CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205834Orig1s000

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 #:	205834
Supplement #:	0000
Drug Name:	Sofosbuvir and Ledipasvir fixed-dose combination
Indication(s):	Treatment of chronic hepatitis C for adults
Applicant:	Gilead Sciences, Inc.
Date(s):	Original NDA Submitted Date: February 10, 2014
	PDUFA date: October 10, 2014
Review Priority:	Priority
Biometrics Division:	DB4
Statistical Reviewer:	Karen Qi, Ph.D.
Concurring Reviewers:	Fraser Smith, Ph.D.
Medical Division:	Antiviral
Clinical Team:	Sarah Connelly, MD
Project Manager:	Linda Onaga, M.P.H.

Keywords:

one-sample binomial test, Clopper-Person exact confidence interval, Zelen's exact test, stratified Cochran-Mantel-Haenszel test, exact confident interval based on inverting a two-sided test, hepatitis C

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Gilead submitted three Phase 3 trials to support the regimens containing Sofosbuvir 400 mg and Ledipasvir 90 mg fixed-dose combination (SOF/LDV) tablet administered once daily in the treatment of subjects infected with genotype (GT) 1 hepatitis C virus (HCV). The three trials studied regimens of different durations of SOF/LDV with or without combined use of Ribavirin (RBV) in either GT1 treatment-naïve (TN) or GT1 treatment-experienced (TE) subjects. All of the trials had the same primary efficacy endpoint which was the SVR12 rate defined as the proportion of subjects who had HCV RNA below the lower of quantitation (LLOQ) 12 weeks after the end of treatment.

The ION-1 study (i.e., Study GS-US-337-0102) evaluated four regimens in cirrhotic and non-cirrhotic GT1 TN subjects. The four regimens were 12 weeks of SOF/LDV, 12 weeks of SOF/LDV with RBV, 24 weeks of SOF/LDV, 24 weeks of SOF/LDV with RBV. In the pre-NDA meeting in June of 2013, the Antiviral Division agreed with the applicant that the efficacy data for the two 24-week arms in the study would not be necessary in this NDA submission if the two 12-week arms were able to achieve SVR rates ≥ 90% in subjects with and without cirrhosis separately. Based on this agreeable criterion, the applicant only summarized the efficacy results for the two 12-week arms in the ION-1 study in the NDA. The study demonstrated that the SVR12 rate for the 12-week SOF/LDV treatment either without or with RBV was greater than 97% in GT1 TN subjects including cirrhotic and non-cirrhotic subjects, which was statistically significantly superior to the pre-specified 60% historical rate. Only one relapse occurred in the two regimens. The use of RBV appeared not to affect the SVR12 rate.

The ION-3 study (i.e., Study GS-US-337-0108) also included GT1 TN subjects. It differed from the ION-1 study mainly in patient population and treatment durations. The study only enrolled non-cirrhotic GT1 TN subjects. The three treatment arms in the study were 8 weeks of SOF/LDV, 8 weeks of SOF/LDV plus RBV, and 12 weeks of SOF/LDV. All the three arms resulted in at least 93% SVR12 rates in non-cirrhotic GT1 TN subjects which were statistically significantly greater than the pre-specified 60% historical rate. The use of RBV again did not show to have an impact on SVR12 rate in the study. No statistically significant difference in SVR12 rates was found between the 8-week and 12-week treatment durations. The main reason that the subjects did not achieve SVR12 was relapse in the 8-week regimens but was discontinuation of study in the 12-week regimen. Relapse was one of the key pre-specified secondary efficacy endpoints. The relapse rate for 8 weeks of SOF/LDV without RBV (5%) was similar to the rate for 8 weeks of SOF/LDV with RBV (4%), which suggested that the use of RBV did not have an impact on relapse. The exploratory analyses to compare the pooled relapse rate for 8 weeks SOF/LDV with and without RBV versus 12 weeks of SOF/LDV revealed that the 12-week duration reduced the relapse rate by approximately 3% (95% CI: 0.2%, 6.0%) in comparison to the 8-week duration. Meanwhile, the safety review performed by the medical officer, Dr. Sarah Connelly, concluded that the 8 weeks and 12 weeks of SOF/LDV had similar safety profiles.

Based on the collective evidence in the ION-1 and ION-3 studies, the statistical reviewer concluded that the 12 weeks of SOF/LDV was a better regimen for treatment of GT1 TN cirrhotic and non-cirrhotic subjects.

The ION-2 study (i.e., Study GS-US-337-109) included cirrhotic and non-cirrhotic GT1 TE subjects where the same four regimens as in the ION-1 study were investigated. The study showed that the 12 weeks of SOF/LDV without or with RBV led to approximately 94% to 96% SVR12 rates and 24 weeks of SOF/LDV without or with RBV had the SVR12 rates as high as 99%. All of the SVR12 rates were statistically significantly superior to the pre-specified 25% historical rate. Also, the relapse rates for the two 12-week regimens were 4% to 6%, whereas no relapse occurred in the two 24-week treatment regimens. The difference in SVR12 rates between the 12-week and 24-week regimens were almost entirely explained by the relapse rate. The study again suggested that the use of the RBV had a minimal impact on the SVR12 and relapse rates. The pre-specified subgroup analysis defined by the baseline cirrhotic status demonstrated that there was an obviously numerical trend that the treatment for 24 weeks resulted in a higher SVR12 rate than the treatment for 12 weeks in the cirrhotic subjects but the two treatment durations had comparable SVR12 rates in the non-cirrhotic subjects. Further exploratory analyses for the relapse rate led to the consistent results that the longer treatment duration had approximately 16% lower relapse rates than the shorter treatment duration in the cirrhotic subjects but was only 2% lower in the non-cirrhotic subjects. The statistical reviewer concluded that 12 weeks of SOF/LDV regimen was sufficient for the non-cirrhotic GT1 TE subjects while 24 weeks of SOF/LDV regimen was optimal for the cirrhotic GT1 TE subjects.

