS
4	867 (SURVY1)	NC	TE-PRS	NS	100 (4/4)	NS
4	868 (SURVY2)	NC	TE-PRS	100 (7/7) 64.6, 100	NS	NS
4	Pooled	NC	TE-PRS	100 (7/7) 64.6, 100	97.1 (34/35) 85.5, 99.5	NS
4	172 (EXPED1)	C	TE-PRS	NS	100 (4/4)	NS

4	410 (MAGEL1)	NC/C	NS3/4A PI (NS5A inhibitor naïve)	NS	NS	100 (1/1)
4	410 (MAGEL1)	NC/C	NS5A inhibitor (NS3/4A PI naïve)	NS	NS	100 (1/1)
4	410 (MAGEL1)	NC/C	NS5A inhibitor & NS3/4 PI	NS	100 (1/1)	100 (1/1)
5	583 (ENDUR4)	NC	TE-PRS	NS	100 (6/6) 61.0, 100	NS
6	583 (ENDUR4)	NC	TE-PRS	NS	100 (2/2)	NS
6	867 (SURVY1)	NC	TE-PRS	NS	100 (1/1)	NS
6	868 (SURVY2)	NC	TE-PRS	100 (2/2)	NS	NS
6	Pooled	NC	TE-PRS	100 (2/2)	100 (3/3)	NS
6	172 (EXPED1)	C	TE-PRS	NS	100 (1/1)	NS

NC=non-cirrhotic; C=cirrhotic; PRS= treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, PI=protease inhibitor; NS=not studied

* Confidence intervals were calculated using the Wilson score method, no CI calculated for group sizes less than 5
 EXPEDITION-4 trial is excluded from this table as results from this trial are presented separately throughout the review.
 Source: reviewer created

ENDUR1=ENDURANCE-1; ENDUR2=ENDURANCE-2; ENDUR3=ENDURANCE-3,
 ENDUR4=ENDURANCE-4; SURV1=SURVEYOR-1; SURV2=SURVEYOR-2; EXPED1=EXPEDITION-1;
 EXPED4=EXPEDITION-4; MAGEL1=MAGELLAN-1

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). 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. 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.

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 (Table 3). 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%. For treatment of GT4 CHC infection, fewer options exist including sofosbuvir plus IFN or a 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 few approved DAA or IFN-free regimens to treat HCV GT6 infection or HCV GT 1, 4, or 6 subgenotype infections in patients receiving hemodialysis.

Table 3: Summary of Currently Approved Interferon-Free Treatments for Chronic HCV Infection

HCV GT	Product (s) Name	Product Class	Dosing/Administration
GT 1	Ledipasvir/ sofosbuvir FDC (Harvoni®)	NS5A inhibitor/ NS5B inhibitor (nucleotide)	12 or 24 weeks
	Paritaprevir/ ombitasvir/ ritonavir FDC + dasabuvir (Viekira Pak®)	NS3/4A PI/ NS5A inhibitor/ NS5B inhibitor (non-nucleoside)	12 or 24 weeks(+/- ribavirin)
	Simeprevir (Olysio®)	NS3/4 PI	12 or 24 weeks (w/sofosbuvir)
	Elbasivir/grazoprevir FDC (Zepatier™)	NS3/4A PI NS5A inhibitor	GT1a w/baseline NS5A polymorphisms for 16 weeks w/RBV; GT1a w/o BL PMs 12 weeks; GT1b 12 weeks
	Sofosbuvir/velpatasvir FDC (Eplusa®)	NS5B inhibitor (nucleotide)/NS5A inhibitor	12 weeks
	Sofosbuvir (Sovaldi®)	NS5B inhibitor (nucleotide)	12 weeks w/PR
	Daclatasvir (Daklinza™)	NS5A inhibitor	12 week +/-RBV
GT2	Sovaldi®	NS5B inhibitor (nucleotide)	12 weeks w/RBV
GT3	Sovaldi®	NS5B inhibitor (nucleotide)	24 weeks w/RBV
	Daklinza™	NS5A inhibitor	12 weeks w/SOF +/-RBV
	Eplusa®	NS5B inhibitor (nucleotide)/NS5A inhibitor	12 weeks
GT4	Harvoni®	NS5A inhibitor/ NS5B inhibitor (nucleotide)	12 weeks
	Eplusa®	NS5B inhibitor (nucleotide)/NS5A inhibitor	12 weeks
	Zepatier™	NS3/4A PI/ NS5A inhibitor	TN: 12 weeks TE: 16 weeks w/RBV
	Olysio®	NS3/4 PI	12 weeks + PR
	Ombitasvir/paritaprevir/ritonavir (Technivie)	NS5A inhibitor/NS3/4A PI/CYP3A inhibitor	12 weeks + PR
GT5	Harvoni®	NS5A inhibitor/ NS5B inhibitor (nucleotide)	12 weeks
	Eplusa®	NS5B inhibitor (nucleotide)/NS5A inhibitor	12 weeks
GT6	Harvoni®	NS5A inhibitor/ NS5B inhibitor (nucleotide)	12 weeks
	Eplusa®	NS5B inhibitor (nucleotide)/NS5A inhibitor	12 weeks

PR=PEGIFN+ribavirin, SOF=sofosbuvir, PI=protease inhibitor

Source: reviewer created

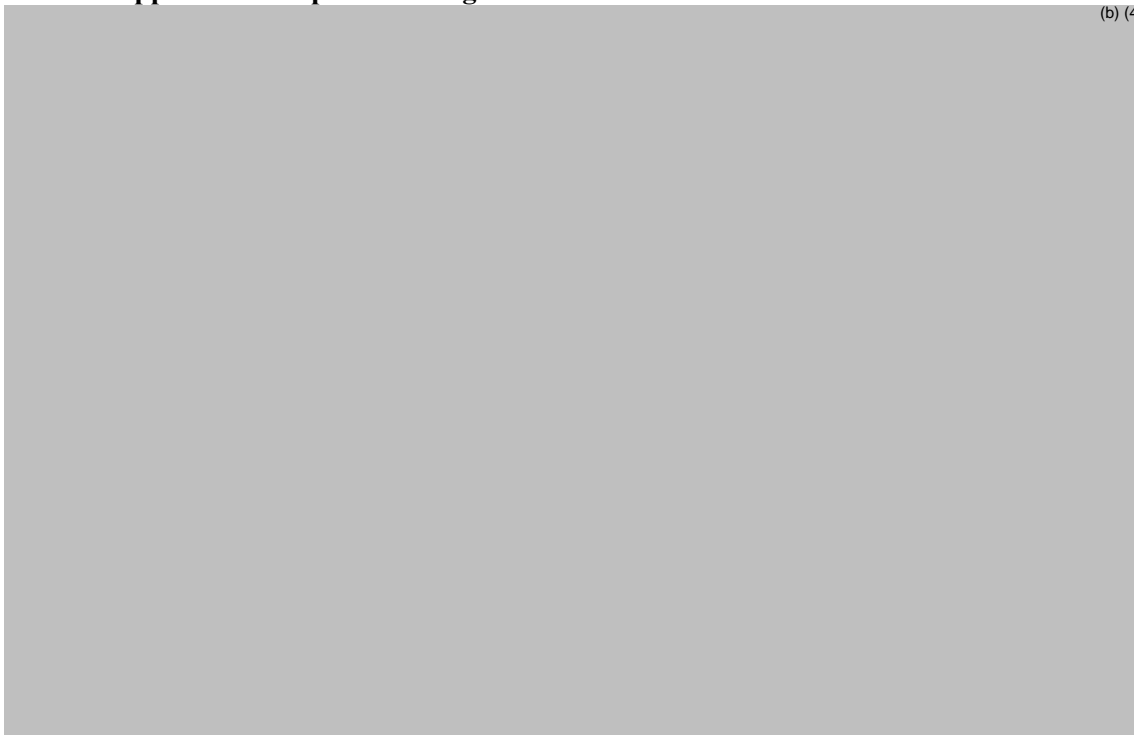
This NDA is for a New Molecular Entity for Mavyret™, which is a fixed-dose combination tablet containing 100 mg of glecaprevir (GLE) and 40 mg of pibrentasvir (PIB). GLE is a NS3/4A protease inhibitor and PIB is a NS5A inhibitor, each targeting multiple steps involved in the hepatitis C viral replication cycle. The indication being sought is for treatment of chronic HCV infection GTs 1-6. The

proposed dose is 3 tablets of GLE/PIB (total dose of 300 mg GLE and 120 mg PIB) once daily for 8 or 12 weeks depending on HCV genotype and cirrhotic status. Specifically, the applicant is seeking GLE/PIB for 8 weeks for all genotypes who are NC and TN. For TN, C patients, the proposed treatment duration is 12 weeks. Among TE, (b) (4)

(b) (4) The proposed dosing is provided in Table 4. The focus of this review will be on these proposed durations for the respective genotypes and subgroups. In addition, several changes to the applicant's proposed dosing and administration were made throughout the review cycle, which are summarized in Section 5.4.

Table 4: Applicant's Proposed Dosing and Administration for GLE/PIB

(b) (4)



Source: proposed GLE/PIB label dosing and administration

A summary of the nine clinical trials submitted in support of the NDA is provided below in Table 5 and Table 6. Among these trials, four were considered Phase 3 in design; two were comparative (ENDURANCE-2 included a placebo-control and ENDURANCE-3 including a SOF/DCV active-control), one (ENDURANCE-1) was a large trial comparing 8-and 12-week durations of GLE/PIB and one (EXPEDITION-4) enrolled subjects with chronic kidney disease stages 4 or 5 or subjects on dialysis. The remaining five trials were designed as Phase 2 trials, three of which were dose-finding trials. The five Phase 2 trials are included in the application and given weight in this review due to their inclusion of 1) subjects with less common genotypes like GT4, GT5, and GT6 and 2) subjects in various subgroups such as treatment-experienced GT3 subjects and subjects with cirrhosis. MAGELLAN-1, a Phase 2 trial, is the only trial that enrolled NS3/4A PI and/or NS5A-experienced subjects.

Table 5: List of Phase 2 Trials Included in Review

Trial ID (NAME)	Design	Population	HCV Treatment History	Treatment (proposed GLE/PIB regimen only)	Endpoint/Analysis
M14-867 (SURVEYOR-1)	NR, OL, MC, MP	Part 1 GT1, NC	TN or TE- PRS	<i>Part 2</i> Arm K (GT1 C): GLE/PIB 8W (n=34)	1°: SVR12 in ITT-PS 2°: SVR4, on-tx VF, post-tx relapse, both in ITT-PS
		Part 2 GT1, 4-6, NC or C		Arm I: (GT4-6 NC): GLE/PIB 12W (n=34)	
M14-868 (SURVEYOR-2)	R, OL, MC, MP	Part 1 GT2, NC or C Part 2 GT2-GT3, NC or C Part 3 GT3, NC or C Part 4 GT2, GT4- GT6, NC	TN or TE- PRS	<i>Part 1</i> Arm A (GT2 NC): GLE/PIB 12W (n=25) Arm D (GT3 NC): GLE/PIB 12W (n=30)	1°: SVR12 in ITT-PS 2°: SVR4, on-tx VF, post-tx relapse, both in ITT-PS
				<i>Part 2</i> Arm J (GT2 NC): GLE/PIB 8W (n=55) Arm L (GT3 NC): GLE/PIB 8w (TN) or 12w (TE) (n=53)	
				Arm O (GT3 C): GLE/PIB 12w (n=28)	
				<i>Part 3</i> Arm Q (GT3 TN C, TE NC): GLE/PIB 12w (n=62) Arm R (GT3 TE C, TE NC): GLE/PIB 16w (n=70)	
M14-172 (EXPEDITION-1)	Single-arm, NR, MC	GT1, GT2, GT4-GT6, C	TN or TE- PRS	GLE/PIB 12w (n=146)	1°: SVR12 (no formal hypothesis)

M15-410 (MAGELLAN-1)	R, OL, MC, MP	GT1, GT4- 6 (Part 2), NC or C	NS5A- and/or NS3/4A PI- experienced	<i>Part 1</i> Arm C (GT1 NC): GLE/PIB 12w (n=22) <i>Part 2</i> Arm D: GLE/PIB 12w (n=44) Arm E: GLE/PIB 16w (n=47)	1°: SVR12 in ITT-PS 2°: SVR4, on-tx VF, post-tx relapse, both in ITT-PS
M13-583 (ENDURANCE-4)	Single-arm, NR, OL, MC	GT4-6, NC	TN or TE- PRS	GLE/PIB 12w (n=121)	1°: SVR12 in ITT-PS 2°: On-tx VF, post-tx relapse, both in ITT-PS

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

Table 6: List of Phase 3 Trials Included in Review

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

M15-462 (EXPEDITION-4)	Single-arm, NR, OL, MC	GT1-6 w/ CKD stages 4, 5 or dialysis, NC or C	TN or TE- PRS	GLE/PIB 12w (n=104)	1°: SVR12 in ITT-PS 2°: On-tx VF, post-tx relapse, both in ITT-PS

R: randomized, MC: multi-center, NR: non-randomized, NI: non-inferiority, PC: placebo-control, OL: open-label, DB: double-blind, PG: parallel-group, AC: active controlled, TN: treatment-naïve, TE-PRS: treatment-experienced with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, GLE: glecaprevir, PIB: pibrentasvir, SOF: sofosbuvir, DCV: daclatasvir, NC: non-cirrhotic, C: cirrhotic, HC: historical control, 2°: secondary endpoint, 1°: primary endpoint, VF: virologic failure, CKD: chronic kidney disease, ITT-PS: intent-to-treat subset of HCV monoinfected DAA-naïve subjects, ITT-PS-PP: ITT-PS subset excluding subjects who prematurely discontinued prior to Week 8, subjects who experienced virologic failure prior to Week 8 (subjects with on treatment virologic failure before Day 52), subjects without virologic failure who had no HCV RNA value in the SVR12 visit window or later, and subjects who are SVR12 non-responders due to reinfection. Source: reviewer created

Breakthrough Therapy Designation

In April 2016, FDA granted Breakthrough Therapy Designation for GLE/PIB acknowledging the unmet medical need in GT1 DAA-experienced subjects.

2.2. Data Sources

The complete submission is located at the EDR Location: <\\CDSESUB1\evsprod\NDA209394\0000>.

Subject-level data, by trial, were provided as analyses legacy files (with relevant programs) and as tabulation (SDTM format) files.

3 STATISTICAL EVALUATION

3.1. Data and Analysis Quality

The quality of the datasets is sufficient for review. From the ADaM datasets, the applicant's calculations were recreated and confirmed. Each trial included an addeffout.xpt data file that was formatted in accordance with the FDA guidance on Efficacy Data Submission in ADaM Conversion for HCV Drugs. Little data processing was required from the ADaM data sets.

The applicant submitted the randomization scheme and codes in the eCTD of every trial that utilized randomization. The applicant also acknowledged its methods of data quality assurances, albeit briefly, in the protocol for the trials. Information regarding blinding was also included in the protocol for the trials. Statistical analysis plans were included in the eCTD.

The Office of Scientific Investigations was consulted in order to determine site inspections. The statistical reviewers were asked to provide a basic assessment of safety in order to help choose sites to be designated for inspection. OSI conducted a data audit regarding study M13-594 (ENDURANCE-3). The inspectors

uncovered minor discrepancies noting that it is “unlikely that the deviation impacted the outcome of the study in terms of validity or reliability of the submitted data”, according to the OSI report.

The Office of Computational Sciences provided assessment of the SDTM datasets submitted in the application and exploratory safety analyses. OCS illustrated some discrepancies in the data, but none has impacted the review of the application.

3.2. Evaluation of Efficacy

3.2.1. Trial Design Characteristics Common to Trials

Analysis Population

Unless otherwise specified, the primary analyses by the applicant was conducted in the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study drug.

Trial Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was defined as Sustained Virologic Response 12 (SVR12), defined as HCV RNA < Lower Limit of Quantification (LLOQ) 12 weeks after the end of all study therapy. The LLOQ pertain to an HCV RNA < 15 IU/mL for all trials except for SURVEYOR-1 and SURVEYOR-2, where LLOQ pertain to an HCV RNA < 25 IU/mL. This endpoint serves as the standard primary endpoint for trials for treating HCV infection and considered highly predictive of long-term virologic suppression or cure.

Specific Secondary Endpoints

- Sustained Virologic Response 4 weeks after the end of all study therapy (SVR4). The subject had HCV RNA < LLOQ 4 weeks after the end of all study therapy.

- Sustained Virologic Response 24 weeks after the end of all study therapy (SVR24). The subject had HCV RNA < LLOQ 24 weeks after the end of all study therapy.

Reviewer’s Comment: SVR24 data are incomplete for most subjects enrolled across the reviewed clinical trials as the trials were ongoing at time of NDA submission. SVR24 data will be submitted at a later time.

- 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 reviewers 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.

Failure to achieve SVR could be due to on-treatment virologic failure, post-treatment relapse, or missing SVR12 due to premature treatment discontinuation with no on-treatment virologic failure or missing data for the post-treatment week 12 assessment.

On-treatment virologic failure (OTVF) was defined as a confirmed increase of $>1 \log_{10}$ IU/mL above nadir during treatment, confirmed HCV RNA ≥ 100 IU/mL after HCV RNA $< \text{LLOQ}$ during treatment, or HCV RNA $\geq \text{LLOQ}$ at the end of treatment with at least 6 weeks of treatment.

Post-Treatment relapse was defined as a subject with a confirmed HCV RNA $\geq \text{LLOQ}$ [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 $\geq \text{LLOQ}$. Relapse was measured in subjects who completed planned treatment and therefore omits subjects who prematurely discontinued treatment.

Handling of Missing Values

A backward imputation approach was used for missing assessment for SVR, if possible. This approach used the nearest HCV RNA value after the SVR window. If this value was undetectable or unquantifiable, then it was used to impute the HCV RNA value in the SVR window. If after performing backward imputation, the subject is missing an HCV RNA value in the appropriate SVR window, then this value will be imputed using an HCV RNA value obtained from a local laboratory, if present and otherwise imputed as missing. Missing is treated as a failure in the primary analyses of SVR12. If a subject begins an alternative treatment for their HCV infection, then all HCV RNA values measured on or after initiation of new treatment were excluded from any analyses and the subject treated as a failure in the primary efficacy analysis.

Regarding values for virologic failure, if HCV RNA values from the central laboratory were missing but a local laboratory value is available that value was used to assess post-treatment relapse and OTVF.

Calculation of Confidence Intervals

In most instances, the applicant used a normal approximation to the binomial method (Wald method) to calculate confidence intervals. A 95% CI is expected to have a 95% coverage rate, defined as the proportion of times the interval contains the true value of interest. However, when using an asymptotic method, such as the Wald method, there is a decreased coverage rate when the response rate (e.g. SVR12) is close to 0% or 100%. Alternative methods, such as the Wilson score method provide adequate coverage levels closer to the nominal level of 95% for a 95% CI without being overly conservative like exact methods (e.g. Clopper-Pearson) when the response rate is close to 100% (Wilson, 1927). Therefore, unless otherwise specified, the reviewers' confidence intervals were calculated using the Wilson method.

3.2.2. Phase 2 Trials

The overall trial design is provided for each trial in the following sections. The overall trial outline can be found in Appendix A - Study Designs.

3.2.2.1 Trial M14-867 (SURVEYOR-1)

Trial Design

SURVEYOR-1 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety, efficacy, and pharmacokinetics of GLE/PIB in adults with HCV GT 1, 4, 5, and 6 infection who were TN or TE-PRS, with or without compensated cirrhosis. M14-867 contained two parts, where Part 2 and its treatment arms were initiated based on safety and efficacy results from Part 1. Those with HCV GT 1 were included in Part 1 and those with HCV GT 4, 5, or 6 were included in Part 2. Of those with compensated cirrhosis, only GT 1 was included in the trial and was only included in Part 2 of the trial. Only two arms in the study used the proposed dosage: Arms K and I-both included in Part 2. Data from Arms A, B, and F were included in total calculations but are not presented separately as they did not use the proposed dose of GLE/PIB. This study was not designed to test a formal hypothesis.

Subject Disposition

A total of 174 subjects were enrolled. The arms that utilized the proposed dosage, Arms K and I, were both in part 2 of the trial. All 174 enrolled subjects were treated. However, two subjects enrolled in Arm I were accidentally given the dosage used in Arm A. One subject was discontinued from the study drug on study day 43 due to non-compliance. The subject achieved SVR12. Another subject, randomized to Arm K, discontinued from the study drug on day 30 due to a SAE of adenocarcinoma and later died on study day 89 due to the adenocarcinoma. The subject did achieve SVR4 but died before SVR12 could be assessed. Four other subjects prematurely discontinued the trial: one who achieved SVR12 but discontinued on study day 234 due to suicide and three subjects who all achieved SVR12 but were considered lost to follow-up on study days 275, 291 and 312. The trial was considered completed at the time of the NDA submission.

Table 7: SURVEYOR-1 Subject Disposition

	<i>Total (n=174)</i>	<i>GLE/PIB 8 wk (K) (n=34)</i>	<i>GLE/PIB 12 wk (I) (n=34)</i>
Enrolled	174	34	34
Treated	174	34	32*
Completed Study Drug	172 (98.9)	33 (97.1)	32 (100)
Discontinued Study Drug	2 (1.1)	1 (2.9)	0
<i>Adverse event</i>	1	1	0
<i>Non-compliance</i>	1	0	0
Completed Trial	169 (97.1)	31 (91.2)	31 (96.9)
Ongoing in Trial	0	0	0
Discontinued Trial	5 (2.9)	3 (8.8)	1 (3.1)
<i>Adverse event</i>	2	1	0
<i>Lost to follow-up</i>	3	2	1

* Two subjects randomized to Arm I were accidentally given the dosage used in Arm A. The two subjects will be included in Arm I, according to the intent-to-treat principle. Source: reviewer created

Subject Demographics and Characteristics

Over 56% of the total subjects in the trial were male. The mean (sd) age of the subjects was 54 (10.0) years of age at baseline. About 84% of subjects were white. Approximately 81%, 13%, 6% of subjects

were GT1, GT4, and GT6, respectively. Less than 1% of subjects were GT5. About 74% of subjects in the trial were treatment-naïve with the remainder being PR-experienced. Approximately 16% of subjects had cirrhosis at baseline. The mean (sd) log₁₀ copies/mL of HCV RNA was 6.52 (0.73) log₁₀ copies/mL. About 83% of the subjects were enrolled at a site in the U.S., including Puerto Rico.

It should be noted that Arm K consisted only of GT1-infected subjects without cirrhosis and Arm I consisted only of GT4, GT5, and GT6 subjects without cirrhosis. There was no randomization between the arms so balanced distributions of characteristics is not expected. The two arms were relatively unbalanced in terms of race and region, as to be expected given the genotypes enrolled in each arm.

Table 8: SURVEYOR-1 Baseline Characteristics/Demographics

	<i>Total (n=174)</i>	<i>GLE/PIB 8 wk (K) (n=34)</i>	<i>GLE/PIB 12 wk (I) (n=34)</i>
Males	98 (56.3)	19 (55.9)	18 (52.9)
Mean (sd) age	54.1 (10.0)	53.5 (10.3)	54.9 (10.8)
Race (majority)			
White	146 (83.9)	33 (97.1)	20 (58.8)
Black	16 (9.2)	1 (2.9)	4 (11.8)
Asian	10 (5.7)	0 (0)	9 (26.5)
HCV genotype			
GT 1	140 (80.5)	34 (100)	0
GT 4	22 (12.6)	0	22 (64.7)
GT 5	1 (0.6)	0	1 (2.9)
GT 6	11 (6.3)	0	11 (32.4)
Treatment Experience			
Treatment Naïve	129 (74.1)	29 (85.3)	29 (85.3)
P/R Experienced	45 (25.9)	5 (14.7)	5 (15.6)
Cirrhosis Status			
Non-Cirrhotic	147 (84.5)	34 (100)	34 (100)
Cirrhotic	27 (15.5)	0	0
Mean (sd) log ₁₀ HCV RNA	6.52 (0.73)	6.31 (0.72)	6.33 (1.05)
IL28 Genotype			
CC	44 (25.3)	11 (32.4)	13 (38.2)
CT	97 (55.7)	17 (50.0)	14 (41.2)
TT	33 (19.0)	6 (17.6)	7 (20.6)
Region*			
North America	154 (88.5)	34 (100)	23 (67.6)
Rest of the World	20 (11.5)	0	11 (32.4)

*Subjects enrolled in 4 countries, 145 (83.3%) of the subjects were enrolled at a site in the US, including Puerto Rico; source: reviewer created

Statistical Methods

The number and percentage of subjects in the ITT population that achieved SVR12 were summarized. The applicant utilized a 2-sided 95% CI, calculated using the Wilson score method, to summarize the SVR12 percentages.