There was no major statistical issue identified in the submission.

2 INTRODUCTION

2.1 Overview

SOF is a novel nucleotide analogue inhibitor of HCV NS5B protein to prevent viral replication. In 2013, the FDA approved SOF in combination with Peg-IFN and RBV for 12 weeks to treat GT1 and GT4 subjects and SOF in combination with RBV to treat GT2 and GT3 subjects. Peg-IFN is well known to have many side effects. The 12-week SOF+PegIFN+RBV regimen in GT1 subjects shortened the PegIFN treatment duration compared with the old standard of care which usually required 48 weeks of PegIFN, and therefore had a better safety profile. However, there is a need to develop safer PegIFN-free treatment regimens. LDV is a novel HCV NS5A inhibitor which has demonstrated potent anti-HCV activity against GT1a and GT1b HCV infection. The SOF/LDV tablet combines these two HCV-specific direct-acting antiviral agents into a single tablet. According to the applicant, the early phase studies showed that the SOF/LDV resulted in 90% SVR12 rates in GT1 subjects without any significant safety concern.

SOF/LDV was shown to be effective. Also, it was Peg-IFN-free and could be RBV-free, and was a single tablet more convenient for patients. Therefore, the regimen is considered to be breakthrough therapy. In this NDA, the applicant submitted the interim clinical study reports for

three pivotal studies to support SOF/LDV in both TN and TE GT1 subjects with and without cirrhosis. The NDA was granted a priority review.

The statistical reviewer focused on reviewing the efficacy of the three studies in this review report. The summaries of the key elements in the study design in each study are displayed in Table 1.

Table 1: List of Studies Reviewed in Report

Study number	Design	Patient population	Treatment arms/ Sample size	Primary efficacy endpoint/ hypothesis
ION-1 (GS-US-337-0102)	phase 3, multicenter, randomized, open-label	cirrhotic or non-cirrhotic TN subjects with genotype 1 (GT1) HCV infection	• 12-week LDV/SOF, n=214 • 12-week LDV/SOF +RBV, n=217 • (24-week LDV/SOF, n=217[1]) • (24-week LDV/SOF+RBV, n=217[1])	The primary efficacy hypothesis was that the primary efficacy endpoint of the SVR12 rate in each treatment arm was superior to the historical rate of 60%.
ION-3 (GS-US-337-0108)	phase 3, multicenter, randomized, open-label	non-cirrhotic TN subjects with GT1 HCV infection	• 8-week SOF/LDV, n=215 • 8-week SOF/LDV+RBV, n=216 • 12-week SOF/LDV, n=216	same as ION-1
ION-2 (GS-US-337-0109)	phase 3, multicenter, randomized, open-label	cirrhotic or non-cirrhotic TE subjects with chronic GT1 HCV infection	• 12-week SOF/LDV, n=109 • 12-week SOF/LDV+RBV, n=111 • 24-week SOF/LDV, n=109 • 24-week SOF/LDV+RBV, n=111	The primary efficacy hypothesis was that the primary efficacy endpoint of the SVR12 rate in each treatment arm was superior to the historical rate of 25%.

[1]not included in this NDA

2.2 Data Sources

The datasets were initially submitted electronically and are located in \\CDSESUB1\evsprod\NDA205834\0000. The updated SVR12 data for two subjects in the ION-3 study is located in \\CDSESUB1\evsprod\NDA205834\0015. The updated SVR12 data for three subjects in the ION-2 study is located in \\CDSESUB1\evsprod\NDA205834\0019.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall the quality of the data in this NDA submission was good. In the initial submission, the applicant did not provide the SVR12 data for five subjects (three in the ION-1 study and two in the ION-3 study) since they did not reach the post-treatment Week 12 visit at the time of the data lock for the clinical reports. The applicant submitted the data upon the Division's request during the course of the review.

3.2 Evaluation of Efficacy

Both ION-1 and ION-3 studies recruited TN subjects, and the ION-2 study enrolled TE subjects. The reviewer will present the review results for the ION-1 and ION-3 studies together and the ION-2 study separately in Section 3.2.

3.2.1 ION-1 and ION-3

3.2.1.1 Study Design and Endpoints

Both ION-1 and ION-3 studies were phase 3, multicenter, randomized, open-label trials to evaluate the efficacy and safety of use of SOF/LDV FDC with or without RBV for different durations in the GT1 TN subjects. The ION-1 study consisted of four treatment groups, namely, 12-week SOF/LDV, 12-week SOF/LDV+RBV, 24-week SOF/LDV, 24-week SOF/LDV+RBV; while the ION-3 study included three arms, namely, 8-week SOF/LDV, 8-week SOF/LDV+RBV, 12-week SOF/LDV. Eligible subjects were equally randomized into the treatment groups in both studies. All subjects were to complete the post-treatment Week 4 and 12 visits regardless of their treatment duration. Subjects who had HCV RNA < LLOQ at the post-treatment Week 12 visit were also to complete the post-treatment Week 24 visit unless a confirmed viral relapse occurred. After completing the current studies, subjects could enroll into either the SVR Registry Study (i.e., GS-US-248-0122) if they achieved SVR24 or the Sequence Registry Study (i.e., GS-US-248-0123) if they did not achieve SVR24.

Of note, in the pre-NDA meeting in June of 2013, the Division agreed with the applicant that the efficacy data for 24-week arms in the ION-1 study would not be necessary in this NDA submission if the two 12-week arms were able to achieve an SVR12 rate ≥ 90% in subjects with and without cirrhosis separately. Therefore this review report focuses on the two 12-week arms in the study.

In addition to the different treatment arms, there were the following three main differences in the study design for the two studies.

1) The two studies had different TN patient populations. The ION-1 study enrolled both cirrhotic and non-cirrhotic subjects. Among the treated subjects in the two 12-week arms in the study, approximately 15% of them had cirrhosis at baseline. On the other hand, the ION-3 study recruited non-cirrhotic subjects only. Also, the ION-1 study recruited subjects both in the US and Europe. Approximately 42% to 46% of the treated subjects in the two 12-week treatment groups in the study were from Europe. In contrast, the subjects in the ION-3 study were all from the US sites.

2) Since the ION-1 study enrolled the cirrhotic subjects, the stratification factors in the randomization included both genotype (1a or 1b) and cirrhotic status (presence or absence). Genotype was the only stratification factor that was used in the randomization procedure for the ION-3 study.

3) There were two parts in subject enrollment in the ION-1 study. Part A planned to randomize approximately 50 subjects in each arm (i.e., 25% of the planned sample size). Enrollment was halted once Part A was fully enrolled. After all subjects in the two 12-week arms completed post-treatment Week 4, an interim analysis was planned to be conducted by the external data monitoring committee to determine whether to terminate or continue the two 12-week regimens. The interim analysis calculated the conditional power based on the SVR4 rates for the two 12-week arms. If the conditional power was less than 5%, the two 12-week arms would be discontinued. If the conditional power was equal to or greater than 5%, Part B would start to enroll and randomize approximately 600 additional subjects into all four treatment groups.

The HCV viral load was assessed every two weeks until the end of the treatment for the five arms in the ION-1 and ION-3 studies. The HCV viral load was measured at 4 and 12 weeks after the end of the treatment to obtain the sustained virologic responses.

The primary efficacy endpoint in both studies was the proportion of subjects achieving SVR12. Also, the two studies had the same primary hypothesis which was that the SVR12 rate in each treatment arm was superior to the historical control rate of 60%.

The secondary efficacy endpoints included the following:

1) on-treatment virologic failure and relapse defined as follows:

- on-treatment virologic failure:
  - Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be post-treatment), or last available on-treatment measurement with no subsequent follow up values
  - Rebound: > 1 log10IU/ml increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be post-treatment), or last available measurement with no subsequent follow up value
  - Non-response: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment
- Relapse:
  - HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at the last observed on-treatment HCV RNA measurement, confirmed with consecutive values or last available post-treatment measurement

2) SVR4 and SVR24 rates
3) proportion of subjects with HCV RNA < LLOQ at each on-treatment visit

4) HCV RNA (log_{10} IU/mL) absolute value and change from baseline in HCV RNA through Week 8

3.2.1.2 Statistical Methodologies

A. Efficacy Analysis

The efficacy analyses were performed among the subjects who were randomized and received at least one dose of study drugs. The applicant referred the efficacy analysis set as full analysis set, while the reviewer referred to them as All Treated in this report. The two-sided one-sample binomial test was used to evaluate whether the SVR12 rate was superior to the 60% historical rate in each treatment group. Also, the exact confidence interval (CI) for the SVR12 rate was constructed for each treatment arm using the Clopper-Pearson method.

In the ION-1 study, the applicant's justification for the 60% historical rate as follows:

- A historical SVR rate of approximately 65% was calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for the expected proportion of subjects with cirrhosis (approximately 20%) in this study.

- A 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment. The weighted average of the telaprevir and boceprevir data was estimated to be approximately 70% in non-cirrhotic subjects and 44% in cirrhotic subjects. The SVR rate for the historical control in this study (ie, a patient population of 80% noncirrhotics and 20% cirrhotics) was then calculated to be approximately 65% (ie, 0.8 × 70% + 0.2 ×44%).

In the ION-3 study, the applicant derived the 60% historical rate as follows:

> The basis for this 60% SVR null rate was derived from the historical SVR rate calculated from the telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data after adjusting for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment. The weighted average of the telaprevir and boceprevir data was estimated to be approximately 70% in noncirrhotic subjects. With an estimated minimum of 8% subjects being IFN ineligible (based on enrollment data from the GS-US-337-0102 study [ION-1]), and assuming a 5% response rate in these subjects, the adjusted rate is estimated to be approximately 65% (70%*0.92 + 5%*0.08 = 64.8%). As noted above, the 60% null SVR rate is obtained after allowing for a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter treatment duration.

The Division agreed with the 60% historical rate in both studies because it was close to the upper bound of the 95% CI of the highest SVR rate for PEG+RBV treatment for GT1 subjects in the historical trial. Of note, the 60% historical rate was previously used in the NEUTRINO study to assess the efficacy of 12 weeks of SOF+PEG+RBV treatment in GT1 TN subjects.

In the ION-1 study, the type I error was controlled using Bonferroni correction method. The Bonferroni correction method not only ensured a strong control of family-wise type I error rate at the 0.05 level, but also ensured strong controls of individual type I error rate at the 0.0125 level for comparison of the SVR12 rate in each treatment group against the historical rate of 60%. In the

ION-3 study, the SVR12 rates in the three groups were tested following a sequential testing procedure. If the SVR12 rate for the 12-week SOF+RBV was statistically significant compared to the 60% historical rate at the 0.05 significance level, the SVR12 rates for the two 8-week groups were compared to the null rate of 60%, respectively, each at the 0.025 significance level.

B. Visit Windows

All available HCV RNA data were included in the efficacy analysis unless a subject started alternative HCV medication. The visit windows were pre-specified for all scheduled visits. A visit window was defined as half of the duration of time between the two consecutive study visits. The on-treatment visit windows were calculated from the first dose of study drug (i.e., study day = collection date – date of the first dose; +1 if the result is ≥0), while the off-treatment visit windows were from the last study drug dosing date (i.e., follow-up day = collection data – last dose date).