Secondary efficacy endpoints were the percentage of subjects that 1) achieved SVR4, 2) experienced on-treatment VF, and 3) experienced post-treatment relapse, both summarized using 95% CIs calculated using the Wilson score method.

Efficacy Findings

All but three subjects achieved SVR12. Two subjects experienced post-treatment relapse, but neither subject received the proposed dosage. One subject in Arm K did not achieve SVR12: the subject that prematurely discontinued from the study before the SVR12 assessment due to death. The subject was a 67-year-old white female, GT1a, treatment-naïve subject with a baseline HCV RNA of 8,550 copies/mL (3.93 log₁₀ copies/mL). The subject did achieve SVR4.

Table 9: SURVEYOR-1: SVR12 and Other Outcomes for GLE/PIB 8 and 12-week Regimens

	<i>GLE/PIB 8 wk (K)</i> <i>(n=34)</i>	<i>GLE/PIB 12 wk (I)</i> <i>(n=34)</i>
SVR12	ITT-PS: 33/34 (97.1) (95% CI: 85.1, 99.5)	ITT-PS: 34/34 (100) (95% CI: 89.8, 100)
OTVF	0/34 (0)	0/34 (0)
Relapse	0/34 (0)	0/34 (0)
Other	1/34 (2.9)	0/34 (0)

Source: reviewer created

Subgroup Analyses

Given the small differences in SVR12 and the small sample sizes of the subgroups, it is not feasible to calculate subgroup estimates within this trial. Pooled subgroup analyses are provided in Section 4.

3.2.2.2 Trial M14-868 (SURVEYOR-2)

Trial Design

SURVEYOR-2 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety and efficacy of GLE/PIB, co-administered or combined, with or without ribavirin (RBV) in adults with HCV GT 2, 3, 4, 5, or 6 infection who were TN or TE-PRS with or without cirrhosis. M14-868 contains four parts – Parts 1 and 2 are considered “supportive/exploratory” and Parts 3 and 4 are considered “confirmatory/registrational”, according to the applicant. Those with HCV GT 4, 5, or 6 were included in Part 4 only and those with cirrhosis were included in Parts 2 and 3 only. Treatment arms in Parts 2 and 3 were opened for enrollment based on safety and efficacy data from Parts 1 and 2, respectively. This study was not designed to test a formal hypothesis.

The following provides descriptions of the subjects and treatment durations in all treatment arms that evaluated the proposed dose:

Part 1

- Arm A: GT2, TN and TE without cirrhosis; 12 weeks
- Arm D: GT3, TN and TE without cirrhosis; 12 weeks

Part 2

- Arm J: GT2, TN and TE without cirrhosis; 8 weeks
- Arm L: GT3, TN and TE without cirrhosis; 8 weeks for TN (L_{TN}), 12 weeks for TE (L_{TE})
- Arm O: GT3, TN with cirrhosis; 12 weeks

Part 3

- Arm Q: GT3 TN with cirrhosis and TE without cirrhosis; 12 weeks
- Arm R: GT3, TE with and without cirrhosis; 16 weeks

NOTE: Subjects that are GT3 TE without cirrhosis were randomized to Arms Q and R in a 1:1 ratio.

Part 4

- Arm S: GT2, GT4-6, TN and TE without cirrhosis; 8 weeks

Results from treatment arms that did not use the proposed dose will not be presented separately.

Subject Disposition

A total of 694 subjects were enrolled, some of whom were randomized. Of those enrolled, 691 subjects received the study drug. Two of the untreated subjects were randomized in error while the third subject was unable to swallow the pills. Two of the three subjects that did not receive the study drug were enrolled in arms that received the recommended dosage.

A total of 679 subjects completed the study drug with 15 subjects discontinuing prematurely from the study drug. The 15 subjects include the three subjects that never received the study drug.

Of the 15 subjects that discontinued from the study drug, five subjects also prematurely discontinued from the trial. One subject discontinued due to adverse events and achieved SVR4 and SVR12. One subject discontinued due to non-compliance and did not achieve SVR4 or SVR12. One subject was lost to follow-up, and two subjects withdrew consent. All three have missing SVR4 and SVR12 values.

Seven subjects discontinued prematurely from the study drug but not the study. Three subjects were discontinued due to virologic failure on study days 39, 58, and 84. None of them achieved SVR4 or SVR12. Two subjects were considered lost to follow-up and were discontinued from the study drug on study days 16 and 72. Both have missing SVR4 and SVR12 values. One subject discontinued on study day 82 due to an adverse event and one subject was discontinued on study day 72 due to non-compliance. Both subjects achieved SVR4 and SVR12.

Of the 19 subjects that discontinued from the trial, seven subjects were considered lost to follow-up. Five of the subjects achieved SVR12 while an additional subject who discontinued on study day 458, achieved SVR4 but was missing a value for SVR12. The other subject, discontinued on study day 339, had missing SVR4 and SVR12 values.

In addition, two subjects discontinued from the trial on study days 227 and 270 due to adverse event. One of the subjects was enrolled in an arm with the recommended dosage, Arm A. Both subjects achieved SVR12. One subject experienced relapse before post-treatment Week 4, enrolled in another study, and was discontinued from the study on study day 249. One subject withdrew consent and was discontinued on study day 57. The subject has missing values for SVR4 and SVR12.

At the time of the NDA submission, Parts 1 and 2 of the trial were completed with most subjects still ongoing in Parts 3 and 4.

Table 10: SURVEYOR-2 Disposition (By Genotype)

	<i>Total</i> (n=691)	<i>GT1</i> [^] (n=4)	<i>GT2</i> (n=269)	<i>GT3</i> (n=360)	<i>GT4</i> (n=46)	<i>GT5</i> (n=2)	<i>GT6</i> (n=10)
Randomized	694	4	270	362	46	2	10
<i>Treated</i>	691*	4	269	360	46	2	10
	(99.6)	(100)	(99.6)	(99.4)	(100)	(100)	(100)
Completed Study	679 (97.8)	4	266	352	45	2	10
<i>Drug</i>		(100)	(98.9)	(97.8)	(97.8)	(100)	(100)
Discontinued Study	15 (2.2)	0				0	0
<i>Drug</i>							
<i>Adverse event</i>	2	0	0	2	0	0	0
<i>Lost to follow up</i>	3	0	1	2	0	0	0
<i>Non-compliance</i>	2	0	0	1	1	0	0
<i>Virologic failure</i>	3	0	0	3	0	0	0
<i>Withdrawal by</i>	2	0	2	0	0	0	0
<i>subject</i>							
<i>Other</i>	3	0	0	0	0	0	0
Completed Trial	346 (49.9)	2 (50.0)	121 (45.0)	223 (61.9)	0	0	0
Ongoing in Trial	329 (47.4)	2 (50.0)	143 (53.2)	127 (35.3)	45 (97.8)	2 (100)	10 (100)
Discontinued Trial	19 (2.7)	0	5 (1.9)	10 (2.8)	1 (2.2)	0	0
<i>Adverse event</i>	3	0	1	2	0	0	0
<i>Lost to follow-up</i>	8	0	2	6	0	0	0
<i>Withdrawal by</i>	3	0	2	1	0	0	0
<i>subject</i>							
<i>Other</i>	5	0	0	1	1	0	0

[^] The four subjects that were GT1 were initially believed to be GT2 at enrollment.

* Three randomized subjects did not receive the study drug: one subject in Arms E, J, and R each.

Analysis of subject disposition by treatment arm did not reveal any unusual frequencies of study drug discontinuation or study discontinuation by arm.

Subject Demographics and Characteristics

About 67% of the subjects in the trial were male. The mean (sd) age of all subjects was 53 (11) years. About 39%, 52%, 7%, and 1% of subjects were GT2, GT3, GT4, and GT6, respectively. Less than 1% of subjects were GT1 or GT5. The GT1 subjects enrolled in the trial were initially believed to be GT2 until further testing determined otherwise. Approximately 75% of subjects were treatment-naïve, with 18% being PR-experienced and 7% being DAA-experienced. About 21% of all subjects have cirrhosis. The mean (sd) log₁₀ HCV RNA at baseline was 6.35 (0.86) log₁₀ copies/mL and 71% of the subjects were enrolled at a site in the United States.

Given that randomization occurred within individual parts of the trial, the parts are not expected to be balanced in terms of the means and percentages of baseline characteristics and demographics.

Table 11: SURVEYOR-2 - Baseline Characteristics/Demographics

	Total (n=691)	GT1* (n=4)	GT2 (n=269)	GT3 (n=360)	GT4 (n=46)	GT5 (n=2)	GT6 (n=10)
Males	398 (57.6)	2 (50.0)	139	220	29	0	8 (80.0)
Mean (sd) age	52.9 (11.1)	53.0 (7.0)	53.9 (11.4)	52.8 (10.1)	47.5 (14.5)	55.0 (17.0)	50.9 (9.9)
Race (majority)							
White	600 (86.8)	4 (100)	234 (87.0)	327 (90.8)	33 (71.7)	1 (50.0)	1 (10.0)
Black	33 (4.8)	0	17 (6.3)	6 (1.7)	10 (21.7)	0	0
Asian	44 (6.4)	0	12 (4.5)	19 (5.3)	3 (6.5)	1 (50.0)	9 (90.0)
Treatment Experience							
Treatment Naïve	516 (74.7)	2 (50.0)	238 (88.5)	227 (63.1)	39 (84.8)	2 (100)	8 (80.0)
P/R Experienced	127 (18.4)	2 (50.0)	25 (9.3)	91 (25.3)	7 (15.2)	0	2 (20.0)
DAA Experienced	48 (6.9)	0	6 (2.2)	42 (11.7)	0	0	0
Cirrhotic Status							
Non-Cirrhotic	549 (79.5)	4 (100)	269 (100)	218 (60.6)	46 (100)	2 (100)	10 (100)
Cirrhotic	142 (20.5)	0	0	142 (39.4)	0	0	0
Mean (sd) log ₁₀ HCV RNA	6.35 (0.86)	6.20 (0.83)	6.49 (0.95)	6.35 (0.73)	5.49 (0.67)	5.23 (0.03)	6.83 (0.85)
IL28 Genotype							
CC	274 (39.7)	1 (25.0)	128 (47.6)	126 (35.0)	11 (23.9)	0	8 (80.0)
CT	318 (46.0)	3 (75.0)	102 (37.9)	185 (51.4)	26 (56.5)	0	2 (20.0)
TT	99 (14.3)	0	39 (14.5)	49 (13.6)	9 (19.6)	2 (100)	0
Region*							
North America	544 (78.7)	4 (100)	244 (90.7)	256 (71.1)	34 (73.9)	2 (100)	4 (40.0)
Europe	12 (1.7)	0	0	12 (3.3)	0	0	0
Rest of the World	135 (19.5)	0	25 (9.3)	92 (25.6)	12 (26.1)	0	6 (60.0)

^ The four GT1 subjects, one in Arms A and C each and two in Arm S, were believed to be GT2 at enrollment

*Subjects enrolled in 8 countries, 493 (71.0%) of the subjects were enrolled at a site in the US

Statistical Methods

The number and percentage of subjects in the ITT population that achieved SVR12 were summarized. The applicant utilized a 2-sided 95% CI, calculated using the Wilson score method, to summarize the SVR12 percentages.

For GT2, DAA-naïve subjects without cirrhosis in Part 4, the observed SVR12 rate was compared to the pre-specified clinical threshold of SVR12 rate representing the current standard of care, SOF + RBV for 12 weeks, for non-inferiority, according to the applicant. The SVR12 rate was defined as 89% and non-inferiority was concluded if the lower bound of the 95% CI of SVR12, calculated using the normal approximation, was greater than 89%.

Reviewer's Comment: Rather than utilizing an active control arm in this trial, the applicant compared SVR12 rate using an external, clinically acceptable threshold of 89%. Therefore, this comparison is not viewed as a non-inferiority comparison by the reviewers and should not be referenced as such. A more accurate description for the comparison is an assessment to determine if the SVR12 rate meets the threshold of 89%, based on the lower bound of the 95% CI.

Secondary efficacy endpoints were the percentage of subjects that 1) achieved SVR4, 2) experienced on-treatment VF and 3) experienced post-treatment relapse, both summarized using 95% CIs calculated using the Wilson score method.

Efficacy Findings

SVR12 was high across the treatment arms with the recommended dosage and their subgroups. Of those who did not achieve SVR12, 11 subjects have non-virologic failures. Two of the non-virologic failures included one subject in Arm J and one cirrhotic subject in Arm R that never received the study drug. The other non-virologic failures included the subjects in Arm A, G, and J that discontinued from the study drug and the trial as well as the subjects that discontinued from the trial on study days 57 and 339. The subjects are described with the subject disposition section for this trial. The other non-virologic failures were missing SVR12 values.

Three subjects experienced on-treatment virologic failure in the treatment arms with the recommended dosage:

1. A 51 year old white male, GT3a, PR-experienced non-cirrhotic subject with baseline HCV RNA of 6.54 log₁₀ copies/mL who received GLE/PIB 300 mg/120 mg for 12 weeks. The subject never achieved viral suppression at any point of the trial.
2. A 56 year old white male, GT3a, PR-experienced cirrhotic subject with baseline HCV RNA of 7.24 log₁₀ copies/mL who received GLE/PIB 300 mg/120 mg for 16 weeks. The subject experienced virologic breakthrough on study day 71 and was discontinued from the study drug on study day 90. The subject did not achieve SVR4 or SVR12.

Reviewer's Comment: It should be noted that both subjects that experienced on-treatment virologic failure enrolled in the same site under the same investigator.

Nine subjects experienced post-treatment relapse in the treatment arms with the recommended dosage. Seven of the nine subjects were male and all nine were white. Seven of the nine subjects were GT3a-infected. Similarly, seven of the nine subjects were PR-experienced while the other two were DAA-experienced. Two of the subjects have cirrhosis. Three of the subjects relapsed before post-treatment Week 2, three others relapsed before post-treatment Week 4, and two subjects relapsed before post-treatment Week 8. Two of the nine subjects achieved SVR4 while the other seven did not.

Table 12: SURVEYOR-2: SVR12 and Other Outcomes

	<i>SVR12</i>	<i>OTVF</i>	<i>Relapse</i>	<i>Other</i>
Arm A	24/25 (96.0) (95% CI: 80.5, 99.3)	0	0	1/25 (4.0)
Arm D	28/30 (93.3) (95% CI: 78.7, 98.2)	0	1/30 (3.3)	1/30 (3.3)
Arm J	53/55 (96.4) (95% CI: 87.7, 99.0)	0	0	2/55 (3.6)
Arm L _{TN}	28/29 (96.6) (95% CI: 82.8, 99.4)	0	0	1/29 (3.4)
Arm L _{TE}	22/24 (91.7) (95% CI: 74.2, 97.7)	1/24 (4.2)	1/23 (4.3)	0
Arm O	27/28 (96.4) (95% CI: 82.3, 99.4)	0	1/28 (3.6)	0
Arm Q (TN, C)	39/40 (97.5) (95% CI: 87.1, 99.6)	0	0	1/40 (2.5)
Arm Q (TE, NC)	20/22 (90.9) (95% CI: 72.2, 97.5)	0	2/22 (9.1)	0
Arm R (TE, NC)	21/22 (95.5) (95% CI: 78.2, 99.2)	0	1/22 (4.5)	0
Arm R (TE, C)	45/48 (93.8) (95% CI: 83.2, 97.9)	1/48 (2.1)	1/46 (2.2)	1/48 (2.1)
Arm S (GT2*)	142/145 (97.9) (95% CI: 94.1, 99.3)	0	2/144 (1.4)	1/145 (0.7)
Arm S (GT4-6)	54/58 (93.1) (95% CI: 83.6, 97.3)	0	0	4/58 (6.9)

* These numbers include two subjects who were later found to be GT1; both subjects achieved SVR12

For GT-2 infected, DAA-naïve, non-cirrhotic subjects in Arm S, 135/137 (98.5%) achieved SVR12 with a Wilson score interval 95% CI of 94.8%, 99.6% and a normal approximation 95% CI of 96.5%, 100%. Both confidence intervals have a lower bound greater than 89%, leading to a conclusion of superiority to the pre-specified clinical threshold.

SVR12 for GT3-infected, treatment-experienced, non-cirrhotic subjects in Arm R was 95.5% (21/22) while SVR12 for the same subpopulation in Arm Q was 90.0% (20/22). Of this subpopulation, two subjects relapsed in Arm Q while only one relapsed in Arm R. No formal comparison of SVR12 for Arm Q vs. Arm R was conducted for this subpopulation.

Subgroup Analyses

Given the small differences in SVR12 and the small sample sizes of the subgroups, it is not feasible to calculate subgroup estimates within this trial. Pooled subgroup analyses are provided in Section 644.

3.2.2.3 Trial M14-172 (EXPEDITION-1)

Trial Design

EXPEDITION-1 was a Phase 2, single-arm, open-label, multicenter study to evaluate the safety and efficacy of a 12-week regimen of GLE/PIB for treating GT 1, 2, 4, 5 or 6 HCV-infected adult subjects with compensated cirrhosis who are either TN or TE-PRS. This study lacked a formal hypothesis but did include a target sample size of 175 subjects with liver cirrhosis.

Reviewer's Comment: In the End-of-Phase 2 guidance, the division recommended that this trial include a placebo-control as the target population for this study, e.g. patients with compensated cirrhosis (CTP-A) are usually not more urgently in need of treatment compared to non-cirrhotic patients. However, as noted this trial was single-arm only. While described as a Phase 3 trial, the reviewer views this as a Phase 2 given the lack of a formal statistical hypothesis or inferential statistics.

Subject Disposition

Among the 146 enrolled subjects, two subjects prematurely discontinued study drug on days 48 and 78, respectively. Both achieved SVR4 and SVR12 and remained on study for purposes of follow-up. The trial was ongoing at time of the NDA submission at which time 140 subjects were ongoing in the trial; three subjects completed the trial and three were discontinued.

Subject Demographics and Characteristics

Over 61% of subjects enrolled were male and the mean (SD) age was 60 (10) years of age at time of enrollment. Over 80% of all enrolled were white and 10% were Black. This trial enrolled both TN (75%) and TE (25%) subjects. Among the TE subjects, 69% had received a prior IFN-based and the 30% had received a SOF-based HCV treatment regimen, 42% had suffered a prior treatment relapse and 25% were prior treatment non-responders. Mean (SD) HCV RNA ($\log_{10}$) was baseline was 6.1 (0.7) c/mL and the proportion of subjects with baseline HCV RNA ≥ 6 million c/mL and ≥ 10 million c/mL was 11.6% and 4%, respectively. Thirty subjects (20.5%) were diabetic at baseline.

Of this small cohort of compensated cirrhotic subjects, the baseline Child-Pugh score 5 for the majority (87%), score 6 for 12% and greater than 6 for less than 1% of subjects. Few subjects overall were enrolled with a Child-Pugh score of 6 or greater, which is a marker of more severe cirrhosis disease. Therefore, findings from this study may not fully extrapolate to HCV infected subjects with more advanced cirrhosis. Refer to the clinical review for a more detailed assessment of baseline cirrhosis severity in this trial.

The proportion (number) of enrolled subjects by genotype was 59.6% (87) GT1, 23.2% (34) GT2; 11%% (16) GT4, 1.4 (2) GT5 and 4.8% (7) GT6. The breakdown by treatment experience is provided by GT below in Table 13. The trial enrolled subjects in Europe (31%), North America (67%), and South Africa (2%).

Table 13: EXPEDITION-1: Subjects Enrolled by Prior Treatment Status

GLE/PIB 12W N=146		
	TN/TE	Total
GT 1 TN/TE	66/21	87
GT2 TN/TE	24/10	34
GT4 TN/TE	12/4	16
GT5 TN/TE	2/0	2
GT6 TN/TE	6/1	7

Source: reviewer created

Reviewer's Comment: These trials used two different methods for genotyping/sub-genotyping HCV; phylogenetic analyses and central laboratory. The number presented in Table 13 and elsewhere in this review are based on the applicant's reporting of genotyping according to the central laboratory results (variable: HCVGTC). In some instances, here for example, there were a few discordant results between the two methods. In the EXPEDITION-1 trial, there were three subjects genotyped as GT2 via central laboratory but GT1 by phylogenetic analyses.

Statistical Methods

The number and percentage of all enrolled subjects achieving SVR12 was described via a two-sided 95% CI calculated using the Wilson method due to the high rate of SVR12.

Efficacy Results

All but one subject achieved SVR12; however all subjects achieved SVR4. The single failure was a relapse in a treatment-experienced (P/R experienced), GT1a-infected male subject who relapsed on day 57 with a viral load of 956 c/mL, which increased to 400,000 c/mL by follow-up week 12. The average time (days) to becoming SVR negative was 23 with a median days of 17 and range of 7-59. Overall SVR12 and results by GT and treatment status are provided in Table 14.

Table 14: EXPEDITION-1 SVR12 and Relapse Overall and by GT and Treatment Status

		<i>GLE/PIB 12W (n=146)</i>
SVR12 Overall		145 (99.3%)
	<i>95% CI (Wilson)</i>	96.2, 99.9
	Relapse	1 (0.7), GT1
<i>SVR12 (95% CI) by GT and Treatment Status</i>		
	<i>GT1 TN/TE</i>	66/66 (94.5, 100); 20/21 (77.3, 99.1)
	<i>GT2 TN/TE</i>	24/24 (86.2, 100); 10/10 (72.2, 100)
	<i>GT4 TN/TE</i>	12/12 (75.7, 100); 4/4
	<i>GT5 TN</i>	2/2
	<i>GT6 TN/TE</i>	6/6 (61, 100); 1/1

CIs not calculated for sample sizes ≤ 5 ; Source: reviewer created

Given the lack of a comparator group and the high SVR12, the reviewer did not perform subgroup analyses of this Phase 2 trial. Findings from this trial were considered in pooled analyses, which are discussed later in the review.

3.2.2.4 Trial M13-583 (ENDURANCE-4)

Trial Design

ENDURANCE-4 was a single-arm, open label Phase 3 trial that evaluated the safety and efficacy of GLE/PIB in adults with HCV GT 4, 5, or 6 infection without cirrhosis who were treatment-naïve or treatment-experienced. M13-583 had duration of 36 weeks, 12 weeks of treatment plus 24 weeks of post-treatment follow-up.

Reviewer’s Comment: While described as a Phase 3 trial, the reviewer views this as a Phase 2 given the lack of statistical testing.

Subject Disposition

Among the 121 enrolled and treated subjects, two subjects prematurely discontinued the study drug: one on day 26 due to non-compliance and one on day 73 due to an adverse event. Both subjects achieved SVR4 and SVR12. An additional subject discontinued the study drug on day 12 due to an adverse event and later withdrew from the trial on day 16 due to an adverse event. The subject did not achieve SVR4. At the time of the NDA submission, 92 subjects were still participating in the trial.

Table 15: ENDURANCE-4: Subject Disposition

	<i>GLE/PIB 12w (n=121)</i>
Enrolled	121
<i>Treated</i>	<i>121</i>
Completed Study Drug	118 (97.5)
Discontinued Study Drug	3 (2.5)
<i>Adverse event</i>	<i>2</i>
<i>Non-compliance</i>	<i>1</i>
Completed Trial	28 (23.1)
Ongoing in Trial	92 (76.0)
Discontinued Trial	1 (0.8)
<i>Withdrawal by subject</i>	<i>1</i>

Source: reviewer created

Subject Demographics and Characteristics

Over 63% of subjects were male and the mean (sd) age was 53 (11) years of age at baseline. Approximately 69% of the subjects were white. Approximately 63%, 22%, and 16% of subjects were GT4, GT5, and GT6, respectively. About 32% of subjects were P/R experienced while the remainder were treatment naïve. The mean (sd) log₁₀ copies/mL of HCV RNA was 6.12 (0.66) log₁₀ copies/mL.

About 8% of the subjects enrolled at a site in North America; none of the subjects enrolled at a site in the United States.

Table 16: ENDURANCE-4 Baseline Characteristics/Demographics

		<i>GLE/PIB 12 wk (n=121)</i>
Males		77 (63.6)
Mean (sd) age		52.7 (11.0)
Race (majority)		
	White	84 (69.4)
	Asian	24 (19.8)
	Black	8 (6.6)
HCV genotype		
	GT 4	76 (62.8)
	GT 5	26 (21.5)
	GT 6	19 (15.7)
Treatment Experience		
	Treatment Naïve	82 (67.8)
	P/R Experienced	39 (32.2)
Mean (sd) log ₁₀ HCV RNA		6.12 (0.66)
IL28 Genotype		
	CC	30 (24.8)
	CT	68 (56.2)
	TT	23 (19.0)
Region*		
	North America	10 (8.3)
	Europe	100 (82.6)
	Rest of the World	11 (9.1)

*Subjects enrolled in eight countries, none of the subjects was enrolled at a site in the US
 Source: reviewer created

Statistical Methods

The number and percentage of subjects in the ITT population that achieved SVR12 were summarized. The applicant utilized a 2-sided 95% CI, calculated using the normal approximation to the binomial distribution, to summarize the SVR12 percentages. If SVR12 was 100%, the applicant indicated that the Wilson score method would be used to calculate the 95% CI.

Secondary efficacy endpoints were the percentage of subjects that 1) experienced on-treatment VF and 2) experienced post-treatment relapse, both summarized using 95% CIs calculated using the Wilson score method. Only completers, subjects receiving study drug for 77 days or more, were included in the analysis of relapse.

Efficacy Findings

All subjects achieved SVR12 except for the subject that withdrew early from the trial. The subject is a 49-year-old white male, GT4a, PR-experienced subject with baseline HCV RNA of 417,000 copies/mL (5.62 log₁₀ copies/mL). This subject had a missing value for SVR12 and a positive value for SVR4 and a change of -4.28 log₁₀ copies/mL HCV RNA.

Table 17: ENDURANCE-4 SVR12

	<i>GLE/PIB 12W</i> <i>(n=121)</i>
SVR12	ITT-PS: 120/121 (99.2) (Wilson* 95% CI: 95.5, 99.9)
OTVF	0/121 (0)
Relapse	0/118 (0)
Other	1/121 (0.8)

Source: reviewer created

* The applicant used the normal approximation to the binomial distribution to calculate the 95% CI for SVR12. Their reported CI is 97.6, 100. Both CIs reach similar conclusions but the Wilson CI has preferable coverage rates to the normal CI.

Subgroup Analyses

Given the small differences in SVR12 due to only one subject not achieving SVR12, it is not feasible to calculate subgroup estimates within this trial. Pooled subgroup analyses are provided in Section 4.

3.2.2.5 Trial M15-410 (MAGELLAN-1)

Trial Design

MAGELLAN-1 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety, efficacy, and pharmacokinetics of GLE/PIB, co-administered or combined, with or without RBV in adults with HCV GT 1, 4, 5, and 6 infection who failed a prior anti-HCV DAA-containing regimen. The trial contained two parts, with Part 2 initiated based on achieving safety and efficacy criteria in Part 1. Those with HCV GT 4, 5, or 6 were included in Part 2 only. Additionally, all subjects in Part 2 had compensated liver disease with or without cirrhosis. Only Arm C in Part 1 and Arms D and E in Part 2 used the proposed dosage. Data from Arms A and B are included in total calculations but are not presented separately as they did not use the proposed dose of GLE/PIB. Note that randomization occurred in a 1:1 ratio between Arms D and E. This study was not designed to test a formal hypothesis, although hypothesis testing was conducted.

Subject Disposition

Of the 141 total subjects, all were treated as assigned. Five subjects were discontinued from the study drug due to virologic failure (Table 18). The subjects were discontinued on study days 47, 67, 80, 87, and 90. All five subjects did not achieve SVR4 or SVR12. Among subjects enrolled in arms including the proposed GLE/PIB dose and durations (Arms C-E), three subjects prematurely discontinued from the trial: one subject discontinued on study day 184 due to adverse event, one subject was considered lost to follow-up on study day 141, and one subject withdrew consent on study day 183 due to post-treatment relapse. The subject that withdrew consent did not achieve SVR4 or SVR12 while the other two subjects achieved SVR4 but have missing values for SVR12. An additional subject discontinued from the study drug on study day 44 and discontinued from the trial on study day 409 and is considered lost to follow-up. The subject achieved SVR12.

Subjects were randomized within the two parts of the trial. Subjects in Part 1 were randomized in a 1:1:1 ratio for Arms A, B, and C until Arm A was discontinued. Subjects in Part 2 were randomized in a 1:1 ratio for Arms D and E.

Table 18: MAGELLAN-1 Subject Disposition

	<i>Total</i> (n=141)	<i>GLE/PIB</i> <i>12 wk (C)</i> (n=22)	<i>GLE/PIB</i> <i>12 wk (D)</i> (n=44)	<i>GLE/PIB</i> <i>16 wk (E)</i> (n=47)
Randomized	141	22	44	47
<i>Treated</i>	<i>141</i>	<i>22</i>	<i>44</i>	<i>47</i>
Completed Study Drug	135 (95.7)	21 (95.5)	44 (100)	43 (91.5)
Discontinued Study Drug	6 (4.3)	1 (4.5)	0	4 (8.5)
<i>Virologic failure</i>	5	1	0	4
<i>Loss to follow-up</i>	1	0	0	0
Completed Trial	47 (33.3)	20 (90.9)	0	0
Ongoing in Trial	90 (63.8)	0 (9.1)	43 (97.7)	47 (100)
Discontinued Trial	4 (2.8)	2	1 (2.3)	0
<i>Adverse event</i>	1	1	0	0
<i>Lost to follow-up</i>	2	1	0	0
<i>Withdrew consent</i>	1	0	1	0

Source: reviewer created; note that the total column includes all assigned subjects including subjects assigned to Arms C-E

Subject Demographics and Characteristics

About 75% of the subjects were male. The mean (sd) age of the subjects was 56 (8) years of age at baseline. Over 72% of the subjects were white. About 97% of subjects in the trial were GT1, while the others were GT4. One-third, 33%, of the subjects was NS5A and NS3/4A PI-experienced. About 37% of subjects were NS5A-naïve and NS3/4A PI-experienced and 30% were NS5A-experienced and NS3/4A PI-naïve. Approximately 19% of the subjects have cirrhosis. The mean (sd) log₁₀ copies/mL of HCV RNA at baseline was 6.27 (0.62). About 69% of subjects were enrolled at a site in the United States, including Puerto Rico (Table 19).

Because subject randomization occurred within Parts 1 and 2 separately, it is expected that Arms D and E have balanced distributions of characteristics and demographics. Most of the characteristics were balanced between Arms D and E. However, Arm E had a lower percentage of cirrhotic subjects, a slightly higher mean log₁₀ HCV RNA at baseline, and a slightly higher percentage of NS5A-experienced subjects compared to Arm D.

Table 19: MAGELLAN-1 Baseline Characteristics/Demographics

	<i>Total (n=141)</i>	<i>GLE/PIB 12 wk (C) (n=22)</i>	<i>GLE/PIB 12 wk (D) (n=44)</i>	<i>GLE/PIB 16 wk (E) (n=47)</i>
Males	105 (74.5)	18 (81.8)	31 (70.5)	33 (70.2)
Mean (sd) age	55.9 (7.9)	58.5 (6.6)	55.6 (8.6)	55.6 (8.3)
Race				
White	102 (72.3)	12 (54.5)	34 (77.3)	35 (74.5)
Black	37 (26.2)	10 (45.5)	9 (20.5)	11 (23.4)
Asian	2 (1.4)	0	1 (2.3)	1 (2.1)
HCV genotype				
GT 1	137 (97.2)	22 (100)	43 (97.7)	44 (93.6)
GT 4	4 (2.8)	0	1 (2.3)	3 (6.4)
Treatment Experience				
NS5A & NS3/4A PI Experienced	47 (33.3)	7 (31.8)	14 (31.8)	16 (34.0)
NS5A Experienced & NS3/4A PI Naïve	42 (29.8)	4 (18.2)	16 (36.4)	18 (38.3)
NS3/4A Experienced & NS5A Naïve	52 (36.9)	11 (50.0)	14 (31.8)	13 (27.7)
Cirrhotic Status				
Non-Cirrhotic	114 (80.9)	22 (100)	29 (65.9)	35 (74.5)
Cirrhotic	27 (19.1)	0	15 (34.1)	12 (25.5)
Mean (sd) log ₁₀ HCV RNA	6.27 (0.62)	6.55 (0.51)	6.01 (0.66)	6.24 (0.56)
IL28 Genotype				
CC	22 (15.6)	3 (13.6)	6 (13.6)	5 (10.6)
CT	87 (61.7)	14 (63.6)	27 (61.4)	30 (63.8)
TT	31 (22.0)	5 (22.7)	11 (25.0)	11 (23.4)
Unknown	1 (0.7)	0	0	1 (2.1)
Region*				
North America	97 (68.8)	22 (100)	23 (52.3)	24 (51.1)
Europe	20 (14.2)	0	8 (18.2)	12 (25.5)
Rest of the World	24 (17.0)	0	13 (29.5)	11 (23.4)

*Subjects enrolled in 5 countries, 97 (68.8%) of the subjects were enrolled at a site in the US, including Puerto Rico; source: reviewer created

Statistical Methods

The applicant utilized a 2-sided 95% CI, calculated using the Wilson score method, to summarize the SVR12 percentages in the ITT population. The differences between treatment arms were tested using the Mantel-Haenszel proportion with a continuity correction for variance to adjust for each randomization stratum. The differences were tested using Fisher's exact test.

Secondary efficacy endpoints were the percentage of subjects that 1) achieved SVR4, 2) experienced on-treatment VF and 3) experienced post-treatment relapse, both summarized using 95% CIs calculated using the Wilson score method.

Efficacy Findings

Of the 141 subjects, 128 subjects achieved SVR12. Among the 13 failures, six subjects experienced on-treatment virologic failure, five subjects experienced post-treatment relapse, and two subjects had missing SVR12 values.

Ten of the subjects that experienced on-treatment virologic failure or post-treatment relapse were infected with GT1a HCV; the eleventh subject was infected with GT1b HCV. Eight out of the eleven subjects were NS3/4A PI- and NS5A-experienced. All six of the subjects that experienced on-treatment virologic failure did not achieve SVR4. Four of the five subjects that experienced post-treatment relapse did not achieve SVR4.

The two subjects that experienced non-virologic failure prematurely discontinued from the study: one that discontinued due to adverse event on study day 184 and one that was considered lost to follow-up on study day 141.

Arm E, with a 16 week treatment duration, had a SVR12 of 91.5% with no relapses, compared to Arm D with a SVR12 of 88.6% with four relapses. In addition, two of the on-treatment virologic failures occurred before study day 84, suggesting that they may have occurred if treated with a 12-week treatment regimen.

Table 20: MAGELLAN-1 SVR12 and Other Outcomes

	<i>GLE+PIB 12 wk (C)</i> (n=22)	<i>GLE/PIB 12 wk (D)</i> (n=44)	<i>GLE/PIB 16 wk (E)</i> (n=47)
SVR12	ITT-PS: 19/22 (86.4) (95% CI: 66.7, 95.3)	ITT-PS: 39/44 (88.6) (95% CI: 76.0, 95.0)	ITT-PS: 43/47 (91.5) (95% CI: 80.1, 96.6)
OTVF	1/22 (4.5)	1/44 (2.3)	4/47 (8.5)
Relapse	0/22 (0)	4/44 (9.1)	0/43 (0)
Other	2/22 (9.1)	0/44 (0)	0/47 (0)
	Mantel-Haenszel	-3.2% (95% CI: -16.7, 10.3)	

Source: reviewer created

Table 21 provides the SVR12 rate and SVR12 failures by treatment experience and treatment duration for those subjects who have NS5A and/or NS3/4A PI experience. The results in Table 21 were calculated by the reviewer. No such calculations were provided by the applicant but are included in the description of MAGELLAN-1 as it includes all the subjects with such experience in this application.

Table 21: SVR12 for NS5A and/or NS3/4A PI Experienced Subjects by Treatment Duration

<i>Treatment Experience</i>	<i>GLE/PIB 12 wk (n=65)</i>	<i>GLE/PIB 16 wk (n=44)</i>
NS5A & NS3/4A PI-experienced	16/20 (80.0) (95% CI: 58.4, 91.9) OTVF: 1/20 (5.0) Relapse: 3/20 (15.0)	12/15 (80.0) (95% CI: 54.8, 93.0) OTVF: 3/15 (20.0)
NS5A-experienced & NS3/4A PI-naïve	18/20 (90.0) (95% CI: 69.9, 97.2) OTVF: 1/20 (5.0) Relapse: 1/20 (5.0)	16/17 (94.1) (95% CI: 73.0, 99.0) OTVF: 1/17 (5.9)
NS5A-naïve & NS3/4A PI-experienced	23/25 (92.0) (95% CI: 75.0, 97.8) 2 missing SVR12	12/12 (100) (95% CI: 75.8, 100)

Subgroup Analyses

Given the overall high SVR12 rate, the SVR12 rate among the various subgroups tended to be high. In addition, the sample sizes for some subgroups were relatively small. It is in those groups where SVR12 tended to be lower.

The small sample sizes contribute to the difficulty in interpreting the differences in SVR12 between subgroups, overall and within appropriate treatment arms. Given the small differences in SVR12 and the small sample sizes of the subgroups, there is not sufficient evidence to support additional analyses for certain subgroups.

Table 22: MAGELLAN-1 SVR12 by Subgroup

	<i>Total (n=141)</i>	<i>GLE/PIB 12 wk (C) (n=22)</i>	<i>GLE/PIB 12 wk (D) (n=44)</i>	<i>GLE/PIB 16 wk (E) (n=47)</i>
Age				
< 65 years	116/126 (92.1) 5 relapses, 4 on-trt VF, 1 missing	16/18 (88.9) 1 on-trt VF, 1 missing	37/41 (90.2) 4 relapse	36/39 (92.3) 3 on-trt VF
≥ 65 years	12/15 (80.0) 2 on-trt VF, 1 missing	3/4 (75.0) 1 missing	2/3 (66.7) 1 on-trt VF	7/8 (87.5) 1 on-trt VF
Race				
White	91/102 (89.2) 5 on-trt VF, 4 relapses, 2 missing	9/12 (75.0) 1 on-trt VF, 2 missing	30/34 (88.2) 3 relapse, 1 on-trt VF	32/35 (91.4) 3 on-trt VF
Black	36/37 (97.3) 1 on-trt VF	10/10 (100)	9/9 (100)	10/11 (90.9) 1 on-trt VF
Asian	1/2 (50.0) 1 relapse	0 subjects	0/1 (0) 1 relapse	1/1 (100)
Gender				
Male	96/105 (91.4)	15/18 (83.3)	27/31 (87.1)	31/33 (93.9)

		4 on-trt VF, 3 relapses, 2 missing	1 on-trt VF, 2 missing	3 relapse, 1 on-trt VF	2 on-trt VF
	Female	32/36 (88.9) 2 on-trt VF, 2 relapses	4/4 (100)	12/13 (92.3) 1 relapse	12/14 (85.7) 2 on-trt VF
BL HCV RNA					
	< 1 mil c/mL	41/42 (97.6) 1 relapse	4/4 (100)	19/20 (95) 1 relapse	14/14 (100)
	≥ 1 mil c/mL	87/99 (87.9) 6 on-trt VF, 4 relapse, 2 missing	15/18 (83.3) 1 on-trt VF, 2 missing	20/24 (83.3) 3 relapse, 1 on-trt VF	29/33 (87.9) 4 on-trt VF
	< 6 mil c/mL	99/107 (92.5) 4 relapse, 3 on-trt VF, 1 missing	11/12 (91.7) 1 missing	35/40 (87.5) 4 relapse, 1 missing	36/38 (94.7) 2 on-trt VF
	≥ 6 mil c/mL	29/34 (85.3) 3 on-trt VF, 1 relapse, 1 missing	8/10 (80.0) 1 on-trt VF, 1 missing	4/4 (100)	7/9 (77.8) 2 on-trt VF
	< 10 mil c/mL	115/125 (92.0) 5 on-trt VF, 4 relapse, 1 missing	15/16 (93.8) 1 missing	37/42 (88.1) 4 relapse, 1 on-trt VF	41/45 (91.1) 4 on-trt VF
	≥ 10 mil c/mL	13/16 (81.3) 1 on-trt VF, 1 relapse, 1 missing	4/6 (66.7) 1 on-trt VF, 1 missing	2/2 (100)	2/2 (100)
HCV Genotype					
	GT 1	124/137 (90.5) 6 on-trt VF, 5 relapse, 2 missing	19/22 (86.4) 1 on-trt VF, 2 missing	38/43 (88.4) 4 relapse, 1 on-trt VF	40/44 (90.9) 4 on-trt VF
	GT 4	4/4 (100)	0 subjects	1/1 (100)	3/3 (100)
Treatment Experience					
	NS5A & NS3/4A PI Experienced	39/47 (82.9) 4 on-trt VF, 4 relapse	6/7 (85.7) 1 on-trt VF	11/14 (78.6) 3 relapse	13/16 (81.3) 3 on-trt VF
	NS5A Experienced & NS3/4A PI Naïve	39/42 (92.9) 2 on-trt VF, 1 relapse	4/4 (100)	14/16 (87.5) 1 on-trt VF, 1 relapse	17/18 (94.4) 1 on-trt VF
	NS3/4A Experienced & NS5A Naïve	50/52 (96.1) 2 missing	9/11 (81.8) 2 missing	14/14 (100)	13/13 (100)
Cirrhotic Status					
	Non-Cirrhotic	105/114 (92.1) 5 relapse, 2 on-trt VF, 2 missing	19/22 (86.4) 1 on-trt VF, 2 missing	25/29 (86.2) 4 relapse	34/35 (97.1) 1 on-trt VF
	Cirrhotic	23/27 (85.2) 4 on-trt VF	0	14/15 (93.3) 1 on-trt VF	9/12 (75.0) 3 on-trt VF
IL28 Genotype					
	CC	22/22 (100)	3/3 (100)	6/6 (100)	5/5 (100)
	CT	76/87 (87.4) 5 relapse, 4 on-trt VF, 2 missing	11/14 (78.6) 1 on-trt VF, 2 missing	22/27 (81.5) 4 relapse, 1 on-trt VF	28/30 (93.3) 2 on-trt VF
	TT	30/31 (96.8) 1 on-trt VF	5/5 (100)	11/11 (100)	10/11 (90.9) 1 on-trt VF

	Unknown	0/1 (0) 1 on-trt VF	0 subjects	0 subjects	0/1 (0) 1 on-trt VF
Region					
North America		88/97 (90.7) 5 on-trt VF, 2 relapse, 2 missing	19/22 (86.4) 1 on-trt VF, 2 missing	21/23 (91.3) 1 on-trt VF, 1 relapse	21/24 (87.5) 3 on-trt VF
Europe		19/20 (95.0) 1 relapse	0 subjects	7/8 (87.5) 1 relapse	12/12 (100)
Rest of the World		21/24 (87.5) 2 relapse, 1 on-trt VF	0 subjects	11/13 (84.6) 2 relapse	10/11 (90.9) 1 on-trt VF

Source: reviewer created

3.2.3. Phase 3 Trials

3.2.3.1 Trial M13-590 (ENDURANCE-1)

Trial Design

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

The primary trial objective was to demonstrate non-inferiority of the 12-week GLE/PIB regimen to a historical control 97% SVR12 using a 6% NI margin.

Subject Disposition

Of 704 randomized subjects, 703 were treated and all but three completed the assigned treatment. The applicant's primary analysis set, comprising all randomized and treated, HCV mono-infected, DAA-naïve subjects was 667, or 95% of all randomized. The ITT comprises 703 subjects of which all but 3 completed assigned treatment. Overall 4 subjects prematurely discontinued from the trial; 3 of which were in the 8-week arm.

Table 23: ENDURANCE-1 Subject Disposition

	GLE/PIB 12 wk	GLE/PIB 8 wk	Total
Randomized	352	352	704
Randomized and Treated (ITT)	352 (100)	351 (99.7)	703 (99.9)
Primary Analysis Set ITT-PS)*	332 (94.3)	335 (95.2)	667 (94.7)
<i>HCV/HIV Co-infected</i>	18 (5.1)	15 (4.3)	33 (4.7)
<i>Prior SOF-based regimen</i>	2 (0.6)	1 (0.3)	3 (0.4)
Completed Assigned Treatment	351 (99.7)	349 (99.1)	700 (99.4)
Premature Treatment D/C	1 (0.3)	2 (0.6)	3 (0.4)
<i>AE</i>	1	0	1
<i>OTVF</i>	0	1	1
Non-Compliance	0	1	1
Premature Trial D/C	1 (0.3)	3 (0.8)	4 (0.6)
<i>LTF</i>	0	1	1
<i>Other</i>	1	1	2
<i>Consent withdrawal</i>	0	1	1

*ITT-PS is subset of ITT including only HCV mono-infected, DAA-naïve

% in parenthesis is of the ITT population

Source: reviewer created

Statistical Methods

ENDURANCE-1 was designed to compare the 12-week GLE/PIB regimen to a pre-specified SVR12 of 97% using a 6% margin, i.e. achieve a lower bound of the 95% CI around the 12-week GLE/PIB SVR12 of 91% of greater. The justification for the 97% pre-specified clinical threshold was based on data from a Phase 3 trial among GT1 HCV DAA-naïve subjects who were non-cirrhotic receiving ombitasvir/paritaprevir/ritonavir+dasabuvir+/-RBV. Also, SVR12 was based on findings from previous trials of SOF/LDV (ION-1, ION-2, and ION-3), which demonstrated a high 97% SVR12. The 6% NI margin was chosen to preserve at least 68% of the treatment effect of the historical control.

Reviewer’s Comment: The trial objective was to show NI of the 12-week regimen to a clinical threshold SVR12, however, in the absence of a concurrent active-control, findings based on non-inferiority hypothesis is not appropriate or interpretable. Therefore, the reviewer views the primary objective as one of superiority versus a clinical threshold SVR12 of 91%.

The protocol-defined analysis populations include:

ITT-Primary Subset (ITT-PS) includes the subset of mono-infected, HCV DAA-naïve, randomized subjects who received at least one dose of study drug. This is the primary efficacy analysis population.

Reviewer’s Comment: It is unclear as to why co-infected subjects were omitted from the primary analysis population. The reviewer’s analysis will consider these subjects among the ITT-PS.

ITT-Mono-Infected Subset (ITT-MS) includes the subset of mono-infected ITT subjects regardless of prior DAA experience.