C. Handling Missing Data or Dropouts

The applicant described their approach to handling missing viral load data in the statistical analysis plans (SAPs) as follows:

> A missing data point for a given study visit may be due to any one of the following reasons:
>
> • A visit occurred but data were not collected or were unusable
> • A visit did not occur
> • A subject permanently discontinued from the study before reaching the window
>
> For analyses of categorical HCV RNA data, if a data point is missing and is preceded and followed in time by values that are "< LLOQ TND", then the missing data point will be set to "< LLOQ TND". If a data point is missing and preceded and followed by values that are "< LLOQ detected", or preceded by "< LLOQ detected" and followed by "< LLOQ TND", or preceded by "< LLOQ TND" and followed by "< LLOQ detected", then the missing value will be set to "< LLOQ detected"; otherwise the data point will be termed a failure (ie, ≥ LLOQ detected).
>
> Subjects with missing data due to premature discontinuation of the study will have missing data imputed up to the time of their last dose (for on-treatment displays). If study days associated with the last dosing date is greater than the lower bound of a visit window, and the value at the visit is missing, then the value will be imputed. If the study days associated with the last dosing date is less than the lower bound of a visit window then the on-treatment value at that visit will remain missing.
>
> If no HCV RNA values are obtained after the last dose of any study drug, the subject will be considered a treatment failure for SVR endpoints. However, success for SVR12 who have no further HCV RNA measurements collected will be counted as a success for SVR24 due to the high correlation between these 2 endpoints.
>
> For the analyses of continuous HCV RNA efficacy data, any subject with a missing value in a visit window that is bracketed by prior and subsequent values of "< LLOQ TND" or "< LLOQ detected" will be set to "< LLOQ TND" (ie, 24 IU/mL). No other imputation will be performed for continuous data.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows the patient disposition for the two 12-week treatment groups in the ION-1 study and all three treatment arms in the ION-3 study. Almost all randomized subjects in these arms were treated, and almost all treated subjects completed the full course of the assigned treatment.

Table 2: Patient Disposition in ION-1 and ION-3

	ION-1		ION-3		
	SOF/LDV 12 Weeks	**SOF/LDV +RBV 12 Weeks**	**SOF/LDV 8 Weeks**	**SOF/LDV +RBV 8 Weeks**	**SOF/LDV 12 Weeks**
Randomized	217	218	215	216	216
Never treated	3	1	0	0	0
Treated	214 (100%)	217 (100%)	215 (100%)	216 (100%)	216 (100%)
Completed study treatment	212 (99.1%)	213 (98.2%)	215 (100%)	213 (98.6%)	211 (97.7%)
Discontinued study treatment	2 (1%)	4 (2%)	0	3 (1.4%)	5 (2.3%)
Adverse event	0	0	0	1 (0.5%)	2 (0.9%)
Protocol violation	1 (0.5%)	1 (0.5%)	0	0	0
Non-compliance with study drug	0	0	0	0	1 (0.5%)
Withdrew consent	0	1 (0.5%)	0	0	0
Lost to follow-up	1 (0.5%)	2 (0.9%)	0	2 (0.9%)	2 (0.9%)

Sources: Table 8-2 in Internal Clinical Study Reports for the ION-1 and ION-3 studies

Table 3 summarizes the patient demographics and HCV disease characteristics at baseline. The demographics and baseline disease characteristics were well balanced between the arms within each study. Except for that there were some cirrhotic and European subjects in the ION-1 study as mentioned in Section 3.2.1.1, the subjects in the two studies had similar patient demographics and baseline disease characteristics. The average age for each of the five treatment arms was approximately 52 years. The majority of the treated subjects in these five arms of two studies were male, white and with baseline body mass index (BMI) < 30 kg/m^2. More than two thirds of the treated subjects in the five arms had HCV genotype 1a infection and non-CC IL28B alleles. The mean baseline HCV viral load was approximately 6.4 log_{10} IU/mL in each arm.

Table 3: Patient Demographics and Baseline HCV Disease Characteristics in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	12-Week SOF/LDV (N=214)	12-Week SOF/LDV+RBV (N=217)	8-Week SOF/LDV (N=215)	8-Week SOF/LDV+RBV (N=216)	12-Week SOF/LDV (N=216)
Age (years)					
Mean (SD)	52 (10.7)	52 (11.5)	53 (10.2)	51 (11.7)	53 (10.6)
Gender					
Male	127 (59.3%)	128 (59.0%)	130 (60.5%)	117 (54.2%)	128 (59.3%)
Female	87 (40.7%)	89 (41.0%)	85 (39.5%)	99 (45.8%)	88 (40.7%)
Race					
White	187 (87.4%)	188 (86.6%)	164 (76.3%)	176 (81.5%)	167 (77.3%)
Black	24 (11.2%)	26 (12.0%)	45 (20.9%)	36 (16.7%)	42 (19.4%)
Other	1 (0.5%)	0	6 (2.8%)	4 (1.9%)	7 (3.2%)
Region					
US	125 (58.4%)	118 (54.4%)	215 (100%)	216 (100%)	216 (100%)
Europe	89 (41.6%)	99 (45.6%)	0	0	0
Baseline BMI					
< 30 kg/m^2	176 (82.2%)	171 (78.8%)	151 (70.2%)	152 (70.4%)	159 (73.6%)
≥ 30 kg/m^2	38 (17.8%)	46 (21.2%)	64 (29.8%)	64 (29.6%)	57 (26.4%)
HCV subgenotype					
1A	144 (67.3%)	148 (68.2%)	171 (79.5%)	172 (79.6%)	172 (79.6%)
1B	66 (30.8%)	68 (31.3%)	43 (20.0%)	44 (20.4%)	44 (20.4%)
1 (no confirmed subtype)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0
4	1 (0.5%)	0	0	0	0
Missing	2 (0.9%)	0	0	0	0
IL28B					
CC	55 (25.7%)	76 (35.0%)	56 (26.0%)	60 (27.8%)	56 (25.9%)
CT	113 (52.8%)	107 (49.3%)	120 (55.8%)	128 (59.3%)	124 (57.4%)
TT	46 (21.5%)	34 (15.7%)	39 (18.1%)	28 (13.0%)	36 (16.7%)
Cirrhosis					
No	178 (83.2%)	183 (84.3%)	215 (100%)	216 (100%)	216 (100%)
Yes	34 (15.9%)	33 (15.2%)	0	0	0
Missing	2 (0.9%)	1 (0.5%)	0	0	0
Baseline HCV RNA (log_{10} IU/mL)					
Mean (SD)	6.4 (0.7)	6.4 (0.6)	6.5 (0.8)	6.4 (0.7)	6.4 (0.8)
Median	6.5	6.5	6.6	6.6	6.6
< 800k IU/mL	41 (21.0%)	44 (20.3%)	34 (15.8%)	45 (20.8%)	44 (20.4%)
≥ 800k IU/mL	169 (79.0%)	173 (79.7%)	181 (84.2%)	171 (79.2%)	172 (79.6%)
ALT					
≤ 1.5 x ULN	94 (43.9%)	98 (45.2%)	128 (59.5%)	121 (56.0%)	117 (54.2%)
> 1.5 x ULN	120 (56.1%)	119 (54.8%)	87 (40.5%)	95 (44.0%)	99 (45.8%)