ITT-Per Protocol PS (ITT-PP-PS) includes all ITT-PS subjects excluding subjects who prematurely discontinued prior to Week 8, subjects who experienced virologic failure prior to Week 8, subjects without virologic failure who have no HCV RNA value in the SVR12 visit window, and subjects who were SVR12 non-responders due to re-infection.

The primary efficacy analyses included three ranked endpoints (tested using a fixed sequential approach): SVR12 of the 12 week regimen vs. a reference rate of 91% (test of superiority) in the ITT-PS population, 8 week versus 12 week SVR12 assessed via evaluating of the lower bound around the difference (test of NI, 5% margin) in the per-protocol ITT-PS and NI of the 8 week regimen to the 12-week regimen (5% margin) in the ITT-PS primary population.

Reviewer's Comment: The applicant's testing strategy included testing for NI of the 8 week to 12 week regimens in the per-protocol population prior to testing NI in the primary efficacy ITT-PS population. The ITT-PP-PS population is subject to bias given the exclusionary nature of the population. Therefore, the reviewer considers the ITT-PS analysis as most relevant for assessing efficacy.

Testing of the 12 week regimen to the 91% historical control (first test) was based on calculating the 95% CI around the single points estimate of the SVR12 using the normal approximation to the binomial or the Wilson's score method in the event of a 100% SVR12. If superiority was achieved based on a lower bound greater than 91%, then testing of the second endpoint was performed. Testing of NI of the 8 week versus 12 week regimens occurred via calculation of 95% CI around the difference between groups using a normal approximation to the binomial method.

Subject Demographics and Characteristics

The trial population comprised nearly half males with a mean age of 51 years (Table 24). Overall, the majority of subjects were white followed by Asian race. Slightly more subjects overall were GT1b subtype (57%) and most (62%) were treatment-naïve. Only three subjects were prior DAA experienced whereas the remainder had received a prior interferon-based HCV treatment regimen. Approximately 5% were co-infected with HIV at baseline and the mean CD4 was 724 cells/mm³. Geographically, this trial enrolled a large proportion (79%) of subjects outside of the United States. Subjects were enrolled across 115 clinical sites and subjects enrolled per site ranged between 2 and 13 therefore preventing any meaningful by-site assessments. There were no identified baseline differences between treatment arms.

Reviewer's Comment: GT1 is the most prevalent HCV genotype in the United States, yet this trial included only 10% subjects from the United States. In addition, the representation of Black/African American subjects in this trial is low (3.7% overall) and not representative of the general distribution of Black or African Americans infected with GT1 HCV.

Table 24: ENDURANCE-1 Subject Baseline Characteristics/Demographics

	GLE/PIB 12 wk (n=352)	GLE/PIB 8 wk (n=351)	Total (n=703)
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
HIV/HCV Co-Infection	18 (5.1)	15 (4.3)	33 (4.7)
Prior Treatment Experience			
Treatment Naïve	217 (61.6)	219 (62.4)	436 (62)
P/R Experienced	133 (37.8)	131 (37.3)	264 (37.6)
Sofosbuvir-Experienced	2 (0.6)	1 (0.3)	3 (0.4)
Male	176 (50)	167 (47.6)	343 (48.8)
Mean (sd) age	50.3 (11.6)	51.6 (11.9)	50.9 (11.8)
Race			
White	302 (85.8)	289 (82.3)	592 (84.1)
Asian	34 (9.7)	44 (12.5)	78 (11.1)
Black of African American	12 (3.4)	14 (4.0)	26 (3.7)
Multiple	4 (1.1)	2 (0.6)	6 (0.8)
Native Hawaiian or Pacific Islander	0	1 (0.3)	1 (0.1)
American Indian or Alaska Native	0	1 (0.3)	1 (0.1)
HIV RNA ≥10 million c/mL	16 (4.5)	16 (4.6)	32 (4.6)
HIV RNA ≥6 million c/mL	43 (12.2)	49 (14)	92 (13.1)
Median (range) HIV RNA Log ₁₀ IU/mL	6.1 (1.2, 7.6)	6.1 (3.2, 7.4)	6.1
Mean (sd) CD4 cells/mm ³	783 (231)	653 (227)	724 (235)
GT1 Subtype			
GT1a	149 (42.3)	153 (43.6)	302 (43)
GT1b	202 (57.4)	197 (56.1)	399 (56.7)
IL28			
CC	86 (24.4)	102 (29.1)	188 (26.7)
CT	210 (59.6)	197 (56.1)	407 (57.9)
TT	56 (15.9)	52 (14.8)	108 (15.4)
Region*			
North America	77 (21.9)	70 (19.9)	147 (20.9)
Europe	198 (56.2)	182 (51.8)	380 (54.0)
Rest of the World	77 (21.9)	99 (29.2)	176 (25.0)

*Subjects enrolled in 24 countries, 10% subjects overall enrolled in the US; source: reviewer created

Efficacy Findings

The SVR12 in 8 week and 12 week GLE/PIB groups was 99.1% and 99.7%, respectively in the ITT-PS population (applicant). One subject in the GLE/PIB 8 week arm was an on-treatment failure, two subjects were missing the SVR12 assessment and one subject prematurely discontinued treatment on study Day 2. The lower bound around the SVR12 in the GLE/PIB 12 week regimen was 98.3% well above the pre-specified 91% target. The difference between treatment groups was -0.6% (8-12 weeks) with a lower bound of -2% above the -5% pre-specified NI margin (Table 25). Hence, the trial achieved both objectives.

The reviewer's analysis of SVR12, when including co-infected subjects and prior treated DAA subjects, i.e. the ITT population, is provided below. Findings from the ITT analysis are commensurate with those using the applicant's primary ITT-PS population. The 95% CI around the difference is -2.2% to 0.8%

when using the Wilson score method. Similarly, when using the Wald method (applicant’s approach), the 95% CI is -1.7% to 0.5%.

Not shown in the table is the SVR12 in the applicant’s ITT-PP-PS (per protocol population), which was 100%; however, given the exclusionary nature of this population the reviewer does not consider this a valid analysis.

Table 25: ENDURANCE-1 SVR12 and Other Outcome, GLE/PIB 8-and 12-week Regimens

		GLE/PIB 8 wk	GLE/PIB 12 wk
ITT-PS (Applicant)*	SVR12 (95% CI)	332/335 (99.1) (97.4, 100)	331/332 (99.7) (98.3, 100)
	8w-12w (95% CI)	-0.6 (-1.8, 0.6)	
Failure to Achieve SVR12			
OTVF		1	0
Other		1 missing assessment 1 premature treatment discontinuation	1 missing assessment
ITT (Reviewer)**	SVR12 (95% CI)	348/351 (99.1) (97.5, 99.7)	351/352 (99.7) (98.4, 100)
	8w-12w (95% CI)	-0.6 (-2.2, 0.8)	
Failure to Achieve SVR12			
OTVF		1	0
Other		1 missing assessment 1 premature treatment discontinuation	1 missing assessment

*Applicant’s primary analysis population: ITT-PS is subset of the ITT excluding prior SOF failures and HIV/HCV co-infected patients, Wilson method used to calculate 95% CI

** Reviewer’s analysis of all randomized and treated regardless of co-infection and prior DAA experience; the Wilson’s score method used to single group 95% CIs, normal approximation to calculate CI around difference; source: reviewer created

Subgroup analyses

Subgroup analyses by race, gender, age, etc. are not feasible given the high SVR12 observed in this trial. Pooled subgroup analyses are provided in Section 644.

3.2.3.2 Trial M15-464 (ENDURANCE-2)

Trial Design

ENDURANCE-2 was a Phase 3, randomized, double-blind, placebo-controlled (delayed treatment) multicenter study to evaluate the safety and efficacy of GLE/PIB in HCV **GT2**-infected adult TN or TE-PRS subjects without cirrhosis. The matched, blinded placebo (PC) was given for the first 12 weeks followed by open-label treatment with GLE/PIB for an additional 12 weeks among subjects randomized to the placebo group. Subjects were randomized in a 2:1 fashion to GLE/PIB or PC, stratified by previous treatment experience (TN, IFN or peg IFN+/-RBV, SOF+RBV+/-peg IFN). All subjects were followed for 24 weeks after the end of treatment.

Reviewer’s Comment: *This trial was ongoing at the time of NDA submission. However, data from all subjects in the GLE/PIB arm collected up through the time point when the last enrolled subject completed the post-treatment week 12 visit were provided in this NDA. SVR12 data from the placebo-controlled subjects were not submitted as these data were incomplete at time of the NDA submission; however safety and disposition data were provided.*

Subject Disposition

Among 304 randomized subjects (204 to GLE/PIB 12 weeks, 100 to matching PC), there were two subjects who did not receive treatment in the GL/PIB arm. Upon excluding prior SOF-based failures, the primary analysis set comprises 294 subjects (196 GLE/PIB and 98 matching PC). The completion rate of the 12 week treatment regimen was 99% (Table 26).

Reviewer’s Comment: *The reviewer considers the ITT as the primary analysis set as there is no rationale for excluding prior SOF-treated failures. Results in both groups are provided.*

Table 26: ENDURANCE-2 Subject Disposition

	<i>GLE/PIB 12W</i>	<i>Matching PC</i>	<i>Total</i>
Randomized	204	100	304
Treated (ITT)	202	100	302
Primary Analysis Set % treated)	196 (97)	98 (98)	294 (97)
<i>Prior SOF failures</i>	6	2	8 (3)
Completed Treatment (% of treated)	201 (99)	99 (99)	300 (99)

PC=placebo control; source: reviewer created

Subject Demographics and Characteristics

The ITT population of HCV GT2-infected was on average 57 years of age with a nearly equal split in gender. The majority were of white with Asian race the second most commonly enrolled racial group. The average baseline HCV RNA level was 6.1 log10 copies/mL and few had baseline values above 6 million copies (22%) and above 10 million copies (9%). All subjects were HBV and HIV negative and non-cirrhotic at baseline. The proportion of subjects having previously received P/R therapy was 27% and fewer (3%) receiving a DAA-based regimen. Over three-fourths of trial subjects were enrolled in sites external to the United States (Table 27).

Table 27: ENDURANCE-2 Subject Baseline Demographics/Characteristics

	<i>GLE/PIB 12 wk</i> <i>N=202</i>	<i>Matching PC</i> <i>N=100</i>	<i>Total</i> <i>N=302</i>
Males	98 (48.5)	45 (45)	143 (47.3)
Mean (sd) age	56.8 (12.8)	57.6 (12.0)	57.0 (12.5)
Race			
White	121 (59.9)	60 (60)	181 (59.9)
Asian	69 (34.1)	32 (32)	101 (33.4)
Black/AA	7 (3.4)	7 (7)	14 (4.6)
Other	5 (2.5)	1 (1)	6 (2)
HCV RNA (log10) c/mL			
Mean (SD)	6.1 (0.9)	6.1 (0.8)	6.1 (0.8)
Median (range)	6.2 (2.5, 7.3)	6.4 (3.4, 7.2)	6.3 (2.4, 7.3)
HCV RNA ≥6 mil c/mL	47 (23.3)	18 (18.0)	65 (21.5)
HCV RNA ≥10 mil c/mL	19 (9.4)	7 (7)	26 (8.6)
Treatment History			
Treatment Naïve	141 (69.8)	71 (71)	212 (70.2)
P/R Experienced	55 (27.2)	27 (27)	82 (27.1)
DAA-Experienced	6 (3)	2 (2)	8 (2.6)
Region*			
North America	33 (16.3)	19 (19)	52 (17.2)
Europe	97 (48.0)	48 (48)	145 (48)
Rest of the World	72 (35.6)	33 (33)	105 (34.8)

*8 countries; 17.2% subjects enrolled in the US; 21.2% Korea; 17.8% Italy; 15% France; 14% Taiwan
 PC=placebo control; source: reviewer created

Statistical Methods

The primary analysis compared the SVR12 of the GLE/PIB arm to a SVR12 reference value of 95% using a 6% NI margin (i.e. lower bound around the GLE/PIB SVR12 must be greater than 89% to be deemed NI) in the ITT population (all randomized who received at least one dose of study drug), excluding prior SOF+RBV+/-pegIFN failures. The target sample size of the trial was 291-321 subjects in a 2:1 ratio of GLE/PIB:placebo based on the premise that with 180 subjects in the GLE/PIB arm and while assuming a 96% SVR12 that the study would have at least 90% power to demonstrate non-inferiority to the pre-specified margin of 89%. This power was derived using a normal approximation around the binomial calculation method. Using a fixed sequence testing strategy, if non-inferiority was demonstrated, then the analysis included a second test for superiority against the same 95% reference rate without adjustment.

Reviewer’s Comment: In the absence of a concurrent active-control regimen, a test for NI is meaningless in this setting. Therefore, the reviewer views the primary objective as one to test if the SVR12 in the GLE/PIB regimen is superior to a pre-specified clinical threshold of 89%.

NI Derivation

While the reviewer disagrees with any NI approach in this trial, the following is a summary of how the applicant arrived at the NI margin.

The value of M1, of the effect size of the active assumed active control (SOF+RBV) over a sub-optimal regimen of pegIFN+RBV was derived by comparing the observed SVR12 (pooled) from five prior clinical trials in GT2-infected, NC subjects receiving sofosbuvir+RBV to the pooled data on the SVR12 among patients treated with pegIFN+RBV. Specifically, the pooled SVR12 among SOF+RBV treated subjects was 95% versus only 76% among those treated with pegIFN+RBV resulting in an M1 of 19%. Preserving a share of the 19%, the applicant chose a 6% margin thereby maintaining 68% of the benefit of SOF+RBV over pegIFN+RBV. Specifically, the 6% margin was based on the estimated benefit of SOF+RBV over the prior standard of care, pegIFN/RBV.

Efficacy Findings

Among this sample of HCV GT2-infected, NC subjects, the SVR12 was 99.5% with only one subject failing to achieve SVR12 due to missing the post-treatment 12 week assessment. The virological SVR12 among GT2-infected subjects treated with 12 weeks of GLE/PIB was 100%. In the small subset of prior-treated (SOF) subjects, the SVR12 was also 100%. The average (SD) time to first HCV RNA value below the lower limit of detection was 19.3 (12.1) days. Among all GLE/PIB subjects, SVR was achieved by post-treatment week 4 (Table 28).

Table 28: ENDURANCE-2 SVR4 and SVR12 and Other Outcomes

	<i>GLE/PIB 12 wk</i>
SVR12 (excluding prior SOF failures)	195/196 (99.5%) 95% CI: (97.2, 100) (SRV12: 6/6 in prior SOF failures)
SVR12 (ITT)	201/202 (99.5%) 95% CI: (97.2, 100)
On-Treatment Virologic Failure	0
Relapse	0
Other	1 (0.5) missing SVR12 assessment
SVR4	202/202 (100%)

95% CI calculated using the Wilson's score method; source: reviewer created

Reviewer's Comment: *This trial provides evidence that a 12-week GLE/PIB regimen is effective for treating NC, GT2-infected subjects; however, it does not provide information regarding a shorter, 8-week duration, which is being sought by the applicant.*

3.2.3.3 Trial M13-594 (ENDURANCE-3)

Trial Design

ENDURANCE-3 is a Phase 3, randomized, open-label, active-controlled (SOF/DCV), multicenter, non-inferiority trial to assess the efficacy and safety of GLE/PIB in **GT3**-infected, TN, non-cirrhotic adult subjects. This trial included three treatment arms, GLE/PIB for 12 weeks (arm A), SOF/DCV for 12 weeks (arm B) and GLE/PIB for 8 weeks (arm C). Randomization was conducted in a 2:1 ratio for arm A: arm B. Once enrollment to arms A and B were completed, subjects were assigned to arm C in a non-

randomized manner. Arm C was added to the trial design following input from the Division and after the trial was initiated.

The trial objectives were first to test for non-inferiority of GLE/PIB for 12 weeks versus SOF/DCV based on a 6% margin followed by a test for superiority of this arm to the active control. The Hochberg procedure was implemented to control for multiplicity.

Reviewer’s Comment: At the DAVP’s recommendation based on review of separate Phase 2 data, Arm C (GLE/PIB for 8 weeks) was added after the trial commenced. Specifically based on findings from a Phase 2 trial, M14-868, showing acceptable SVR4 results in 29 subjects treated with 8 weeks of GLE/PIB, the DAVP suggested adding an 8-week GLE/PIB treatment arm to trial M13-594 rather than conducting a stand-alone trial to test the 8-week GLE/PIB duration. Enrollment to the GLE/PIB 8 week arm commenced once enrollment to Arms A and B was complete.

Subject Disposition

The total randomized subjects include 233 in the GLE/PIB 12 week arm and 116 in the SOF/DCV active-control arm (Table 29). An additional 157 subjects were enrolled to the GLE/PIB 8 week duration. All but one subject received treatment leading to a total ITT population of 505 subjects. The overall trial discontinuation rate was low between 2.6% and 0.9%. There were three subjects lost to follow-up in the GLE/PIB 12 week arm versus zero in the other two arms.

Table 29: ENDURANCE-3 Subject Disposition

	<i>GLE/PIB 12 wk</i>	<i>SOF/DCV 12 wk</i>	<i>GLE/PIB 8 wk</i>
	Randomized		Non-Randomized
Randomized/enrolled	233	116	157
<i>Treated</i>	233	115	157
Completed Trial	35 (15)	20 (17.4)	0
Ongoing in Trial	192 (82.4)	94 (81.7)	155 (98.7)
Discontinued Trial	6 (2.6)	1 (0.9)	2 (1.3)
Reasons for Premature Discontinuation			
<i>Treatment-Emergent AE</i>	1	1	1
<i>Lost to Follow-Up</i>	3	0	0
<i>Subject Withdrawal</i>	2	0	1
Premature Treatment Discontinuation	8 (3.4)	3 (2.6)	3 (1.9)
<i>AE</i>	3	1	0
<i>Lost to Follow-Up</i>	1	1	1
<i>Non-compliance</i>	2	0	0
<i>Other</i>	1	1	2
<i>Withdrawal by Subject</i>	1	0	0

Source: reviewer created

Subject Demographics and Characteristics

The majority of randomized or enrolled subjects were male (53%) with an average age of 47 years. The population was mostly white (88%) and more than a quarter were enrolled in North America or Europe. The mean baseline HCV RNA levels were similar across groups and ranged from 5.9-6.1 log₁₀ c/mL. Approximately 22% and 13% of the study sample had a baseline HCV RNA of 6 million copies/mL or

greater and 10 million copies/mL or greater, respectively. No differences among groups were identified across the three treatment arm including the non-randomized GLE/PIB 8-week arm (Table 30).

Table 30: ENDURANCE-3 Subject Demographics/Characteristics

	<i>GLE/PIB 12 wk</i> (n=233)	<i>SOF/DCV 12 wk</i> (n=115)	<i>GLE/PIB 8wk</i> (n=157)	<i>Total</i> (n=505)
Males	121 (51.9)	52 (45.2)	92 (58.6)	265 (52.5)
Mean (sd) age	47.2 (10.7)	47.1 (11.3)	45.4 (12.2)	46.6 (11.3)
Race				
White	205 (88)	103 (89.6)	134 (85.3)	442 (87.5)
Asian	19 (8.1)	4 (3.5)	13 (8.3)	36 (7.1)
Black/AA	3 (1.3)	3 (2.6)	3 (1.9)	9 (1.2)
Other	6 (2.6)	5 (4.3)	7 (4.4)	18 (3.6)
HCV RNA (log ₁₀) c/mL				
Mean (sd)	6.1 (0.8)	5.9 (0.7)	6.0 (0.9)	6.0 (0.8)
Median (range)	6.1 (3.5, 7.5)	6.0 (3.8, 7.4)	6.1 (1.2, 7.5)	6.1 (1.2, 7.5)
HCV RNA ≥10 mil c/mL	39 (16.7)	5 (4.3)	20 (12.7)	64 (12.7)
HCV RNA ≥6 mil c/mL	65 (27.8)	14 (12.2)	34 (21.6)	113 (22.4)
IL28 Genotype				
CC	91 (39.0)	39 (33.9)	60 (38.2)	190 (37.6)
CT	115 (49.3)	66 (57.4)	78 (49.7)	259 (51.2)
TT	27 (11.6)	10 (8.7)	19 (12.1)	56 (11.1)
Region				
North America (82% US)	77 (33.0)	41 (35.6)	58 (36.9)	176 (34.8)
Europe	91 (39.0)	42 (36.5)	82 (52.2)	215 (42.6)
Rest of the World	65 (27.8)	32 (27.8)	17 (10.8)	114 (22.6)

Source: reviewer created

Statistical Methods

- ☐ SVR12 CIs using Wald method (normal approximation to the binomial distribution)
 - ☐ Note: We advised that they use an exact approach when the SVR12 is high
 - ☐ 1st Primary Objective: Non-inferiority (6%) in SVR12: 12-week GLE/PIB versus SOF/DCV if:
 - 95% CI LB for diff (GLE/PIB 12 w-SOF/DCV) is above -6% AND 95% LB for GLE/PIB 12 weeks SVR12 > 92%; or
 - 95% CI LB for difference (GLE/PIB 12 w-SOF/DCV) is below -6% AND 97.5% LB for Arm A SVR12 > 92%; or
 - 97.5% CI LB for difference (GLE/PIB 12 w-SOF/DCV) is above -6% and 95% LB for SVR12 (ARM A only) is < 92%
 - ☐ 2nd Primary Objective: Non-inferiority (6%) in the SVR₁₂ rate of the 8 week GLE/PIB (Arm C) to 12-week GLE/PIB (Arm A) will be demonstrated applying same rules as above
 - Hochberg procedure to control for multiplicity within each objective; fixed sequential testing applied to allow for testing of the second primary efficacy objective
- Test for superiority of Arm A to B only if both primary objectives are met

Reviewer’s Comment: *The reviewer disagrees with the approach outlined for evaluating the efficacy of the GLE/PIB 8 week treatment regimen by comparing this regimen to the experimental GLE/PIB 12w regimen, when the later has yet to be proven effective and the 8-week arm was not randomized. The*

reviewer’s assessment of the efficacy of the 8-week regimen is based mainly on the comparison of the SVR12 to the historical control of 92% as a superiority assessment. As a secondary analysis, the reviewer calculated the difference in SVR12 against the SOF/DCV active control.

NI Margin Justification

The margin was based on the estimated effect size of SOF/DCV over the previous standard-of-care (SOC) pegIFN/RBV. Based on findings from three prior trials, the applicant estimated the SVR12 of the SOC to be 68%. Findings from the ALLY-3 trial (reference: Daklinza package insert) showed a regimen of SOF/DCV confers an SVR12 of 98% suggesting a benefit over SOC of 30% (M1). The choice of a 6% NI was based on the goal to preserve 80% benefit of the SOF/DCV regimen over the SOC.

The sample size target of 230 and 115 subjects in the GLE/PIB 12 week and SOF/DCV arms respectively was based on the goal to obtain a lower CI around the difference in SVR12 between groups greater than 92% with at least 90% power. With a sample size of 115 subjects in the GLE/PIB 8 week arm, the trial had approximately 80% power to show NI of this regimen to the 12-week regimen; however as stated above this comparison is invalid. The 92% lower bound was based on applying the 6% NI margin to the expected SVR12 of 98% for the active control.

Efficacy Findings

In this trial of GT3-infected, TN, NC subjects, the overall SVR12 was high across the three treatment groups (Table 31); however, more virologic failures were observed among subjects treated with the GLE/PIB 8w arm compared to the other two regimens. Specifically, the SVR12 was 95.3%, 96.5% and 94.9% in the GLE/PIB 12w, SOF/DCV and GLE/PIB 8w arms, respectively. There was one subject in both GLE/PIB arms with virologic failure while on-treatment compared to zero in the active control. Relapse was higher in both GLE/PIB arms compared to the active control but nearly double in the GLE/PIB 8w arm compared to the 12w arm (Table 31). Numerically, the numbers are small; however, virologically these relapses are potentially related to baseline polymorphisms. Refer to the clinical pharmacology review for an assessment of these virologic failures. Of the five relapses in the 8W GLE/PIB arm, two had baseline HCV RNA level ≥6 million c/mL and one had a baseline HCV RNA ≥10 million c/mL.

In the GLE/PIB 12-week arm, the days (reasons) of premature discontinuation in the 12-week regimen were 62 (lost to follow-up), 15 (adverse event), 121 (lost to follow-up) and 8 (subject withdrawal due to marital issues). One subject in the SOF/DCV arm prematurely discontinued on study day 22 due to an adverse event.

Table 31: ENDURANCE-3 SVR12 and Other Outcomes by Treatment Arm

	GLE/PIB 12 wk (n=233)	SOF/DCV 12 wk (n=115)	GLE/PIB 8 wk (n=157)
SVR12	222 (95.3)	111 (96.5)	149 (94.9)
Failure to Achieve SVR12	11 (4.7)	4 (3.5)	8 (5.1)
Reasons for Failure to Achieve SVR12			
On-Treatment Virologic Failure	1 (0.4)	0	1 (0.6)
Relapse through PTW12	3 (1.3)	1 (0.9)	5 (3.2)
Premature Treatment D/C	4 (1.7)	1 (0.9)	0
Missing SVR12 Data	3 (1.3)	2 (1.7)	2 (1.3)

Source: reviewer created

Results from the pre-specified statistical comparisons using either the Wald method (applicant) or Wilson score method (reviewer) to calculate the confidence intervals are presented below (Table 32).

Analysis of the 1st Primary Objective: GLE/PIB 12w efficacy

Findings from the applicant's analysis of the 1st primary objective yield a difference in SVR12 between the GLE/PIB 12s and active-control (primary comparison) of -1.2 with a 95% CI (Wald) (-5.6, 3.1) and lower bound around the SVR12 in the GLE/PIB 12w arm was 92.6% (Wald). Given that the lower bound of the 95% CI around the difference is above the -6% NI margin and the lower bound of the 95% CI around the SVR12 of the GLE/PIB 12w regimen is 92.6%, which slightly exceeds the pre-specified historical threshold of 92%, the trial was successful in achieving the primary objective of demonstrating that the GLE/PIB 12w regimen is effective for treating TN, GT3-infected, NC subjects. The SVR12 achieved in the active-control SOF/DCV arm was slightly lower than previously observed (i.e. 98%).

The reviewer's analysis generated at a lower bound of the 95% CI around the SVR12 difference of -5.6%, which is above the -6% NI margin and a lower bound around the SVR12 in the GLE/PIB 12w regimen of 91.7% or 92%, which also meets the 92% historical rate criterion.

These analyses suggest that the GLE/PIB 12w regimen yields a high SVR12 ranging from 92% to 98% (depending on method used to generate the CI) and NI to a regimen of SOF/DCV based on a pre-specified margin of 6%. Overall, the 12-week GLE/PIB regimen is effective for treating HCV-infection in subjects with GT3 subtype, who are treatment-naïve and non-cirrhotic.

Analysis of the 2nd Primary Objective: GLE/PIB 8w efficacy

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

The reviewer's assessment of the 8w arms' efficacy differs from the applicant's. Specifically, the reviewer focused on the lower bound around the SVR12 of 90.3% (Wilson method), which is slightly below than the target historical rate of 92%. Secondly, the reviewer's analysis of the difference (8W-SOF/DCV) in SVR12 generated a difference of -1.6% and corresponding 97.5% (adjusted for multiple testing) of -7.7% to 5.1%. These findings suggest that the 8w regimen confers an acceptable SVR12 ranging from 90% to 97% and as much as 8% worse than the active-comparator, SOF/DCV but fails to demonstrate superiority over the historical threshold of 92%.

Table 32: ENDURANCE-3 Statistical Comparisons of SVR12

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

Source: reviewer created

SVR12 by Subgroup

The SVR12 was numerically lower among GLE/PIB 8 week treated subjects with a baseline HIV RNA $\geq$ 6 million/copies (91%) compared to subjects with a baseline level $<$ 6 million/copies (98%). This difference was less notable in the GLE/PIB 12 week and SOF/DCV arms. There were no other trends or findings across the other subgroups considered. Subgroup by race was not performed due to the high preponderance of white subjects (88%) and too few subjects belonging to one of the other racial categories (Table 33).

Table 33: ENDURANCE-3 SVR12 by Subgroup

SVR12	GLE/PIB 12 wk (n=233)	SOF/DCV 12 wk (n=115)	GLE/PIB 8 wk (n=157)
Gender (male)	112/121 (92.6)	48/52 (92.3)	86/92 (93.5)
Gender (female)	110/112 (98.2)	63/63 (100)	63/65 (96.9)
Age $\leq$ 47 years (median)	107/116 (92.2)	54/56 (96.4)	68/72 (94.4)
Age $>$ 47 years (median)	115/117 (98.3)	57/59 (96.6)	81/85 (95.3)
BL HIV RNA $<$ 10 mil c/mL	188/194 (96.9)	106/110 (96.4)	130/137 (94.9)
BL HIV RNA $\geq$ 10 mil c/mL	34/39 (87.2)	5/5 (100)	19/20 (95)
BL HIV RNA $<$ 6 mil c/mL	166/168 (98.8)	100/101 (99)	120/123 (97.6)
BL HIV RNA $\geq$ 6 mil c/mL	63/65 (96.9)	14/14 (100)	31/34 (91.2)
IL28 Genotype			
CC	87/91 (95.6)	36/39 (92.3)	56/60 (93.3)
Non-CC	108/115 (93.9)	65/66 (98.5)	75/78 (96.2)
TT	27/27 (100)	10/10 (100)	18/19 (94.7)
Region			
North America (82% US sites)	74/77 (96.1)	40/41 (97.6)	57/58 (98.3)
Europe	84/91 (92.3)	41/42 (97.6)	77/82 (93.9)
Rest of the World	64/65 (98.5)	30/32 (96.9)	15/17 (88.2)

Source: reviewer created

3.2.3.4 Trial M15-462 (EXPEDITION-4)

Trial Design

EXPEDITION-4 was a single-arm Phase 3 trial that evaluated the safety and efficacy of ABT-493/ABT-530 in adults with HCV GT 1, 2, 3, 4, 5, and 6 infection who are TN or TE with or without cirrhosis and who have severe renal impairment or end-stage renal disease: stage 4 without dialysis, stage 5 without dialysis, or dialysis. M15-462 included 12 weeks of treatment plus 24 weeks of post-treatment follow-up. This study was not designed to test a formal hypothesis. However, the study investigated a subpopulation with unmet medical need: HCV-infected adults with chronic kidney disease

Subject Disposition

Among the 104 enrolled and treated subjects, four subjects prematurely discontinued the study drug. All four discontinued the study drug due to adverse events. Three of the subjects discontinued the study drug on study days 61, 73, and 83 and all achieved SVR12. The fourth subject discontinued from the study drug on study day 27 and did not achieve SVR4 or SVR12. One subject discontinued the trial on study day 102 due to death from a SAE, a cerebral hemorrhage.

Table 34: EXPEDITION-4 Subject Disposition

	<i>GLE/PIB 12 wk (n=104)</i>
Enrolled	104
<i>Treated</i>	<i>104</i>
Completed Study Drug	100 (96.2)
Discontinued Study Drug	4 (3.8)
<i>Adverse event</i>	<i>4</i>
Completed Trial	2 (1.9)
Ongoing in Trial	101 (97.1)
Discontinued Trial	1 (1.0)
<i>Other (Unknown)</i>	<i>1</i>

Source: reviewer created

Subject Demographics and Characteristics

Male subjects comprised 76% of the total study population. The mean (sd) age of subjects was 58 (11) years of age at baseline. About 62% of the subjects were white. Approximately 53%, 15%, 11%, 19%, 1%, and 1% were GT1-6, respectively. About 58% of the subjects were treatment-naïve. The remainder were PR-experienced, with the exception of two subjects (2%) who were DAA-experienced. About 19% of the subjects have cirrhosis and 82% of subjects are on kidney dialysis. The mean (sd) log₁₀ copies/mL of HCV RNA was 5.85 (0.74) log₁₀ copies/mL (2,401,821 copies/mL). About 14% of the subjects were enrolled at a site in the United States.

Table 35: EXPEDITION-4 Subject Baseline Characteristics/Demographics

		<i>GLE/PIB 12 wk</i> <i>(n=104)</i>
Males		79 (76.0)
Mean (sd) age		57.5 (11.1)
Race (majority)		
	White	64 (61.5)
	Black	25 (24.0)
	Asian	9 (8.7)
HCV genotype [^]		
	GT 1	55 (52.9)
	GT 2	16 (15.4)
	GT 3	11 (10.6)
	GT 4	20 (19.2)
	GT 5	1 (1.0)
	GT 6	1 (1.0)
Treatment Experience		
	Treatment Naïve	60 (57.7)
	P/R Experienced	42 (40.4)
	DAA Experienced	2 (1.9)
Cirrhotic Status		
	Non-Cirrhotic	84 (80.8)
	Cirrhotic	20 (19.2)
Chronic Kidney Stage		
	Stage 4 Without Dialysis	13 (12.5)
	Stage 5 Without Dialysis	6 (5.8)
	Dialysis	85 (81.7)
Mean (sd) log ₁₀ HCV RNA		5.85 (0.74)
IL28 Genotype		
	CC	24 (23.1)
	CT	56 (53.8)
	TT	24 (23.1)
Region*		
	North America	27 (26.0)
	Europe	65 (62.5)
	Rest of the World	12 (11.5)

*Subjects enrolled in 9 countries, 15 (14.4%) of the subjects were enrolled at a site in the US

[^]According to HCV genotyping via central lab, there were 54 (51.9%) GT1 and 17 (16.3%) GT2 subjects

Source: reviewer created

Statistical Methods

The number and percentage of subjects in the ITT population that achieved SVR12 were summarized. The applicant utilized a 2-sided 95% CI, calculated using the normal approximation to the binomial

distribution, to summarize the SVR12 percentages. If SVR12 was 100%, the applicant indicated that the Wilson score method would be used to calculate the 95% CI.

Secondary efficacy endpoints were the percentage of subjects that 1) experienced on-treatment VF and 2) experienced post-treatment relapse, both summarized using 95% CIs calculated using the Wilson score method. Only completers, subjects receiving study drug for 77 days or more, were included in the analysis of relapse.

Efficacy Findings

All subjects achieved SVR12 except for two subjects: the subject that permanently discontinued from the study due to death and the subject that discontinued from the study drug on study day 27. The subject that died during the trial was a 41 year old Asian male, GT1b-infected, treatment-naïve subject on kidney dialysis with baseline HCV RNA of 992,000 copies/mL (6.00 log₁₀ copies/mL). The subject that discontinued the study drug on study day 27 is a 69 year old white male, GT1a-infected, treatment-naïve subject on kidney dialysis with baseline HCV RNA of 808,000 copies/mL (5.91 log₁₀ copies/mL). The deceased subject achieved SVR4 but died before the SVR12 assessment. The subject that discontinued the study drug did not achieve SVR4 or SVR12.

Table 36: EXPEDITION-4 SVR12 and Other Outcomes

	<i>GLE/PIB 12 wk (n=104)</i>
SVR12	ITT-PS: 102/104 (98.1) (Wilson* 95% CI: 93.3, 99.5)
OTVF	0/104 (0)
Relapse	0/103 (0)
Other	2/104 (1.9)

Source: reviewer created

* The applicant used the normal approximation to the binomial distribution to calculate the 95% CI for SVR12.

Their reported CI is 95.4, 100. Both CIs reach similar conclusions but the Wilson CI has preferable coverage rates to the normal CI.

Subgroup Analyses

Given that only two subjects did not achieve SVR12, the SVR12 rate among the various subgroups was also high. There were no obvious differences in SVR12 rates that might suggest the need for additional analyses for certain subgroups.

Table 37: EXPEDITION-4 SVR12 by Subgroup

		<i>GLE/PIB 12 wk</i> <i>(n=104)</i>
Age		
< 65 years		75/76 (98.7) 1 missing
≥ 65 years		27/28 (96.4) 1 SDD
Race		
White		63/64 (98.4) 1 SDD
Black		25/25 (100)
Asian		8/9 (88.9) 1 missing
Other		6/6 (100)
Gender		
Male		77/79 (97.5) 1 missing, 1 SDD
Female		25/25 (100)
BL HCV RNA		
< 6 mil c/mL		94/96 (97.9) 1 missing, 1 SDD
≥ 6 mil c/mL		8/8 (100)
< 10 mil c/mL		98/100 (98.0) 1 missing, 1 SDD
≥ 10 mil c/mL		4/4 (100)
HCV Genotype		
GT 1		53/55 (96.4) 1 missing, 1 SDD
GT 2		16/16 (100)
GT 3		11/11 (100)
GT 4		20/20 (100)
GT 5		1/1 (100)
GT 6		1/1 (100)
Treatment Experience		
Treatment Naïve		58/60 (96.7) 1 missing, 1 SDD
P/R Experienced		42/42 (100)
DAA Experienced		2/2 (100)
Cirrhotic Status		
Non-Cirrhotic		84/84 (100)
Cirrhotic		18/20 (90) 1 missing, 1 SDD
IL28 Genotype		
CC		24/24 (100)

	CT	54/56 (96.4)
		1 missing, 1 SDD
	TT	24/24 (100)
Chronic Kidney Stage		
	Stage 4 Without Dialysis	13/13 (100)
	Stage 5 Without Dialysis	6/6 (100)
	Dialysis	83/85 (97.6)
		1 missing, 1 SDD
Region		
	North America	26/27 (96.3)
		1 SDD
	Europe	65/65 (100)
	Rest of the World	11/12 (91.7)
		1 missing

Source: reviewer created

3.3. Pooled Efficacy Analysis

As summarized in section 3.2, the SVR12 across all GLE/PIB 8-, 12- and 16-week regimens ranged from 88% to 100% depending on the genotype, cirrhotic status and prior HCV treatment. Therefore, along with independent analyses of each of the nine clinical trials submitted to support this NDA, the reviewers performed analyses of pooled data to explore overall trends in SVR12 by clinically-relevant population and HCV genotype. Findings from these analyses are intended to serve as supportive to findings in each trial arm. These analyses are not weighted by individual trial or treatment arm sample size and do not include comparator data due to the limited amount of comparator data. Furthermore, there is no attempt to draw statistical conclusions from these pooled estimates.

3.3.1. Treatment-Naïve HCV Subjects

The pooled (unweighted) SVR12 for the 8 and 12 week GLE/PIB regimens across the key Phase 2 and 3 trials (omitting MAGELLAN-1 as this trial studied subjects who had previously failed a DAA-containing regimen and is analyzed independently) by genotype and cirrhotic status among all TN subjects are presented in Table 38.

Among TN, NC, GT1-infected subjects the pooled SVR12 was 98.8% (259/260) and 99.6% (245/248) in the 8- and 12-week GLE/PIB durations, respectively, suggesting that either treatment duration is adequate to achieve and maintain HCV virologic suppression. Among 77 TN, GT1-infected subjects who were cirrhotic, the pooled SVR12 was 97.4%.

Among TN, NC, GT2-infected subjects, the data also support either an 8- or 12- week regimen given high SVR12 of 98.8% (174/176) and 98.9% (172/174), respectively. None of the failures were virologic related. Although the NDA included fewer GT2-infected, TN, cirrhotic subjects (than NC subjects), the overall SVR12 of the GLE/PIB 12-week regimen was 100%.

The pooled SVR12 among TN, GT3, NC subjects treated with 12-weeks of GLE/PIB was 95.5% (258/270) of which there was one OTVF, three relapses and the remaining failures due to missing data or premature treatment discontinuation. Similarly, the overall SVR12 in subjects treated for 8 weeks was 95.2% (177/186) but there were slightly more relapses (n=5) and one OTVF. Some concern exists over the high number of treatment relapses on the 8 week regimen; however, the overall SVR12 is acceptable, this regimen is only proposed for use in TN, NC subjects and the relapse rate is lower than observed in Harvoni®, which was 5% among GT1-infected, TN subjects treated for 8-weeks. Further, it was concluded by the review team that there are other treatment options available for TN, GT3-infected subjects (SOF+RBV or SOF+P/R) that could be utilized for the few patients who might suffer relapse on an 8-week GLE/PIB regimen.

Among GT4-infected, TN, NC subjects, a subtype with a lower prevalence (approximately 2% worldwide), the SVR12 was 100% among 79 subjects treated for 12 weeks and slightly lower at 92.3% among only 39 subjects treated with the shorter, 8-week duration. Among the failures, all were non-virologic related. Therefore, these data suggest that either an 8- or 12-week regimen is likely to confer acceptable SVR12 among GT4-infected subjects. The evidence supporting the proposed 12-week GLE/PIB regimen for treating GT4-infected, C, TN subjects is based on data in only 16 subjects; however, all achieved SVR12.

Evidence supporting treatment in TN, NC, GT5 and GT6 subjects is less adequate compared to that for the other genotypes discussed above. Specifically, 22 and 28 TN, NC GT5 and GT6 subjects respectively were treated with a 12 week course of GLE/PIB resulting in a 100% SVR12. Only 2 and 8 TN, NC GT5 and GT6 subjects, respectively, were treated for 8 weeks with GLE/PIB. While all achieved SVR12, these data are too small to provide sufficient evidence in support of the 8-week duration for treating TN, GT5 and GT6-infection in NC subjects. Note also that overall only 10 GT6 subjects were studied on the 8-week GLE/PIB regimen and all but two were TN. Similarly, few cirrhotic, TN, GT5 (n=2) or GT6 (n=6) subjects were evaluated in the GLE/PIB 12-week program though all achieved SVR12. In summary, the review team concluded that the 12-week GLE/PIB regimen should be the recommended duration for all TN, GT5 and GT6 subjects regardless of cirrhotic status.

Table 38: Pooled SVR12 by Genotype and Cirrhosis Status in Treatment Naïve GT1-6

GLE/PIB 12 wk	GT1 (590, 172, 462)	GT2 (172, 868, 464, 462)	GT3 (594, 868, 462)	GT4 (583, 172, 867, 462)	GT5 (583, 172, 867, 462)	GT6 (583, 172, 867, 462)
Non-cirrhotic						
SVR12	259/260 (99.6) (97.8, 99.9)	174/176 (98.9) (95.9, 99.7)	258/270 (95.5) 92.4, 97.4	79/79 (100) (95.4, 100)	22/22 (100) (85.1, 100)	28/28 (100) (87.9, 100)
OTVF	0	0	1	0	0	0
Relapse	0	0	3	0	0	0
Other	1 missing SVR12	1 d/c trt, 1 missing SVR12	4 d/c trt, 4 missing SVR12	0	0	0
Cirrhotic						
SVR12	75/77 (97.4) 91, 99.3	28/28 (100) 87.9, 100	64/65 (98.5) (91.8, 99.7)	16/16 (100) (80.6, 100)	2/2 (100) -	6/6 (100) -
Other	2 missing SVR12	0	1 missing SVR12	0	0	0
GLE/PIB 8 wk						
Non-Cirrhotic						
SVR12	245/248 (98.8) (96.5, 99.6)	172/174 (98.8) (95.9, 99.6)	177/186 (95.2) (91.1, 97.4)	36/39 (92.3) (79.7, 97.3)	2/2 (100)	7/8 (87.5)
OTVF	0	0	1	0	0	0
Relapse	0	0	5	0	0	0
Other	2 d/c trt, 1 missing SVR12	2 d/c trt	3 missing SVR12	1 d/c trt, 2 missing SVR12	0	1 missing SVR12

Trials Included: 590 (ENDURANCE 1), 583 (ENDURANCE-4), 172 (EXPEDITION-1); 867 (SURVEYOR-1); 868 (SURVEYOR-2); 464 (ENDURANCE-2); 594 (ENDURANCE-3), and 462 (EXPEDITION-4)
 Used central laboratory HCV determination (variable=HCVGTC); source: reviewer created

3.3.2. Treatment-Experienced

The pooled, unweighted SVR12 for non-cirrhotic, DAA- and PR-experienced, NS5A naïve subjects across the key Phase 2 and 3 trials are presented by genotype in Table 39. Subjects with genotypes 1, 2, 4, 5, or 6 received treatment durations of 8 weeks or 12 weeks of GLE/PIB. Subjects with genotype 3 received treatment durations of 12 weeks or 16 weeks of GLE/PIB.

Among GT1-infected subjects, the overall SVR12 rate was 100% for those treated with 12 weeks of GLE/PIB and 99.3% for those treated with 8 weeks of GLE/PIB, indicating that both durations are adequate in achieving and maintaining HCV virologic suppression.

Among GT2-infected subjects, the overall SVR12 rate was 100% for those who received GLE/PIB for 12 weeks and 91.3% for those who received GLE/PIB for 8 weeks. However, the smaller sample size for the 8 week duration (n=23) as well as a lack of testing creates difficulty in assessing whether the SVR12 rate is statistically significantly lower in the 8 week treatment duration, compared to the 12 week duration. In addition, both treatment durations exhibit SVR12 rates above 90%. Therefore, both treatment durations can be seen as adequate to achieve and maintain HCV virologic suppression.

Among GT3-infected subjects, the overall SVR12 rate was 95.5% for those treated with 16 weeks of GLE/PIB and 89.8% for those treated with 12 weeks of GLE/PIB. Of those who received the 12 week treatment duration, four subjects experienced post-treatment relapse and one subject experienced on-treatment virologic failure. In contrast, of those who received the 16 week treatment duration, only one subject experienced post-treatment relapse. This is coupled with the fact that GT3 is believed to be the hardest genotype to treat, the evidence points to 16 weeks as the more optimal GLE/PIB treatment duration.

Among GT4-infected subjects, the overall SVR12 rate was 97.6% for those treated with 12 weeks of GLE/PIB and 100% for those treated with 8 weeks of GLE/PIB. Although the sample size is seven subjects for the 8 week treatment duration, there is no evidence to suggest that longer treatment duration for GT4-infected, non-cirrhotic, DAA- and PR-experienced (NS5A-naïve) is warranted, compared to GT4-infected, non-cirrhotic, treatment-naïve subjects. Therefore, the 8 week treatment duration is deemed adequate to achieve and maintain HCV viral suppression.

Among GT5-infected subjects, the overall SVR12 rate was 100% in six subjects that received 12 weeks of GLE/PIB. No non-cirrhotic, treatment experienced, GT5-infected subjects received the 8 week treatment duration. Among GT6-infected subjects, the overall SVR12 rate was 100% in three subjects that received 12 weeks of GLE/PIB and 100% in two subjects that received 8 weeks of GLE/PIB. The sample sizes are inadequate support treatment durations in treatment experienced, non-cirrhotic, GT5- and GT6-infected. Therefore, data from treatment-experienced subjects with other genotypes and from treatment-naïve, GT5- and GT-6 infected subjects must be taken into consideration in order to determine the appropriate treatment duration.