Sources: Tables 8-4 and 8-5 in Internal Clinical Study Reports for the ION-1 and ION-3 studies

3.2.1.4 Results and Conclusions

A. Primary Efficacy Endpoint

The applicant's primary efficacy analysis showed that the SVR12 rates for the five treatment arms in both ION-1 and ION-3 studies were at least 93% (Table 4). These SVR12 rates were statistically significantly superior to the 60% historical rate (p-values based on one-sample binomial test < 0.001). In the ION-1 study, the SVR12 rates were 97% in both 12-week arms, which suggested the use of RBV did not impact the SVR12 rate. In the ION-3 study, 93% to 95% SVR12 rates were observed in the three treatment arms. There was no statistically significant difference in SVR12 rates between any two groups (Table 5). The study again demonstrated the use of RBV did not influence the SVR12 rate. In the three 12-week arms, the subjects failed to achieve SVR12 mainly due to other reasons rather than relapse. The other reasons were either that the subjects did not have a post-treatment Week 12 visit or that the subjects discontinued from the study. In the two 8-week arms, relapse was mainly attributed as the reason for not achieving SVR12. The statistical reviewer conducted additional analyses to explore the differences in the relapse rates among the treatment groups, and the results are displayed in Sections C and 4.

Table 4: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=214)	**SOF/LDV +RBV 12 Weeks (N=217)**	**SOF/LDV 8 Weeks (N=215)**	**SOF/LDV +RBV 8 Weeks (N=216)**	**SOF/LDV 12 Weeks (N=216)**
SVR12 rate	97.7%	97.2%	94.0%	93.1%	95.4%
(# of responders/N)	(209/214)	(211/217)	(202/215)	(201/216)	(206/216)
[95% CI]	[94.6%, 99.2%]	[94.1%, 99.0%]	[89.9%, 96.7%]	[88.8%, 96.1%]	[91.7%, 97.8%]
Not achieving SVR12					
On-treatment virologic failure	0% (0/214)	0% (0/217)	0% (0/215)	0% (0/216)	0% (0/216)
Relapse	0.5% (1/213)	0% (0/217)	5.1% (11/215)	4.2% (9/214)	1.4% (3/216)
Other	1.9% (4/214)	2.8% (6/217)	0.9% (2/215)	2.8% (6/216)	3.2% (7/216)

Sources: Tables 9-1, 9-2 in Internal Clinical Study Reports for the ION-1 and ION-3 studies

Table 5: Applicant's Results for Inter Group Comparison of SVR12 Rates in ION-3 (All Treated)

	Proportion Difference (97.5% CI)[1]	**P-value[2]**
8-Week SOF/LDV vs. 8-Week SOF/LDV+RBV	0.9% (-3.9%, 5.7%)	0.70
8-Week SOF/LDV vs. 12-Week SOF/LDV	-1.4% (-6.4%, 3.6%)	0.52
8-Week SOF/LDV+RBV vs. 12-Week SOF/LDV	-2.3% (-7.5%, 2.9%)	0.30

Sources: Table 9-1 in Internal Clinical Study Reports for the ION-3 study
[1]Differences in proportions between treatment groups and associated 97.5% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
[2]P-values were based on a stratified Cochran-Mantel-Haenszel test.

One GT4 subject was mistakenly enrolled in the 12-week SOF/LDV group in the ION-1 study. Also, three subjects in the ION-1 study (two in the 12-week SOF/LDV group and one in the 12-week SOF/LDV+RBV group) and two subjects in the ION-3 study (both in the 12-week SOF/LDV

group) did not have the SVR12 data at the time the datasets lock for the clinical reports and therefore their SVR12 data was not included in the original NDA submission. During the review cycle, the applicant provided the review team the updated SVR12 data for these subjects. Table 6 and Table 7 show the updated results for SVR12 after excluding the GT4 subjects and including the SVR12 data for the five subjects.

Table 6: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=213)	**SOF/LDV +RBV 12 Weeks (N=217)**	**SOF/LDV 8 Weeks (N=215)**	**SOF/LDV +RBV 8 Weeks (N=216)**	**SOF/LDV 12 Weeks (N=216)**
SVR12 rate	98.6%	97.2%	94.0%	93.1%	96.3%
(# of responders/N)	(210/213)	(211/217)	(202/215)	(201/216)	(208/216)
[95% CI][1]	[95.9%, 99.7%]	[94.1%, 99.0%]	[89.9%, 96.7%]	[88.8%, 96.1%]	[92.8%, 98.4%]
Not achieving SVR12					
On-treatment virologic failure	0% (0/213)	0% (0/217)	0% (0/215)	0% (0/216)	0% (0/216)
Relapse	0.5% (1/212)	0% (0/217)	5.1% (11/215)	4.2% (9/214)	1.4% (3/216)
Other	0.9% (2/213)	2.8% (6/217)	0.9% (2/215)	2.8% (6/216)	2.3% (5/216)

Table 7: Reviewer's Results for Inter Group Comparison of SVR12 Rates in ION-3 (All Treated)

	Proportion Difference (97.5% CI)[1]
8-Week SOF/LDV vs. 8-Week SOF/LDV+RBV	0.9% (-3.9%, 5.7%)
8-Week SOF/LDV vs. 12-Week SOF/LDV	-2.3% (-7.2%, 2.5%)
8-Week SOF/LDV+RBV vs. 12-Week SOF/LDV	-3.2% (-8.2%, 1.8%)

[1]Differences in proportions between treatment groups and associated 97.5% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.