Table 39: Pooled SVR12 by Genotype and Treatment Duration in DAA- & PR-Experienced, NS5A Naïve, Non-Cirrhotic Subjects

<i>GLE/PIB</i>	<i>GT1</i> (462, 590, 867)	<i>GT2</i> (462, 464, 868)	<i>GT3</i> (594, 868)	<i>GT4</i> (462, 583, 867, 868)	<i>GT5</i> (583, 867, 868)	<i>GT6</i> (462, 583, 867, 868)
16 wk	0	0	21/22 (95.5) (78.2, 99.2)	0	0	0
OTVF	0	0	0	0	0	0
Relapse	0	0	1/22 (4.5)	0	0	0
Other	0	0	0	0	0	0
12 wk	159/159 (100) (97.6, 100)	65/65 (100) (94.4, 100)	44/49 (89.8) (78.2, 95.6)	40/41 (97.6) (87.4, 99.6)	6/6 (100) (61.0, 100)	4/4 (100) (51.0, 100)
OTVF	0	0	1/49 (2.0)	0	0	0
Relapse	0	0	4/48 (8.3)	0	0	0
Other	0	0	0	1/35 (2.9) 1 d/c trt	0	0
8 wk	138/139 (99.3) (96.0, 99.9)	21/23 (91.3) (73.2, 97.6)	0	7/7 (100) (64.6, 100)	0	2/2 (100) (34.2, 100)
OTVF	1/139 (0.7)	0	0	0	0	0
Relapse	0	2/23 (8.7)	0	0	0	0
Other	0	0	0	0	0	0

Trials Included: 590 (ENDURANCE-1), 464 (ENDURANCE-2), 594 (ENDURANCE-3), 583 (ENDURANCE-4), 867 (SURVEYOR-1), 868 (SURVEYOR-2), 462 (EXPEDITION-4); source: reviewer created

The pooled, unweighted SVR12 for cirrhotic, DAA- and PR-experienced, NS5A naïve subjects across the key Phase 2 and 3 trials are presented by genotype in Table 40. Subjects with genotypes 1, 2, 4, or 6 received 12 weeks of GLE/PIB while subjects with genotype 3 received 16 weeks of GLE/PIB. No GT5-infected, DAA- and PR-experienced subjects with cirrhosis were enrolled in the trials.

Among GT1-infected subjects, the overall SVR12 rate was 96.7% in 30 subjects, with one subject experiencing post-treatment relapse. While the sample size is arguably small, the high SVR12 rate provides evidence that the 12 week treatment duration is adequate for achieving and maintaining HCV virologic suppression.

Among GT3-infected subjects, the overall SVR12 rate was 94.1% in 51 subjects, with two subjects experiencing post-treatment relapse and one subject experiencing on-treatment virologic failure. Given that GT3 has historically been the hardest genotype to treat, the relatively high SVR12 rate along with the other findings support a 16-week treatment duration for GT3 in this subpopulation.

Among GT2-, GT4-, and GT6-infected subjects, the overall SVR12 rate was 100%. However, the sample sizes are nine, eight, and one for genotypes 2, 4, and 6, respectively. In addition, no cirrhotic, DAA- & PR-experienced (NS5A-naïve), GT5-infected subjects were enrolled in the trials. As a result, data must be borrowed from treatment-experienced cirrhotic subjects from GT1 as well as from treatment-naïve, cirrhotic, GT2-, GT4-, and GT6-infected subjects. Among treatment-naïve, cirrhotic subjects, the overall

SVR12 rate was 100% for genotypes 2, 4, and 6. Therefore, the collective findings support the 12-week treatment duration for genotypes 2, 4, and 6 in this subpopulation.

Table 40: Pooled SVR12 by Genotype in DAA- & PR-Experienced, NS5A Naïve, Cirrhotic Subjects

<i>GLE/PIB</i> 12 wk (16 W for GT3)	<i>GT1</i> (172, 462)	<i>GT2</i> (172, 462)	<i>GT 3</i> (868)	<i>GT4</i> (172, 462)	<i>GT6</i> (172)
SVR12	29/30 (96.7) (83.3, 99.4)	9/9 (100) (70.1, 100)	48/51 (94.1) (84.1, 98.0)	8/8 (100) (67.6, 100)	1/1 (100) (20.7, 100)
OTVF	0	0	1/51 (2.0)	0	0
Relapse	1/24 (4.2)	0	2/50 (4.0)	0	0
Other	0	0	0	0	0

Trials Included: 172 (EXPEDITION-1), 868 (SURVEYOR-2), 462 (EXPEDITION-4); source: reviewer created

3.4. Evaluation of Safety

Overall, there were seven (7) patient deaths, none viewed as related to study drug and the majority of deaths occurred several months following the last dose of study drug (see clinical review for future assessment of these deaths).

In the one placebo-controlled clinical trial, ENDURANCE-2, the most common adverse events (AE) (reported incidence of at least 5% in either treatment group) in the GLE/PIB and PBO arms, respectively was headache (12% in both arms), fatigue (11.4% and 10%), diarrhea (9.9% vs. 3.0%), nausea (7.4% and 3%), pruritus (6% in both arms), dizziness (3% and 5%), oropharyngeal pain (2% and 5%) and hypertension (1% and 5%). AEs related to study drug include headache, fatigue, asthenia and nausea.

Targeted statistical assessments of blood pressures changes and increases in uric acid at the request of the clinical reviewer were performed. These analyses include data across key trials where appropriate.

Change in Blood Pressure Assessment

Blood pressure changes from baseline were assessed via the four criteria:

Severe Hypotension:

- Diastolic blood pressure (DBP) ≤ 50 mmHg AND ≥ 15 mmHg decrease from baseline
- Systolic BP (SBP) ≤ 90 mmHg AND ≥ 20 mmHg decrease from baseline

Severe Hypertension:

- DBP ≥ 105 mmHg AND ≥ 15 mmHg increase from baseline
- SBP ≥ 180 mmHg AND ≥ 20 mmHg increase from baseline

As shown in the table below, there is no clear dose-response in the incidences of clinically-relevant deviations in blood pressure. However, the incidence of each deviation was numerically larger among subjects with renal impairment compared to those without and this was shown across each of the four BP criteria.

Table 41: Incidence of Severe Hypotension/Severe Hypertension across Trials

GLE/PIB Duration	8 Weeks	12 Weeks	16 Weeks	w/o Renal Impairment	w/Renal Impairment
<i>N</i>	852	1401	116	2369	104
BP Flag Criterion					
Severe Hypotension					
DBP ≤50 mmHg AND ≥15 mmHg decrease from BL	13/852 (1.5)	13/1401 (0.9)	2/116 (1.7)	24/2263 (1.1)	4/104 (3.8)
SBP ≤90 mmHg AND ≥20 mmHg decrease from BL	7/852 (0.8)	27/1401 (1.9)	2/116 (1.7)	29/2263 (1.3)	7/104 (6.7)
Severe Hypertension					
DBP ≥ 105 mmHg AND ≥15 mmHg increase from BL	13/852 (1.5)	20/1401 (1.4)	1/116 (0.9)	28/2263 (1.2)	6/104 (5.8)
SBP ≥ 180 mmHg AND ≥20 mmHg increase from BL	3/852 (0.3)	19/1401 (1.4)	2/116 (1.7)	17/2263 (0.7)	7/104 (6.7)

Source: reviewer created, DPB=diastolic blood pressure; SPB=systolic blood pressure, BL=baseline

The following figures illustrate the mean changes from baseline (with 95% CIs around the mean) in blood pressure among the subjects meeting one of the four criteria described above separately by renal impairment. Overall patterns suggest an initial decrease or increase (depending on the criterion) followed by a general increase or decrease over time. It is unclear if these changes are commensurate with natural history among persons studied or related to treatment and/or drug-drug interactions. These findings were further assessed by the clinical reviewer, Dr. Lara Stabinski (see review for details).

Figure 1: Mean Change from Baseline in DBP among subjects (n=28) with DBP≤50 mmHg AND ≥15 mmHg decrease from baseline on treatment

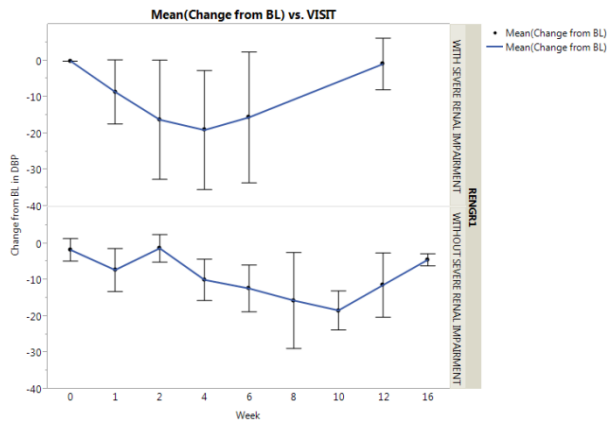


Figure 2: Mean Change from Baseline in DPB among subjects (n=34) with DBP ≥ 105 mmHg AND ≥ 15 mmHg increase from baseline on treatment

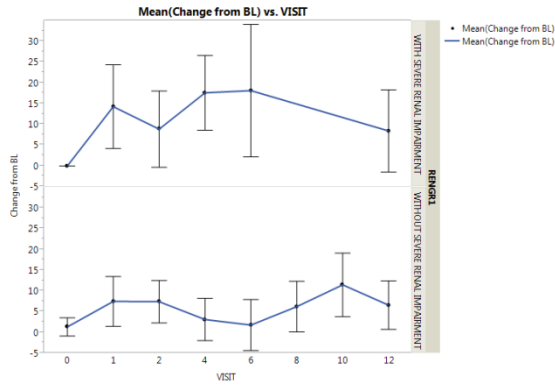


Figure 3: Mean Change from Baseline in BBP among subjects (n=36) with a SBP ≤ 90 mmHg AND ≥ 20 mmHg decrease from baseline on treatment

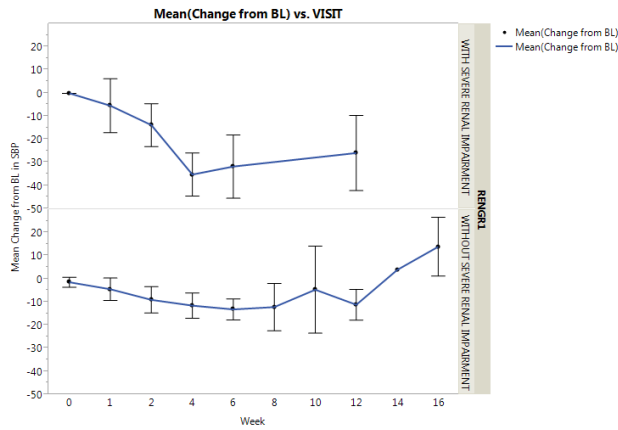
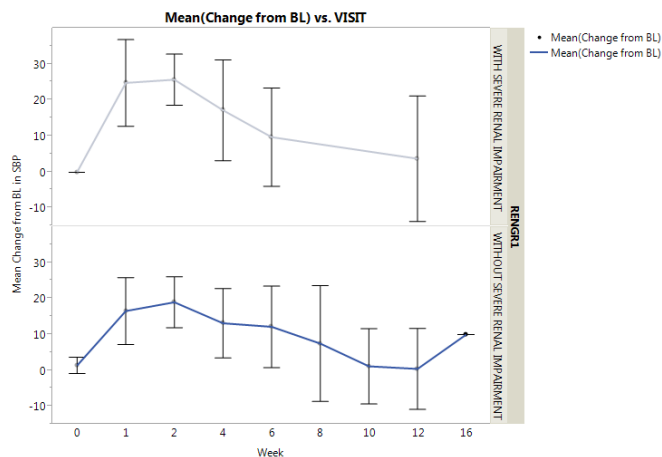


Figure 4: Mean Change from Baseline in SBP among subjects (n=24) with a SBP $\geq$ 180 mmHg AND $\geq$ 20 mmHg increase from baseline on treatment



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race, Age, and Geographic Region

These pooled subgroup analyses exclude the MAGELLAN-1 trial, as it studied NS5A and/or NS3/4A PI-experienced, and is therefore assessed independently because of the different patient population. Subgroup analyses for these two trials are provided in Sections 3.2.2.5 and 3.2.3.4, respectively.

Given the overall high SVR12 rate, the pooled rate among the various subgroups also tends to be high. Despite the pooling of the DAA- and PR-experienced subjects across several trials, the sample sizes for some subgroups are relatively small particularly for the GT5 and 6 subtypes. The small sample sizes contribute to the difficulty in interpreting the differences in SVR12 between subgroups within HCV genotypes. Taking the small differences in SVR12 and the small sample sizes into consideration, there is not enough evidence to suggest the need for additional analyses by gender, race, age, or geographic region for most subgroups.

The following table provides the subgroup findings among pooled trials for TN subjects receiving 12 weeks of GLE/PIB.

Table 42: Pooled SVR12 by Age, Race, Gender, and Region in TN Subjects, GLE/PIB 12 weeks

<i>GLE/PIB 12 wk</i>	GT1	GT2	GT3	GT4	GT5	GT6
Pooled Trials	590, 172	172, 868, 464	594, 868	583, 172, 867, 868	583, 172, 867, 868	583, 172, 867, 868
N total	283	187	297	75	23	33
Age						
< 65 years	248/249 (99.6)	129/131 (98.5)	273/285 (95.8)	67/67 (100)	15/15 (100)	30/30 (100)
≥ 65 years	34/34 (100)	56/56 (100)	12/12 (100)	8/8 (100)	8/8 (100)	3/3 (100)
Race						
White	251/251 (100)	127/129 (98.4)	256/265 (96.6)	61/61 (100)	16/16 (100)	4/4 (100)
Black	14/15 (93.3)	7/7 (100)	4/4 (100)	10/10 (100)	3/3 (100)	0
Asian	15/15 (100)	47/47 (100)	18/20 (90)	4/4 (100)	1/1 (100)	28/28 (100)
Other	2/2 (100)	4/4 (100)	4/5 (80)	0	2/2 (100)	1/1 (100)
Gender						
Male	140/140 (100)	88/90 (97.8)	148/158 (93.7)	46/46 (100)	13/13 (100)	15/15 (100)
Female	142/143 (99.3)	97/97 (100)	137/139 (98.6)	29/29 (100)	10/10 (100)	18/18 (100)
Region						
North America	103/104 (99.0)	66/68 (97.1)	122/125 (97.6)	22/22 (100)	2/2 (100)	16/16 (100)
Europe	141/141 (100)	72/72 (100)	85/93 (91.4)	50/50 (100)	13/13 (100)	10/10 (100)
Rest of the World	38/38 (100)	47/47 (100)	78/79 (96)	3/3 (100)	8/8 (100)	7/7 (100)

Values in parenthesis are proportions of SVR12 by subgroup by genotype; Trials include: 590 (ENDURANCE-1), 172 (EXPEDITION-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2), 464 (ENDURANCE-2), 583 (ENDURANCE-4), and 594 (ENDURANCE-3); source: reviewer created

The results of the pooled analyses by subgroup among all TN subjects treated with a GLE/PIB 8 week regimen are shown below with the exception of results in the GT5 and GT6 groups, which include too few subjects; 2 and 8 subjects, respectively, to justify subgroup analyses.

Table 43: Pooled SVR12 by Age, Race, Gender, and Region in TN Subjects, GLE/PIB 8 weeks

<i>GLE/PIB 8 wk</i>	GT1	GT2	GT3	GT4
Pooled Trials	590, 867	868	594, 868	868
N total	248	174	186	39
Age				
< 65 years	221/223 (99.1)	150/152 (98.7)	172/180 (95.6)	32/34 (94.1)
≥ 65 years	24/25 (96)	22/22 (100)	5/6 (83.3)	4/5 (80)
Race				
White	209/212 (98.6)	151/153 (98.7)	152/160 (95)	28/29 (96.5)
Black	12/12 (100)	11/11 (100)	4/4 (100)	6/7 (85.7)
Asian	20/20 (100)	5/5 (100)	13/14 (92.9)	2/3 (66.7)
Other	3/3 (100)	4/4 (100)	7/7 (100)	0
Gender				
Male	109/110 (99.1)	94/94 (100)	101/107 (94.4)	21/24 (87.5)
Female	136/138 (98.6)	78/80 (97.5)	76/79 (96.2)	15/15 (100)
Region				
North America	82/83 (98.8)	155/157 (98.7)	65/66 (98.5)	29/32 (90.6)
Europe	110/110 (100)	0	77/82 (93.9)	0
Rest of the World	53/55 (96.4)	17/17 (100)	35/38 (92.1)	7/7 (100)

Values in parenthesis are proportions of SVR12 by subgroup by genotype; Trials include: 590 (ENDURANCE-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2), and 594 (ENDURANCE-3); source: reviewer created

Table 44, Table 45, and Table 46 show the results of the pooled analyses by subject demographics among DAA- and PR-experienced, NS5A naïve subjects by genotype for GT1-4 for 8, 12, and 16 week treatment durations, respectively. Pooled analyses by subgroup for GT5 and GT6 are excluded due to their small sample sizes.

Table 44: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR-Experienced, NS5A Naïve Subjects for 8 Week Treatment Duration

<i>GLE/PIB 8 wk</i>	<i>GT1 (590, 867, 868)</i>	<i>GT2 (868)</i>	<i>GT4 (868)</i>
Age			
< 65 years	115/116 (99.1)	16/18 (88.9)	6/6 (100)
≥ 65 years	23/23 (100)	5/5 (100)	1/1 (100)
Race			
White	111/112 (99.1)	14/16 (87.5)	4/4 (100)
Black	3/3 (100)	1/1 (100)	3/3 (100)
Asian	24/24 (100)	5/5 (100)	0
Other	0	1/1 (100)	0
Gender			
Male	76/77 (98.7)	12/13 (92.3)	5/5 (100)
Female	62/62 (100)	9/10 (90.0)	2/2 (100)
Region			
North America	23/23 (100)	14/15 (93.3)	2/2 (100)
Europe	72/72 (100)	0	0
Rest of the World	43/44 (97.7)	7/8 (87.5)	5/5 (100)

Trials Include: 590 (ENDURANCE-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2); source: reviewer created

Table 45: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR-Experienced, NS5A Naïve Subjects for 12 Week Treatment Duration

<i>GLE/PIB</i>	<i>GT1 (590, 867, 462, 464)</i>	<i>GT2 (462, 464, 868, 172)</i>	<i>GT 3 (868)</i>	<i>GT4 (583, 867, 172, 462)</i>
Age				
< 65 years	150/151 (99.3)	52/52 (100)	39/44 (88.6)	42/43 (97.7)
≥ 65 years	38/38 (100)	22/22 (100)	5/5 (100)	3/3 (100)
Race				
White	148/149 (99.3)	47/47 (100)	37/42 (88.1)	38/39 (97.4)
Black	14/14 (100)	3/3 (100)	0	6/6 (100)
Asian	23/23 (100)	23/23 (100)	7/7 (100)	4/4 (100)
Other	3/3 (100)	1/1 (100)	0	0
Gender				
Male	113/113 (100)	47/47 (100)	28/32 (87.5)	37/38 (97.4)
Female	75/76 (98.7)	27/27 (100)	16/17 (94.1)	11/11 (100)
Region				
North America	37/38 (97.4)	19/19 (100)	18/21 (85.7)	8/8 (100)
Europe	109/109 (100)	30/30 (100)	6/6 (100)	37/38 (97.4)
Rest of the World	42/42 (100)	25/25 (100)	20/22 (90.9)	3/3 (100)

Trials Include: 590 (ENDURANCE-1), 464 (ENDURANCE-2), 583 (ENDURANCE-4), 867 (SURVEYOR-1), 868 (SURVEYOR-2), 172 (EXPEDITION-1), and 462 (EXPEDITION-4); source: reviewer created

Table 46: Pooled SVR12 by Genotype and Age, Race, Gender, and Region in DAA- & PR- Experienced, NS5A Naïve Subjects for 16 Week Treatment Duration

<i>GLE/PIB 16 wk</i>		<i>GT 3 (868)</i>
Age	< 65 years	57/61 (93.4)
	≥ 65 years	12/12 (100)
Race	White	61/65 (93.8)
	Black	0
	Asian	6/6 (100)
	Other	2/2 (100)
Gender	Male	48/52 (92.3)
	Female	21/21 (100)
Region	North America	47/48 (97.9)
	Europe	3/3 (100)
	Rest of the World	19/22 (86.4)

Trials Include: 868 (SURVEYOR-2); source: reviewer created

4.2. Other Special/Subgroup Populations

Treatment-Naïve, GLE/PIB 12 weeks

Among TN subjects treated with 12W GLE/PIB, the SVR12 was slightly higher among those subjects with baseline HCV RNA values less than 6 or 10 million c/mL compared to those with value above 6 or 10 million c/mL among GT1, GT2, and GT4 subjects. Numbers were too small among GT5 and GT5 subjects to evaluate this subgroup fully. Cirrhosis at baseline did not seem to impact overall SVR12 across the genotypes nor did IL28 genotype. Note that the applicant is not seeking the 12w regimen for TN, NC GT1-6 subjects but rather an 8-week course.

Table 47: Pooled SVR12 by Genotype and Subgroup, TN Subjects, GLE/PIB 12 weeks

<i>GLE/PIB 12wk</i>	GT1	GT2	GT3	GT4	GT5	GT6
Pooled Trials	590, 172	172, 868, 464	594, 868	583, 172, 867, 868	583, 172, 867, 868	583, 172, 867, 868
N total	283	187	297	75	23	33
BL HCV RNA						
< 6 mil c/mL	250/250 (100)	139/140 (99.3)	218/225 (96.9)	69/69 (100)	21/21 (100)	17/17(100)
≥ 6 mil c/mL	32/33 (97)	46/47 (97.9)	67/72 (93.1)	6/6 (100)	2/2 (100)	16 (100)
BL HCV RNA						
< 10 mil c/mL	268/268 (100)	162/163 (99.4)	249/256 (97.3)	74/74 (100)	23/23 (100)	25/25 (100)
≥ 10 mil c/mL	14/15 (93.3)	23/24 (95.8)	36/41 (87.8)	1/1 (100)	0	8/8 (100)
Cirrhotic Status						
Non-Cirrhotic	216/217 (99.5)	161/163 (98.8)	222/233 (95.3)	63/63 (100)	21/21 (100)	27/27 (100)
Cirrhotic	66/66 (100)	24/24 (100)	63/64 (98.4)	12/12 (100)	2/2 (100)	6/6 (100)
IL28 Genotype						
CC	67/67 (100)	87/88 (98.9)	116/120 (96.7)	11/11 (100)	10/10 (100)	24/24 (100)
CT	171/172 (99.4)	65/66 (98.5)	137/145 (94.5)	47/47 (100)	8/8 (100)	7/7 (100)
TT	44/44 (100)	33/33 (100)	32/32 (100)	17/17 (100)	5/5 (100)	2/2 (100)

Trials include: 590 (ENDURANCE-1), 172 (EXPEDITION-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2), 583 (ENDURANCE-4), and 594 (ENDURANCE-3); source: reviewer created

The following table provides additional pooled subgroup analysis among TN subjects treated with GLE/PIB for 8 weeks among GT1-4 infected subjects. Subgroup analyses among GT5 or GT6 subjects treated with the 8 week regimen were not performed due to small numbers. In addition, all subjects treated with 8 weeks of GLE/PIB were non-cirrhotic; hence no subgroup by cirrhotic status applies. Virologic success was higher in subjects with lower baseline HCV RNA (< 6 million c/mL) compared to having a higher baseline RNA values among GT3-infected subjects. No clear pattern by baseline HCV RNA was observed among GT1- and GT2-infected subjects and there was only one subject in the GT-4 group with a baseline values > 6 million copies/mL, thereby preventing any meaningful comparisons. Overall, SVR12 was high across all three IL28 genotypes across HCV genotypes though again numbers were few for GT4-infected subjects.