Of note, the ION-1 study had two parts as mentioned in Section 3.2.1.1. The SVR4 rates in the two 12-week arms in Part A were used to determine whether the 12-week treatment arms should be continued or terminated. The SVR4 rates in the two 12-week arms in Part A turned out at least 95% (i.e., 96.2% [50/52] for the 12-week SOF/LDV group, 98.1% [51/52] for the 12-week SOF/LDV+RBV group), and therefore all four treatment arms in the study continued to enroll the subjects in Part B. Furthermore, the SVR12 rates for the subjects in these two arms in Part A remained the same as SVR4 rates. Part A represented approximately 25% of all treated subjects. The SVR12 rates in Part A for the two 12-week regimens were consistent with the overall results.

B. Key Secondary Efficacy Endpoints

When evaluating the on-treatment virologic response, the reviewer utilized the non-complete = failure (NC=F) approach to impute the missing data. That is, the subjects who prematurely discontinued the study drugs were considered as failure regardless of the reasons for discontinuation in the NC=F analysis. The results from the NC=F analysis were very close to the applicant's observed case analysis due to few discontinuation in the studies.

Figure 1 shows the on-treatment response rates by the treatment groups in both studies based on the NC=F approach. The SOF/LDV treatment suppressed the viral load quickly. Nearly all treated subjects achieved HCV RNA < LLOQ within 4 weeks after the treatment. The high response rates were maintained at the end of the treatment regardless of the treatment duration.

Figure 1: Reviewer's Results for On-Treatment Virologic Response by Treatment Groups in ION-1 and ION-3 (All Treated, NC=F)

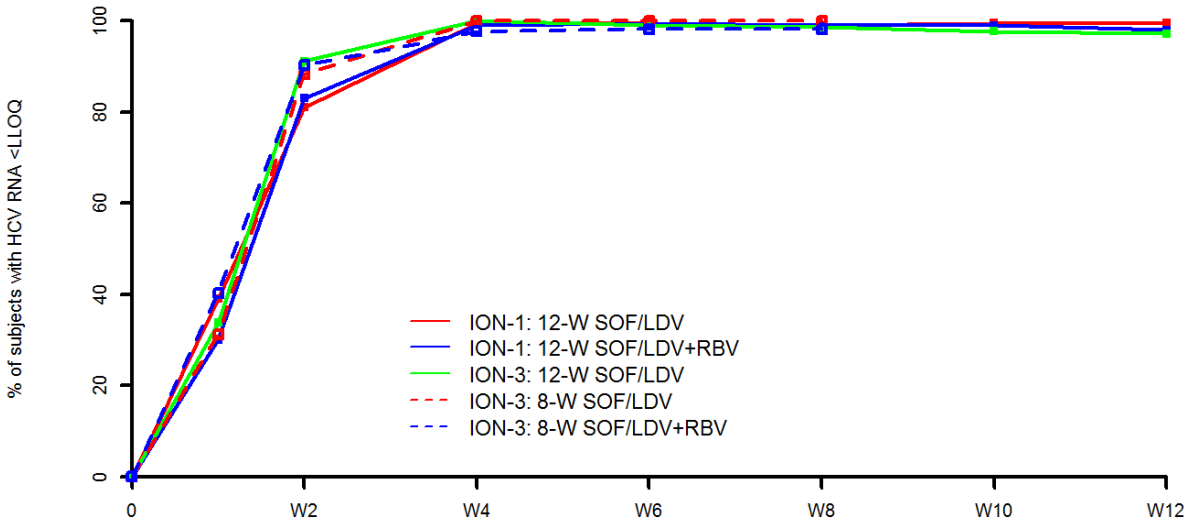


Table 8 displays the post-treatment relapse rates. There was only one relapse in the ION-1 study which occurred in the first 4 weeks after the end of the SOF/LDV treatment for 12 weeks. In the ION-3 study, the 12 week treatment duration led to a lower relapse rate compared to the 8 week treatment duration. Also, all three relapses in the 12-week SOF/LDV group occurred in the first 4 weeks after the end of treatment, while more than two thirds of the relapses in the two 8-week treatment arms occurred within 4 weeks after the end of treatment. The reviewer conducted post hoc exploratory analyses for relapse rates which will be presented in next section.

Table 8: Reviewer's Results for Relapse Rates in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=214)	**SOF/LDV +RBV 12 Weeks (N=217)**	**SOF/LDV 8 Weeks (N=215)**	**SOF/LDV +RBV 8 Weeks (N=216)**	**SOF/LDV 12 Weeks (N=216)**
Number of virologic responders at end of treatment	213	217	215	214	216
Relapse					
By 4 weeks post-treatment	0.5% (1/213)	0% (0/217)	3.7% (8/215)	2.8% (6/214)	1.4% (3/216)
By 12 weeks post-treatment	0.5% (1/213)	0% (0/217)	5.1% (11/215)	4.2% (9/214)	1.4% (3/216)

The SVR4 and SVR12 rates were identical in the 12-week SOF/LDV arms in both studies. In other arms in the two studies, the two rates were fairly close because the majority of relapses

occurred within four weeks after the end of the treatment and there were few subjects discontinuing from the trials (Table 9).