Table 48: Pooled SVR12 by Genotype and Subgroup, TN Subjects, GLE/PIB 8 weeks

<i>GLE/PIB 8 wk</i>	GT1	GT2	GT3	GT4
<i>Pooled Trials</i>	590, 867	868	594, 868	868
N total	248	174	186	39
BL HCV RNA				
< 6 mil c/mL	197/200 (98.5)	93/93 (100)	140/145 (96.5)	35/38 (92.1)
≥ 6 mil c/mL	48/48 (100)	79/81 (97.5)	37/41 (90.2)	1/1 (100)
BL HCV RNA				
< 10 mil c/mL	227/230 (98.7)	126/127 (99.2)	154/162 (95.1)	35/38 (92.1)
≥ 10 mil c/mL	18/18 (100)	46/47 (97.9)	23/24 (95.8)	1/1 (100)
IL28 Genotype				
CC	77/77 (100)	80/82 (97.6)	66/71 (93)	11/11 (100)
CT	135/137 (98.5)	92/92 (100)	90/93 (96.8)	20/23 (87)
TT	33/34 (97.1)	20/20 (100)	21/22 (95.4)	5/5 (100)

Trials include: 590 (ENDURANCE-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2), and 594 (ENDURANCE-3)
 source: reviewer created

Treatment-Experienced

Table 49, Table 50, and Table 51 show the results of the pooled analyses by baseline characteristics among DAA- and PR-experienced, NS5A naïve subjects by genotype for GT1-4 for 8, 12, and 16 week treatment durations, respectively. GT5 and GT6 are excluded from the analyses due to small sample sizes. The issues of high overall SVR12 rate and small sample sizes remain regarding the subgroup analyses for baseline health characteristics. As a result, there is insufficient evidence to recommend additional analyses for most subgroups. A subgroup of potential interest, however, is HCV RNA < and ≥ 6,000,000 copies/mL among GT3-infected subjects. Subjects with baseline HCV RNA < 6,000,000 copies/mL achieved a SVR12 of 96.7% under the 12 week treatment duration compared to a SVR12 of 78.9% among subjects with baseline HCV RNA ≥ 6,000,000 copies/mL. Similarly, subjects with baseline HCV RNA < 6,000,000 copies/mL achieved a SVR12 of 98.1% under the 16 week treatment duration compared to a SVR12 of 84.2% among subjects with baseline HCV RNA ≥ 6,000,000 copies/mL. However, the sample sizes for GT3-infected DAA- and PR-experienced subjects are relatively small for the 12 and 16 week treatment durations, which contribute to difficulty in determining if the difference is meaningful.

Table 49: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 8 Week Treatment Duration

<i>GLE/PIB 8 wk</i>	<i>GT1 (590, 867, 868)</i>	<i>GT2 (868)</i>	<i>GT4 (868)</i>
BL HCV RNA			
< 6 mil c/mL	124/125 (99.2)	10/11 (90.9)	7/7 (100)
≥ 6 mil c/mL	14/14 (100)	11/12 (91.7)	0
Treatment Experience			
P/R Experienced	137/138 (99.3)	16/17 (94.1)	7/7 (100)
DAA Experienced	1/1 (100)	5/6 (83.3)	0
Cirrhotic Status			
Non-Cirrhotic	138/139 (99.3)	21/23 (91.3)	7/7 (100)
Cirrhotic	0	0	0
IL28 Genotype			
CC	36/36 (100)	8/9 (88.9)	0
CT	78/79 (98.7)	5/6 (83.3)	3/3 (100)
TT	24/24 (100)	8/8 (100)	4/4 (100)
Unknown	0	0	0

Trials Include: 590 (ENDURANCE-1), 867 (SURVEYOR-1), 868 (SURVEYOR-2); source: reviewer created

Table 50: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 12 Week Treatment Duration

<i>GLE/PIB 12 wk</i>	<i>GT1 (590, 867, 172, 462)</i>	<i>GT2 (464, 868, 172, 462)</i>	<i>GT 3 (594, 868)</i>	<i>GT4 (583, 867, 868, 172, 462)</i>
BL HCV RNA				
< 6 mil c/mL	165/165 (100)	54/54 (100)	29/30 (96.7)	41/42 (97.6)
≥ 6 mil c/mL	23/24 (95.8)	20/20 (100)	15/19 (78.9)	7/7 (100)
Treatment Experience				
P/R Experienced	179/180 (99.4)	63/63 (100)	36/41 (87.8)	47/48 (97.9)
DAA Experienced	9/9 (100)	11/11 (100)	8/8 (100)	1/1 (100)
Cirrhotic Status				
Non-Cirrhotic	159/159 (100)	65/65 (100)	44/49 (89.8)	40/41 (97.6)
Cirrhotic	29/30 (96.7)	9/9 (100)	0	8/8 (100)
IL28 Genotype				
CC	43/44 (97.7)	28/28 (100)	13/15 (86.7)	4/4 (100)
CT	104/104 (100)	34/34 (100)	27/29 (93.1)	32/33 (97.0)
TT	41/41 (100)	12/12 (100)	4/5 (80.0)	11/11 (100)
Unknown	0	0	0	1/1 (100)

Trials Include: 590 (ENDURANCE-1), 464 (ENDURANCE-2), 583 (ENDURANCE-4), 867 (SURVEYOR-1), 868 (SURVEYOR-2), 172 (EXPEDITION-1), and 462 (EXPEDITION-4); source: reviewer created

Table 51: Pooled SVR12 by Genotype and Baseline Characteristics in DAA- & PR-Experienced, NS5A Naïve Subjects for 16 Week Treatment Duration

<i>GLE/PIB 16w</i>	<i>GT 3 (594, 868)</i>
BL HCV RNA	
< 6 mil c/mL	53/54 (98.1)
≥ 6 mil c/mL	16/19 (84.2)
Treatment Experience	
P/R Experienced	36/39 (92.3)
DAA Experienced	33/34 (97.1)
Cirrhotic Status	
Non-Cirrhotic	21/22 (95.5)
Cirrhotic	48/51 (94.1)
IL28 Genotype	
CC	18/19 (94.7)
CT	39/42 (92.9)
TT	12/12 (100)
Unknown	0

Trials Include: 868 (SURVEYOR-2); source: reviewer created

5 SUMMARY AND CONCLUSIONS

5.1. Statistical Issues

The primary efficacy endpoint for the trials was the proportion of subjects who achieve SVR12, which is the clinical endpoint most predictive of long-term HCV cure. For the Phase 2 trials and the single-arm Phase 3 trials, the primary efficacy analysis was to summarize SVR12 via the 95% CI. While the analysis is fairly straightforward for most trials, there are some statistical issues present in the analyses for this application, particularly for the pooled analyses.

1. Lack of Comparative Trials

The NDA included only two randomized comparative trials from which to enable head-to-head comparisons. ENDURANCE-2 was a placebo-controlled trial allowing for comparative safety only. ENDURANCE-3 included a SOF/DCV active-control for purposes of comparative efficacy; however, it was limited in scope to only TN, GT3-infected subjects. There are no comparative trials for GT4, GT5, or GT6, due to a lower prevalence of these subtypes. Nevertheless, a lack of a control arm for the majority of the trials obscures the evidence of efficacy. The lack of control arms can lead to unbalanced values of measured and unmeasured confounders that could affect the treatment estimates in the trials. While some of the trials compared the SVR12 to a pre-specified clinical threshold SVR12, it is likely that the populations studied previously differ in some characteristics to those studied in these new clinical trials.

2. Large Proportion of Data from Exploratory Phase 2 Trials

In addition, approximately 44% of the overall pool of subjects comes from trials that lacked formal hypothesis testing, and are therefore considered proof-of-concept. As a result, the reviewers are unable to make decisions or draw statistical conclusions from the individual trials lacking formal hypothesis testing.

3. Pooling of Data across Trials

Pooling of the results across trials allows for larger sample sizes for subgroup analyses, particularly for determining the proper treatment duration for subpopulations of the HCV infected. However, caution must be taken when interpreting the results of the pooled analyses. Only four of the nine clinical trials were randomized, which is not accounted for in the un-weighted pooling.

4. Calculation of Confidence Intervals

For some of the individual trial analyses, the applicant used a normal approximation to the binomial distribution to calculate the 95% CI for SVR12. The approximation improves as the sample size increases and performs best when the probability of interest is away from boundary values, 0 or 1. Given that the SVR12 rates across trials are fairly high, mostly above 90%, the coverage probability of the CIs is estimated to be less than 95%, the expected coverage of a 95% CI. The applicant sometimes utilized the Wilson score method to calculate the 95% CI, which typically has a higher coverage than the normal approximation (Wilson, 1927). Therefore, the Wilson score method is also presented by the reviewers when the applicant utilized the normal approximation.

5. Limited Data in Various Subgroups

Some genotypes and subgroups were limited in sample size. Among all the trials, there were a total of 31 GT5 subjects and 47 GT6 subjects. Of the GT5 and GT6 subjects:

- Two GT5 subjects received the 8 week treatment duration, both of whom were treatment-naïve
- 30 GT5 subjects received the 12 week treatment duration, 24 of whom were treatment-naïve
- 10 GT6 subjects received the 8 week treatment duration, eight of whom were treatment-naïve
- 38 GT6 subjects received the 12 week treatment duration, 33 of whom were treatment-naïve

It is expected that the sample sizes for GT5 and GT6 are smaller than the sample sizes for the other genotypes due to their low prevalence worldwide. However, the small sample sizes contribute to less evidence of efficacy for GT5 and GT6, particularly for the 8-week treatment duration. Under such circumstances, it can become necessary to extrapolate knowledge from the other genotypes regarding the efficacy of GLE/PIB.

In addition, there are limited data supporting the efficacy of GLE/PIB among NS5A and/or NS3/4A PI-experienced subjects. MAGELLAN-1 was the only trial that investigated the safety and efficacy of GLE/PIB in NS5A and/or NS3/4A PI-experienced subjects. In MAGELLAN-1, 113 subjects received the recommended dosage of GLE/PIB. Of the 113 subjects enrolled, 38 subjects were NS5A-experienced, 38 subjects were NS3/4A PI-experienced, 37 subjects were both NS5A and NS3/4A PI-experienced and all but four were infected with GT1.

A thorough efficacy evaluation of the proposed GLE/PIB durations requires assessing the treatment effect among race, gender, age, geographic region and relevant baseline factors germane to HCV subgroups.

Given the overall high SVR12 and small numbers enrolled for 4-6 genotypes, overall subgroup analyses are not informative.

5.2. Collective Evidence

Among TN, NC subjects with GT1-6 CHC infection, the applicant originally proposed GLE/PIB for 8 weeks, and for TN, C subjects with GT1-6 CHC infection a 12-week regimen of GLE/PIB was proposed. During the mid-cycle review, it was communicated to the applicant that data do not support the 8-week duration for the GT5-6 subgenotypes. (b) (4)

The collective evidence supporting this NME NDA comes from nine clinical trials, four of which are viewed as Phase 3 confirmatory trials. The data covers treatment received for all six genotypes, those with and without compensated cirrhosis, a subgroup with renal impairment and data from subject who were prior treatment-failures with DAAs. Across the five Phase 2 clinical trials, 1273 subjects received the study drug of which 970 received GLE/PIB 300 mg/150 mg for either 8- 12- or 16-weeks. Across the four Phase 3 clinical trials, there were a total of 1614 subjects received treatment, of which 1399 received GLE/PIB 300 mg/120 mg for either 8- or 12-week in duration. The remaining subjects received placebo (n=100) or SOF/DCV for 12 weeks (n=115). The overall pertinent findings by trials are summarized below.

ENDURANCE-1 was a randomized, open-label trial in **GT1**, NC subjects with or without HIV co-infection (n=33 total co-infected) who were either TN or TE-PRS to compare 8- and 12-week duration of GLE/PIB 300 mg/150 mg. The 8- and 12-week SVR12 (95% CI) rates were 99.1 (97.5, 99.7) and 99.7 (98.4, 100), respectively in the ITT leading to a difference between groups (8-12 weeks) of -0.6%, (-2.2, 0.8). The trial primary objectives to demonstrate superiority of the 12-week regimen against a 91% target historical control followed by a second objective to demonstrate non-inferiority of the 8-week regimen to the 12-week using a 5% margin were achieved.

ENDURANCE-2 was a Phase 3, randomized, double-blind, placebo-controlled (delayed treatment) multicenter study to evaluate the safety and efficacy of GLE/PIB in HCV **GT2**-infected adult subjects without cirrhosis and where either TN or TE-PRS. The overall SVR12 (95% CI) was 99.5% (97.2, 100) with one failure due to missing the SVR12 assessment. The trial objective to achieve superiority of the GLE/PIB 12-week regimen versus a target historical control of 89% was achieved as the lower CI was well above the target. One subjects had on-treatment virologic failure in the 8-week arm and the remaining failures were due to missing assessments at the SVR12 time point.

ENDURANCE-3 was a Phase 3, randomized, open-label, active-controlled (SOF/DCV), multicenter, non-inferiority trial to assess the efficacy and safety of GLE/PIB in **GT3**-infected, TN, non-cirrhotic adult subjects. This trial included three treatment arms, GLE/PIB for 12 weeks, SOF/DCV for 12 weeks and GLE/PIB for 8 weeks. The 8-week GLE/PIB arm was non-randomized. The SVR12 (95% CI, Wilson's method) was 95.3% (91.7, 97.3), 96.5% (91.4, 98.6) and 94.9% (90.3, 97.4). The primary objective was to demonstrate non-inferiority of the 12-week GLE/PIB regimen to SOF/DCV based on a -6% margin. The difference (GLE/PIB 12w-SOF/DCV) was -1.2% with a resulting 95% CI of -5.6% to 3.1%, which

excludes -6%. Since the 8-week arm was non-randomized, no direct comparison of the 8-week arm to the one of the two randomized arms was done by the reviewer. Instead, the reviewer assessed the SVR12 of the 8-week arm against the pre-specified 92% pre-specified clinical threshold using an adjusted 97.5% CI of -7.7% to 5.1%. This CI suggests that the SVR12 of the GLE/PIB 8-week regimen fails to demonstrate superiority over the clinical threshold. It is important to note that the lower SVR12 in the 8-week arm was driven by more relapses compared to the 12-week arm. Specifically, failure to achieve SVR12 was due to one OTVF and 5 relapses in the 8-week arm compared to one OTVF and 3 relapses in the 12-week arm. No OTVFs were reported for the SOF/DCV arm and only one relapse.

EXPEDITION-4 was a single-arm Phase 3 trial that evaluates the safety and efficacy of ABT-493/ABT-530 in adults with **HCV GT 1, 2, 3, 4, 5, and 6** infection who are TN or TE with or without cirrhosis and who have severe renal impairment or end-stage renal disease: stage 4 without dialysis, stage 5 without dialysis, or dialysis. SVR12 was 98.1% (102/104) with two subjects failing due to premature treatment discontinuation and one death deemed unrelated to study drug.

EXPEDITION-1 was a Phase 2, single-arm, open-label, multicenter study to evaluate the safety and efficacy of a 12-week regimen of GLE/PIB for treating **GT 1, 2, 4, 5 or 6** HCV-infected adult subjects with compensated cirrhosis who are either TN or TE-PRS. All but one subject achieved SVR12 and all subjects achieved SVR4 leading to a SVR12 of 99.3% (145/146). The single failure was a relapse in a treatment-experienced (P/R experienced), GT1a-infected subject.

ENDURANCE-4 was a single-arm, open label Phase 3 trial that evaluated the safety and efficacy of GLE/PIB in adults with **HCV GT 4, 5, or 6** infection without cirrhosis who were TN or TE-PRS. The SVR12 was 99.2% (120/121) with one subject failing due to premature discontinuation.

MAGELLAN-1 was a multi-arm, two-part, open label Phase 2 trial that evaluated the safety, efficacy, and pharmacokinetics of GLE/PIB, co-administered or combined, with or without RBV in adults with **HCV GT 1, 4, 5, and 6** infection who failed a prior anti-HCV DAA-containing regimen. Out of 141 subjects enrolled in the trial, all but four subjects were GT1. GT1, NS3/4A PI-experienced subjects that received the proposed dosage for 12 weeks achieved a SVR12 rate of 92.0% (23/25; 2 missing SVR12) across two treatment arms with equivalent dosages and treatment durations. Those who received 16 weeks of the proposed dosage achieved a SVR12 of 100% (12/12). GT1, NS5A-experienced subjects that received the proposed dosage achieved a combined SVR12 rate of 90.0% (18/20) in a 12 week treatment regimen with one on-treatment VF and one post-treatment relapse and a SVR12 rate of 94.1% in a 16 week treatment regimen with one on-treatment VF. GT1 subjects who were both NS3/4A PI- and NS5A-experienced achieved SVR12 rates of 80.0% in both 12 week (16/20; 1 on-treatment VF and 3 post-treatment relapses) and 16 week (12/15; 3 on-treatment VF) treatment durations.

SURVEYOR-1 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety, efficacy, and pharmacokinetics of GLE/PIB in adults with **HCV GT 1, 4, 5, and 6** infection who were TN or TE-PRS, with or without compensated cirrhosis. GT1 subjects without cirrhosis received the proposed dosage for 8 weeks and achieved an SVR12 rate of 97.1% (33/34) with one subject failing due to premature discontinuation. GT 4, 5, and 6 subjects without cirrhosis received the proposed dosage for 12 weeks and achieved an SVR12 rate of 100% (34/34).

SURVEYOR-2 was a multi-arm, multi-part, open label Phase 2 trial that evaluated the safety and efficacy of GLE/PIB, co-administered or combined, with or without ribavirin (RBV) in adults with HCV **GT 2, 3, 4, 5, or 6** infection who were TN or TE-PRS with or without cirrhosis.

5.3. Conclusions and Recommendations

Considering the total amount of evidence from nine clinical trials evaluating GLE/PIB 300 mg/120 mg for the treatment of CHC infection, the conclusions of the statistical reviewers are as follows:

1. GLE/PIB 8-weeks for TN, NC GT 1, 2 and 4: A regimen of GLE/PIB 300 mg/120 mg once daily for 8 weeks achieved a clinically acceptable SVR12 rate among treatment-naïve CHC subjects with GT 1, 2, and 4. Among TN, NC subjects treated with an 8-week GLE/PIB regimen, the SVR12 were 98.8% (245/248), 98.8% (172/174), and 92.3% (36/39) in the GT1, GT2, GT4 pooled groups, respectively. None of the failures were due to virologic failure or relapse.
2. GLE/PIB 8-weeks for TN and TE-PRS, NC, GT5 and 6: Too few TN and TE-PRS, NC GT5- and GT6- subjects, 2 and 8 respectively, were studied on the 8-week GLE/PIB regimen. However, among subjects treated with the 12-week GLE/PIB regimen, the SVR12 was 100% for GT5 (22/22) and for GT6 (28/28), providing evidence to support the 12-week regimen for these less-common genotypes.
3. GLE/PIB 8-weeks for TN, NC GT 3: A regimen of 8-week GLE/PIB for GT3-infected, NC, TN subjects resulted in an SVR12 of 95% (90, 97) with one OTVF and five relapses from the ENDURANCE-3 trial suggesting an inferior rate of SVR12 versus a 92% historical control on the basis of the statistical target alone. However, the SVR12 is high and a 3% relapses is not viewed by the review team as problematic therefore an 8-week regimen for this subpopulation is viewed as acceptable.
4. GLE/PIB 12-weeks for TN, C, GT 1, 2, 3, 4, 5, and 6: Subjects with cirrhosis with GT1, 2, 4, 5, or 6 CHC infection received GLE/PIB 300 mg/120 mg for 12 weeks. The sample sizes for subjects with cirrhosis are limited. Nevertheless, SVR12 rates were 100% in all GTs with the exception of the GT3, which was 98.4%. (NOTE: Please refer to the Clinical review of GLE/PIB for greater exploration of overall severity of cirrhosis.)
5. GLE/PIB 16-week for PRS-Experienced, GT3: The data support a 16-week regimen of GLE/PIB regardless of cirrhotic status (pooled SVR12 (95% CI) of 95% (87, 98) over a 12-week regimen that conferred lower a SVR12 of 88%.
6. GLE/PIB 8-weeks for DAA-and PRS-experienced, NC GT 1, 2 and 4: An 8 week treatment regimen achieved a clinically acceptable SVR12 rate among DAA- and PRS-experienced CHC subjects with GT 1, 2, and 4 and without cirrhosis. The SVR12 rates among DAA- and PRS-experienced, NC subjects treated for 8 weeks are 99.3%, 91.3%, and 100% for GT 1, 2, and 4, respectively. The sample sizes for PRS-experienced CHC subjects with GT 2 and 4 and without cirrhosis that received 8 weeks of GLE/PIB are limited. However, the SVR12 rates observed are similar (although no testing was done) from the SVR12 rates among subjects of the same subgroup that received a 12-week

treatment duration. In addition, there were only two virologic failures in DAA- and PRS-experienced, GT2-infected subjects without cirrhosis that received the 8 week treatment duration.

7. GLE/PIB 16-weeks for DAA-and PRS-Experienced, NC, GT3: A 16 week treatment regimen achieved a clinically acceptable SVR12 rate of 95.5% among DAA- and PRS-experienced, GT3-infected subjects without cirrhosis that were pooled across trials. In contrast, DAA- and PRS-experienced, GT3-infected subjects without cirrhosis that received GLE/PIB for 12 weeks achieved a SVR12 rate of 89.8%, only slightly lower than 90%. However, there were four post-treatment relapses and one on-treatment virologic failure among those that received the 12 week treatment duration, compared to one post-treatment relapse among those that received the 16 week treatment duration.
8. GLE/PIB 16-weeks for NS3/4A PI- and/or NS5A-Experienced, non-GT1: In the one trial that assessed efficacy of GLE/PIB in NS3/4A PI- and/or NS5A-experienced subjects, all but four subjects were GT1-infected, with the other four being GT4-infected. As a result, the reviewers only considered indications for GT1-infected patients with NS3/4A PI and/or NS5A experience.
9. GLE/PIB 16-weeks for NS5A-Naïve, NS3/4A PI-Experienced, GT1: Sample sizes are relatively small for the relevant sub-populations of subjects with prior HCV treatment experience. Nevertheless, the SVR12 rate for 12 weeks of treatment in GT1, NS3/4A PI-experienced subjects was 92.0% and no such subjects experienced virologic failure, providing evidence to support a 12-week indication.
10. GLE/PIB 16-weeks for NS5A-Experienced, NS3/4A PI-Naïve, GT1: The SVR12 rate for 12 weeks of treatment in GT1, NS5A-experienced subjects that received 12 weeks of treatment was 90.0%. However, there were two virologic failures in such subjects, one of whom experienced a post-treatment relapse. In contrast, NS5A-experienced subjects that received 16 weeks of treatment achieved a SVR12 of 94.1% with no post-treatment relapses. Therefore, the evidence supports a 16 week treatment duration for GT1-infected, NS5A-experienced subjects.
11. GLE/PIB 16-weeks for NS3/4A PI- and NS5A-Experienced, GT1: For subjects that are both NS3/4A PI- and NS5A-experienced, the SVR12 rate was 80% for both the 12 and 16 week treatment durations. In addition, there were three post-treatment relapses and one on-treatment virologic failure in the 12 week treatment arm and three on-treatment virologic failures in the 16 week treatment arm. The lower SVR12 rate and higher number of virologic failures indicated that GLE/PIB 300 mg/120 mg did not achieve an acceptable threshold of efficacy among GT1-infected subjects who are both NS3/4A PI- and NS5A-experienced.
12. GLE/PIB 12 weeks in CHC subjects with renal impairment: Subjects with renal impairment, including dialysis, received only GLE/PIB for 12 weeks. Nevertheless, all but two subjects (102/104, 98.1%) achieved SVR12 with no virologic failures. While the applicant did not evaluate an 8-week GLE/PIB treatment regimen in subjects with renal impairment, the evidence does not suggest the need for separate indications for CHC-infected patients with renal impairment.

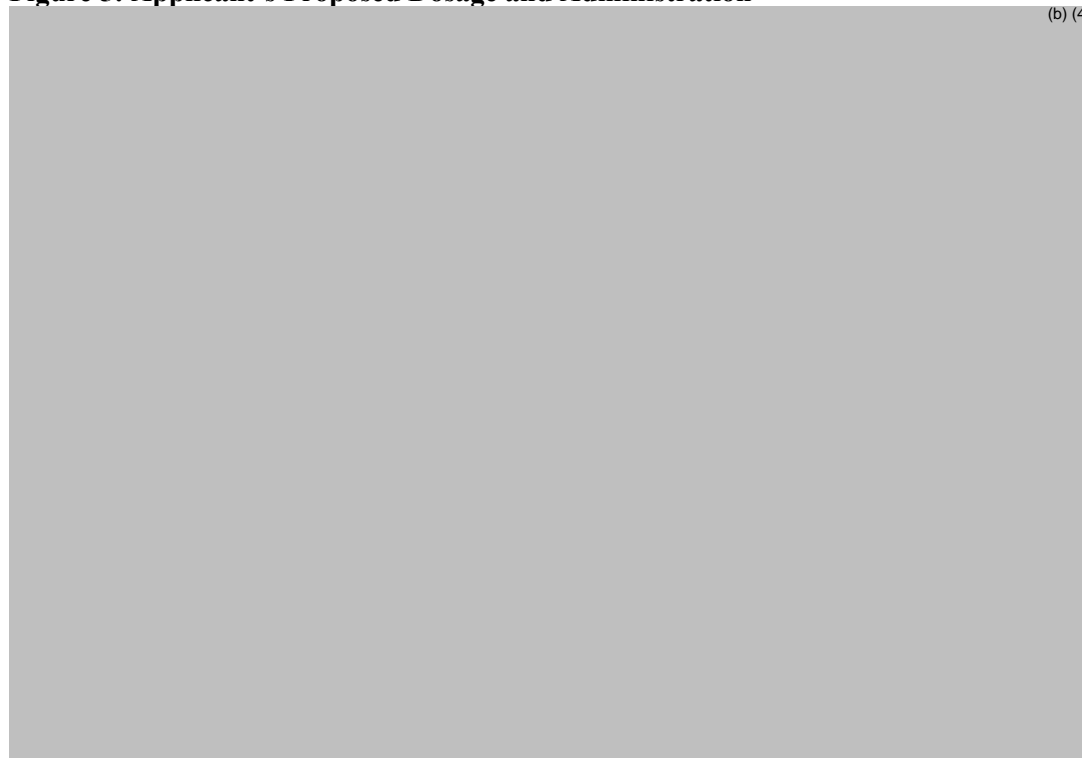
5.4. Labeling Recommendations

NDA 209394 Mavyret™ (Indication: Treatment of Chronic HCV GT1-6 Infection)
Statistical Review: LaRee A. Tracy, MA, PhD (DB4) & Therri Usher, PhD (DB4)

The agency's labeling negotiations with the applicant are ongoing. The summary given represents key changes recommended by the statistical reviewers to Sections 2 and 14 as of May 2, 2017.

The applicant submitted the dosage and administration presented in Figure 5.

Figure 5: Applicant's Proposed Dosage and Administration



Based on collaboration with the other review divisions, we recommend the following dosage and administration presented in Figure 6.

Figure 6: Review Team's Proposed Dosage and Administration

----- DOSAGE AND ADMINISTRATION -----

- Testing Prior to the Initiation of Therapy: Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Recommended dosage: Three tablets taken orally once daily with food. (2.2)
- See recommended treatment duration in tables below. (2.2)

Recommended Duration for Treatment-Naïve Patients

HCV Genotype	Treatment Duration	
	Without Cirrhosis	With Compensated Cirrhosis
1, 2, 3, 4	8 weeks	12 weeks
5, 6	12 weeks	12 weeks

Recommended Duration for Treatment-Experienced Patients

HCV Genotype	Prior Treatment Experience	Treatment Duration	
		Without Cirrhosis	With Compensated Cirrhosis
1	PRS ¹	8 weeks	12 weeks
	NS3/4API (NS5A inhibitor naïve) ²	12 weeks	12 weeks
	NS5A inhibitor (NS3/4API naïve) ³	16 weeks	16 weeks
2, 4	PRS ¹	8 weeks	12 weeks
3	PRS ¹	16 weeks	16 weeks
5, 6	PRS ¹	12 weeks	12 weeks

1. PRS=Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.
2. Regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with interferon and ribavirin or pegylated interferon and ribavirin.
3. Regimens containing ledipasvir or daclatasvir in combination with sofosbuvir (with or without ribavirin or interferon).

- HCV/HIV-1 co-infection: Follow the dosage recommendations in the table above. (2.1)

In particular, the statistical reviewers recommend a 12-week treatment duration for GT5- and GT6-infected treatment-naïve and PRS-experienced patients without cirrhosis. This recommendation is based on much smaller sample sizes for GT5- and GT6-infected subjects that received an 8-week treatment duration, compared to those that received a 12 week treatment duration. The smaller sample sizes translate to stronger evidence of efficacy for a 12, rather than 8, week treatment duration.

In addition, we do not recommend [REDACTED] (b) (4). We also do not recommend an indication for GLE/PIB in NS3/4A PI-experienced patients who are also NS5A-experienced. This

decision is based on a lower SVR12 rate and a higher rate of on-treatment virologic failure in this subpopulation. Additionally, viral resistance may play a role in virologic failures in this subpopulation (see the virology review for further elaboration). However, we do recommend a 12 week treatment duration for GT1-infected, NS3/4A PI-experienced (NS5A-naïve) patients due to the high SVR12 rate observed among such subjects.

Based on the recommendations for indications and treatment durations, we recommend changes to the applicant's Table 10, which is presented below and contains a summary of clinical studies conducted in this application. The changes in the summary were made so that only subjects with the recommended treatment duration were included. Note that the recommended changes made in red and bolded.

Figure 7: Recommended Changes to Applicant's Summary of Clinical Trials

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

TN=treatment naïve

TE-PRS= defined as prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A protease inhibitor or NS5A inhibitor.

PI=protease inhibitor

CKD=chronic kidney disease

Also, we recommend that the applicant’s Table 17, presented as Figure 8, that summarizes the results from MAGELLAN-1 should be changed to reflect the results from subjects in MAGELLAN-1 with the proposed dosage and recommended treatment duration based on their treatment experience.

Figure 8: Applicant’s Results From MAGELLAN-1 Part 2



Figure 9: Review Team’s Proposed Results From MAGELLAN-1

	Genotype 1 NS3/4A PI- Experienced¹ Who are NS5A Inhibitor- Naive	Genotype 1 NS5A Inhibitor- Experienced² Who are NS3/4A PI Naive
	TRADENAME 12 weeks (N=25)	TRADENAME 16 weeks (N=17)
SVR12	92% (23/25)	94% (16/17)
Outcome for Subjects without SVR		
On-treatment Virologic Failure	0% (0/25)	6% (1/17)
Relapse	0% (0/25)	0% (0/16)
Other ⁴	8% (2/25)	0% (0/17)
¹ Includes subjects who previously failed boceprevir-, simeprevir-, or telaprevir- containing regimens, without NS5A inhibitors. ² Includes subjects who previously failed daclatasvir- or ledipasvir/sofosbuvir-containing regimens, without NS3/4A PIs. ³ Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.		

Additionally, we recommend that the applicant separate the submitted Table 1, presented in Figure 10 below, into three different tables. Since the findings for GT1 given in the applicant’s Table 11 come from ENDURANCE-1, which is a comparative trial of two different GLE/PIB treatment durations, the results for GT1 should stand alone. In addition, the results from GT5 and GT6 should be changed to reflect our recommendation for a 12-week treatment duration, as shown in Figure 11. Finally, findings for non-GT3 infected subjects with compensated cirrhosis should stand alone in a separate table, presented as the results from one trial, EXPEDITION-1.

Figure 10: Applicant’s Pooled Results for GT1, 2, 4, 5, and 6 With and Without Cirrhosis



Figure 11: Review Team’s Proposed Pooled Results for GT2, 4, 5, and 6 Without Cirrhosis

	TRADENAME 8 weeks		TRADENAME 12 weeks	
	Genotype 2 N=197	Genotype 4 N=46	Genotype 5 N=27	Genotype 6 N=30
SVR12	98%	93%	100%	100%
Outcome for Subjects without SVR12				
On-treatment VF	0	0	0	0
Relapse	1% (2/197)	0	0	0
Other*	1% (2/197)	7% (3/46)	0	0

Finally, we recommend the removal of the (b) (4).
 The proper comparison would have been GLE/PIB 8 weeks versus SOF+DCV 12 weeks had the study planned for a GLE/PIB 8 week treatment comparison. Additional details regarding the statistical comparison between GLE/PIB 12 weeks and SOF+DCV can be included as a footnote.

Figure 12: Recommended Changes to Applicant’s Results From ENDURANCE-3

	TRADENAME¹ 8 weeks (N=157)	TRADENAME 12 weeks (N=233)	DCV+SOF 12 weeks (N=115)
SVR12	94.9% (149/157)	95.3% (222/233)*	96.5% (111/115)*
(b) (4)			
Outcome for Subjects without SVR12			
On-treatment VF	(b) (4) 1% (1/157)	(b) (4) <1% (1/233)	0% (0/115)
Relapse	3% (5/150)	(b) (4) 1% (3/222)	(b) (4) 1% (1/114)
Other ²	1% (2/157)	3% (7/233)	(b) (4) 3% (3/115)
(b) (4)			
¹TRADENAME 8 weeks was a non-randomized arm, (b) (4)			
² Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.			
(b) (4)			

6 References

1. Wilson, E. B. (1927). "Probable inference, the law of succession, and statistical inference". Journal of the American Statistical Association. 22: 209–212.

7 Appendix A - Study Designs

Note that the sources for the trial designs in Appendix A are the study reports for each trial, provided by the applicant.

Figure 13: ENDURANCE-1 (M13-590) Trial Design

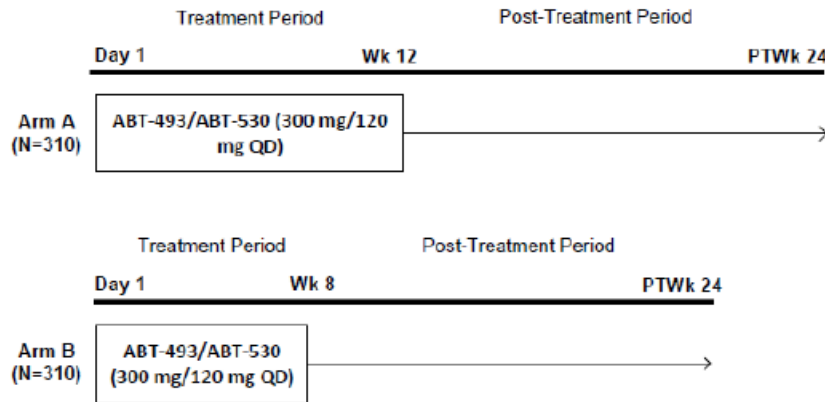


Figure 14: ENDURANCE-2 (M15-464) Trial Design

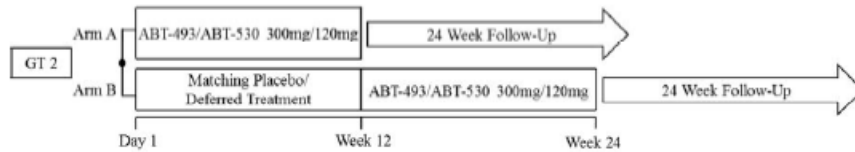
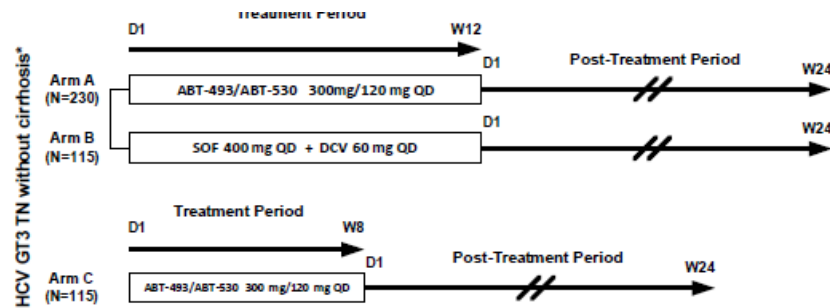


Figure 15: ENDURANCE-3 (M14-594) Trial Design



* Arms A and B are randomized; Arm C is sequentially enrolled after Arms A and B complete enrollment.

NDA 209394 Mavyret™ (Indication: Treatment of Chronic HCV GT1-6 Infection)
 Statistical Review: LaRee A. Tracy, MA, PhD (DB4) & Therri Usher, PhD (DB4)

Figure 16: ENDURANCE-4 (M13-583) Trial Design

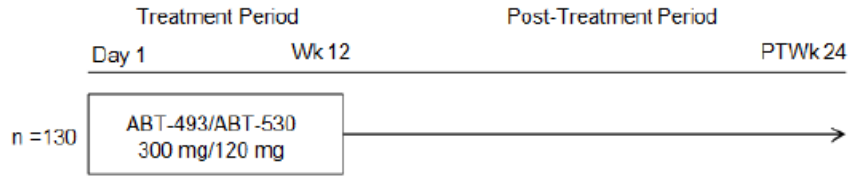


Figure 17: EXPEDITION-1 (M14-172) Trial Design

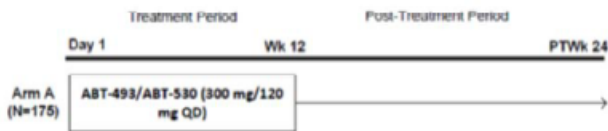
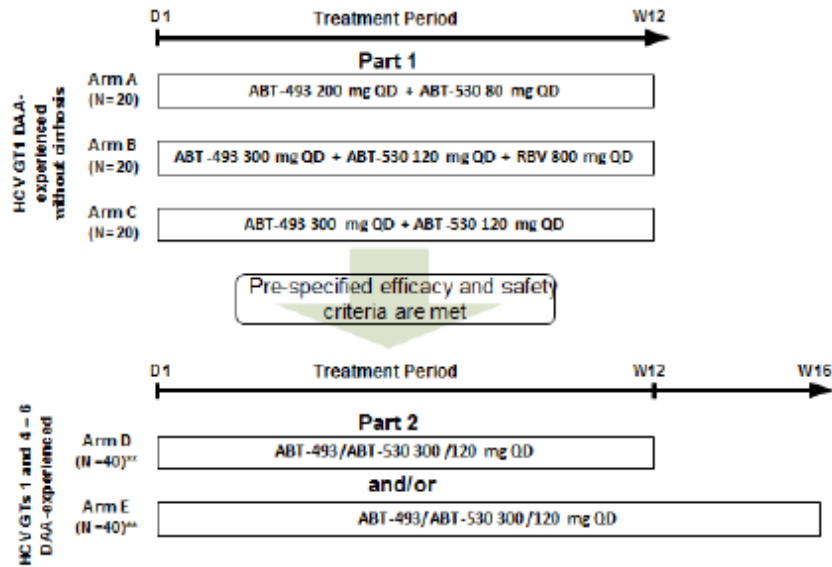


Figure 18: MAGELLAN-1 (M15-410) Trial Design



** If 1 arm is opened for enrollment, the sample size will be 40 – 60.

Figure 19: SURVEYOR-1 (M14-867) Trial Design

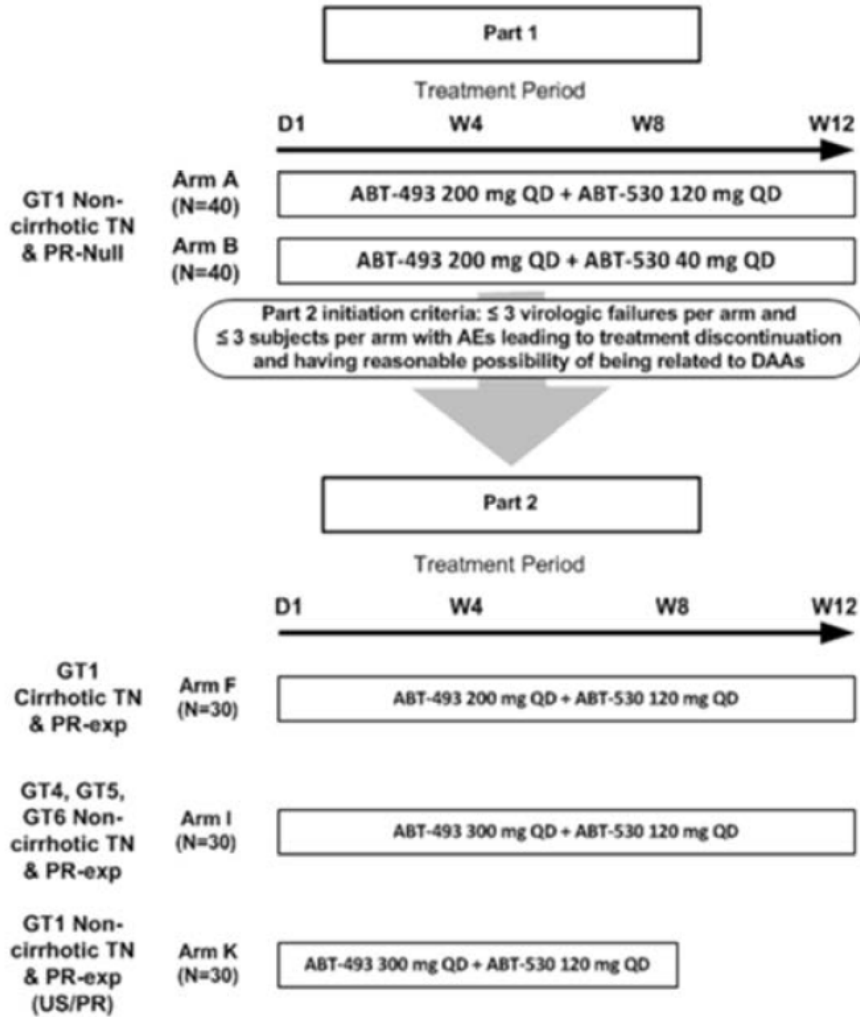


Figure 20: SURVEYOR-2 (M14-868) Parts 1 & 2 Trial Design

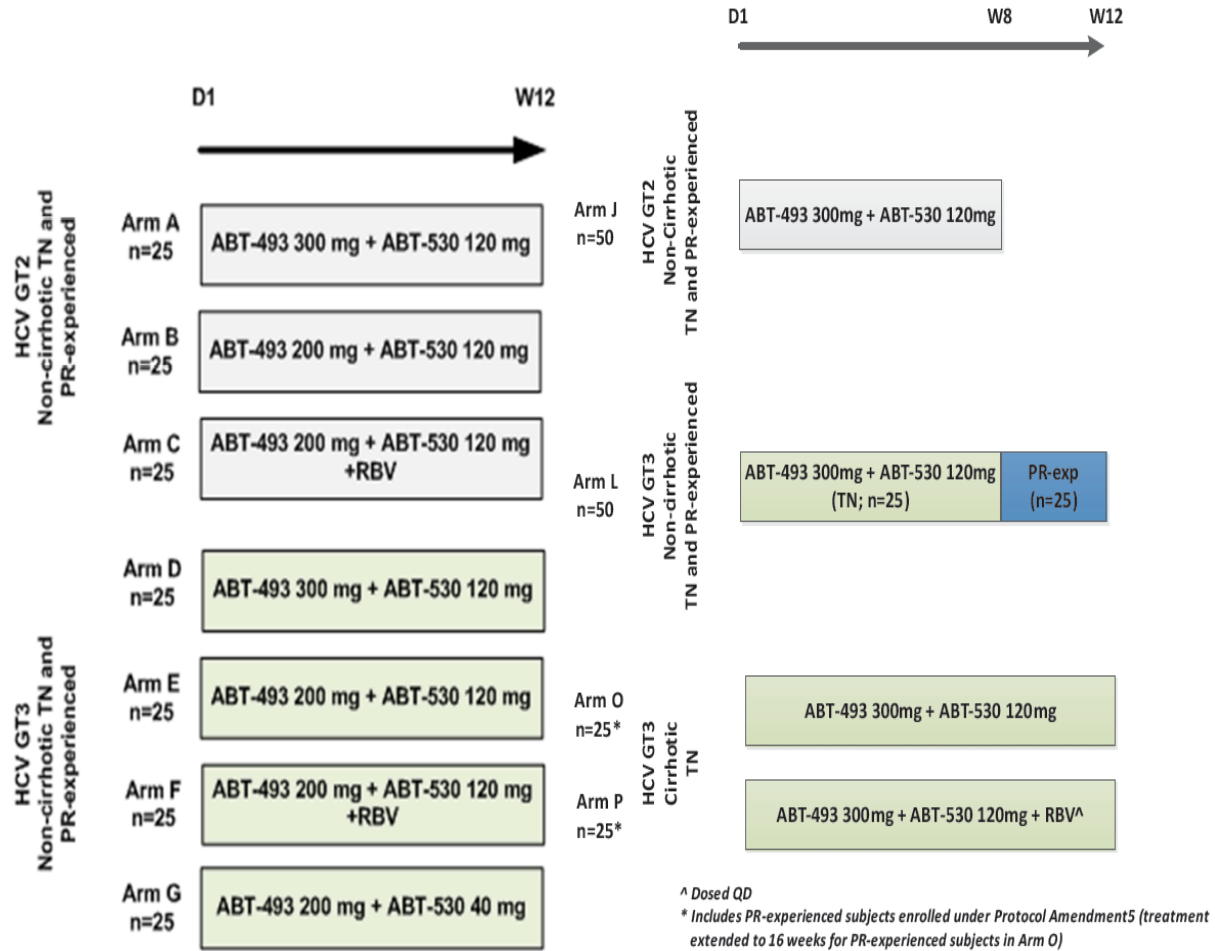
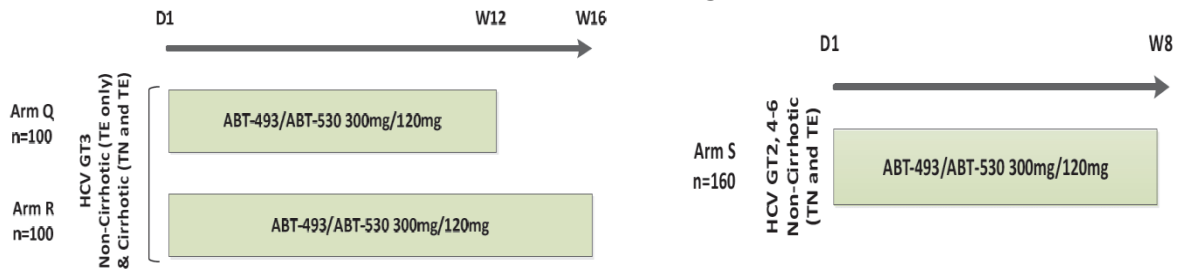


Figure 21: SURVEYOR-2 (M14-868) Parts 3 & 4 Trial Design

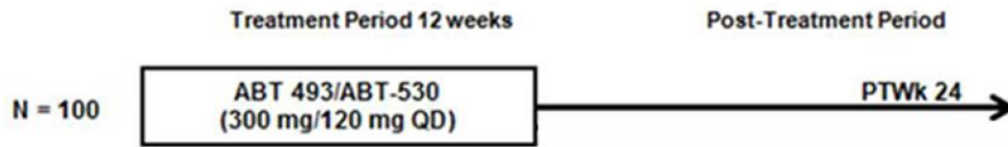


GT = genotype; HCV = hepatitis C virus; TE = treatment-experienced; TN = treatment-naïve

GT = genotype; HCV = hepatitis C virus; TE = treatment-experienced; TN = treatment-naïve

NDA 209394 Mavyret™ (Indication: Treatment of Chronic HCV GT1-6 Infection)
Statistical Review: LaRee A. Tracy, MA, PhD (DB4) & Therri Usher, PhD (DB4)

Figure 22: EXPEDITION-4 (M15-462) Trial Design



PTWk = Post-Treatment Week; QD = once daily

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

/s/

LAREE A TRACY
05/18/2017

THERRI A USHER
05/18/2017

THAMBAN I VALAPPIL
05/18/2017

DIONNE L PRICE
05/18/2017
concur