Table 9: Reviewer's Results for SVR Rates in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=214)	SOF/LDV +RBV 12 Weeks (N=217)	SOF/LDV 8 Weeks (N=215)	SOF/LDV +RBV 8 Weeks (N=216)	SOF/LDV 12 Weeks (N=216)
SVR4	98.6% (211)	98.2% (213)	96.3% (207)	94.9% (205)	96.3% (208)
Achieving SVR12	98.6% (211)	97.2% (211)	94.0% (202)	93.1% (201)	96.3% (208)
Not achieving SVR12	0% (0)	0.9% (2)	2.3% (5)	1.9% (4)	0% (0)
Relapse between post-trt WKs 4 and 12	0% (0)	0% (0)	1.4% (3)	1.4% (3)	0% (0)
Missing post-trt WK12 data due to discontinuation	0% (0)	0.9% (2)	0.9% (2)	0.5% (1)	0% (0)

The applicant provided the SVR24 data for all four treatment arms in Part A of the ION-1 study. Among the subjects having both SVR12 and SVR24 data available, all of them achieved both SVR12 and SVR24 (Table 10). The reviewer agreed with the applicant's results.

Table 10: Applicant's Results for Concordance between SVR12 and SVR12 in Part A of ION-1 (All Treated)

	12-week SOF/LDV SVR24		12-week SOF/LDV+RBV SVR24		24-week SOF/LDV SVR24		24-week SOF/LDV+RBV SVR24	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
SVR12								
Yes	47	0	51	0	49	0	50	0
No	0	0	0	0	0	0	0	0

Source: Table 9-4 in Internal Clinical Study Reports for the ION-1study

C. Exploratory Analysis for Relapse in TN Subjects

The SVR12 rates for the five treatment arms in the two phase 3 studies were at least 93%. It was of clinical interest to explore the optimal treatment regimen by evaluating the impact of the use of RBV and treatment duration on relapse rate and identifying a subgroup that may benefit from the longer treatment duration. To address these clinical questions, the statistical reviewer performed post hoc exploratory analyses. The results regarding the impact of use of RBV and treatment duration are summarized in the following sections, while the results for the subgroup analyses are displayed in Section 4.2.

C1. Impact of Use of RBV on Relapse

As shown in Table 4 above, the relapse rate was 0.5% for the 12-week SOF/LDV arm compared with 0% for the 12-week SOF/LDV+RBV arm in the ION-1 study. In the ION-3 study, the relapse rates were approximately 5% and 4% for the 8-week SOF/LDV and 8-week SOF/LDV+RBV, respectively. The use of RBV appeared not to have an impact on the relapse.

C2. Impact of Treatment Duration on Relapse

The ION-3 study was the only trial to compare the 8-week and 12-week treatment durations in the TN subjects. Although the SVR12 rates were similar in the 8-week and 12-week SOF+RBV arms, the difference in the relapse rates between the two arms was 3.7% with the 95% CI of (0.4%, 7.7%) (Table 11). Also, the use of RBV did not have an impact on the relapse rate, and therefore the two 8-week groups were combined to compare with the 12-week SOF+RBV regimen. The difference in the relapse rates between the combined 8-week arms and the 12-week SOF+RBV was 3.3% with the 95% CI of (0.2%, 6.0%). Both of the 95% CIs did not cover zero, which suggested that the 12-week treatment duration statistically significantly reduced the relapse rate as compared to the 8-week duration.

Table 11: Reviewer's Results for Comparison of Relapse Rates Between Different Treatment Durations in ION-3 (All Treated)

	Proportion Difference in Relapse Rate	Exact 95% CI[1]
8-Week SOF/LDV vs. 12-Week SOF/LDV	3.7%	(0.4%, 7.7%)
combination of 8-Week SOF/LDV and 8-Week SOF/LDV+RBV vs. 12-Week SOF/LDV	3.3%	(0.2%, 6.0%)

[1]based on inverting a two-sided test

3.2.2 ION-2

3.2.2.1 Study Design and Endpoints

The ION-2 study had similar key elements for study design to those of the ION-1 and ION-3 studies with the major differences arising for the patient population, treatment arms and the historical rate used for testing the primary hypothesis. Unlike the ION-1 and ION-3 studies, the ION-2 study enrolled the TE subjects. These TE subjects were either cirrhotic or non-cirrhotic and were all from US sites. Also, the ION-2 study had four treatment groups: 12-week SOF/LDV, 12-week SOF/LDV+RBV, 24-week SOF/LDV, and 24-week SOF/LDV+RBV. The subjects were equally randomized into the four treatment groups stratified by their genotype (1a or 1b; subjects with mixed genotype 1a/1b were stratified as 1a) and cirrhotic status (absence or presence). The primary efficacy hypothesis was that the primary efficacy endpoint of the SVR12 rate in each treatment group was superior to the historical SVR rate of 25%.

3.2.2.2 Statistical Methodologies

The statistical methodologies were similar to Section 3.2.1.2. The one-sample binomial test was performed to evaluate whether the SVR12 rate in each treatment group was superior to the 25% historical rate. A Hochberg procedure was applied to control the family-wise type I error rate. The applicant's justification for the 25% historical rate as follows:

- For treatment-experienced subjects (eg, Peg-IFN+RBV) receiving a PI-based triple therapy regimen, a historical retreatment SVR rate of approximately 65% was calculated from the telaprevir (REALIZE study) and boceprevir (RESPOND-2 study) data after adjusting for the expected proportion of subjects with cirrhosis (approximately 20%) in this study. The weighted average of the telaprevir and boceprevir data provided an estimate of SVR rate to be approximately 69% in noncirrhotic subjects and 50% in cirrhotic subjects. The retreatment SVR rate for the historical control in this study (ie, a patient population of 80% noncirrhotics and 20% cirrhotics) was then calculated to be approximately 65% (ie, $0.8 \times 69\% + 0.2 \times 50\%$)

- For subjects who had failed treatment with a PI+Peg-IFN+RBV regimen, retreatment options are currently lacking. A conservative retreatment SVR rate of 5% was, therefore, used.

In this study, the expected proportion of subjects having had prior treatment with a PI+Peg-IFN+RBV regimen was approximately 50%. A 35% null SVR rate was obtained after averaging a 65% retreatment SVR control rate for treatment-experienced subjects (eg, Peg-IFN+RBV) being retreated with PI+Peg-IFN+RBV (current standard of care), and a 5% SVR control rate for subjects who failed prior treatment with a PI+Peg-IFN+RBV regimen, if retreated with a PI+Peg-IFN+RBV regimen. In addition, a discount of 10 percentage points in efficacy was allowed due to the expected improved safety profile and significantly shorter duration associated with the treatment, which resulted in a null SVR rate for this study of 25%.

The Division agreed with the historical rate of 25% based on considering historical data and clinical factors (Poynard et al, Gastroenterology 2009).

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 12 displays the patient disposition. Almost all randomized subjects received at least one dose of study medication. Furthermore, almost all treated subjects stayed in the study until they completed the assigned treatment.

Table 12: Patient Disposition in ION-2

	SOF/LDV 12 Weeks	SOF/LDV +RBV 12 Weeks	SOF/LDV 24 Weeks	SOF/LDV +RBV 24 Weeks
Randomized	109	111	110	111
Never treated	0	0	1	0
Treated	109 (100%)	111 (100%)	109 (100%)	111 (100%)
Completed study treatment	109 (100%)	111 (100%)	107 (98.2%)	110 (99.1%)
Discontinued study treatment	0	0	2 (1.8%)	1 (0.9%)
Lack of efficacy	0	0	0	1 (0.9%)
Protocol violation	0	0	2 (1.8%)	0

Sources: Table 8-2 in Internal Clinical Study Report for Studies GS-US-337-0102 and GS-US-337-0108, respectively

Table 13 displays patient demographics and baseline characteristics in the ION-2 study. The demographics and baseline characteristics were well balanced among the four treatment groups. The average age of the treated subjects was approximately 56 years old. The majority of subjects were male and white. Also, majority of them had BMI < 30 kg/m^2. Approximately 80% of the treated subjects had GT1a HCV infection, and 20% of them had cirrhosis at baseline. The majority of subjects had the non-CC IL28B allele. The mean baseline HCV RNA was approximately 6.5 $\log_{10}$ IU/mL. Slightly more than half of the subjects received PegINF and RBV previously, while the reminder of subjects had a regimen with PI in combination of PegINF and RBV. The proportion of subjects who previously received the regimen with PI in combination of PegINF and RBV was higher in the two 12-week arms than those in the 24-week arms.

Table 13: Applicant's Results for Demographics and Baseline Characteristics in ION-2 (All Treated)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
Age				
Mean (SD)	56 (6.9)	57 (8.0)	56 (8.3)	55 (7.8)
Median	57	59	58	56
Gender				
Male	74 (67.9%)	71 (64.0%)	74 (67.9%)	68 (61.3%)
Female	35 (32.1%)	40 (36.0%)	35 (32.1%)	43 (38.7%)
Race				
White	84 (77.1%)	94 (84.7%)	91 (83.5%)	89 (80.2%)
Black	24 (22.0%)	16 (14.4%)	17 (15.6%)	20 (18.0%)
Other	1 (0.9%)	1 (0.9%)	1 (0.9%)	2 (1.8%)
Baseline BMI				
< 30 kg/m^2	66 (60.6%)	74 (66.7%)	75 (68.8%)	83 (73.9%)
≥ 30 kg/m^2	43 (39.4%)	37 (33.3%)	34 (31.2%)	29 (26.1%)
HCV subgenotype				
1A	86 (78.9%)	88 (79.3%)	85 (78.0%)	88 (79.3%)
1B	23 (21.1%)	23 (20.7%)	24 (22.0%)	23 (20.7%)
IL28B				
CC	10 (9.2%)	11 (9.9%)	16 (14.7%)	18 (16.2%)
CT	70 (64.2%)	77 (69.4%)	68 (62.4%)	68 (61.3%)
TT	29 (26.6%)	23 (20.7%)	25 (22.9%)	25 (22.5%)
Cirrhosis				
No	87 (79.8%)	88 (79.3%)	86 (78.9%)	89 (80.2%)
Yes	22 (20.2%)	22 (19.8%)	22 (20.2%)	22 (19.8%)
Missing	0	1 (0.9%)	1 (0.9%)	0
Baseline HCV RNA ($\log_{10}$ IU/mL)	6.5 (0.4)	6.4 (0.5)	6.4 (0.6)	6.5 (0.6)
Mean (SD)	6.6	6.5	6.5	6.6
Median				
	6 (5.5%)	13 (11.7%)	16 (14.7%)	15 (13.5%)
< 800k IU/mL	103 (94.5%)	98 (88.3%)	93 (85.3%)	96 (86.5%)
≥ 800k IU/mL				

Sources: Tables 8-4 and 8-5 in Internal Clinical Study Reports for the ION-2 study

(to be continued)

Table 13: Applicant's Results for Demographics and Baseline Characteristics in ION-2 (All Treated) (Continued)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
ALT				
≤ 1.5 x ULN	56 (51.4%)	60 (54.1%)	49 (45.0%)	62 (55.9%)
> 1.5 x ULN	53 (48.6%)	51 (45.9%)	60 (55.0%)	49 (44.1%)
Prior HCV treatment history				
Peg-IFN + RBV	43 (39.4%)	47 (42.3%)	58 (53.3%)	59 (53.2%)
PI + Peg-IFN +RBV	66 (60.6%)	64 (57.7%)	50 (45.9%)	51 (45.9%)
Other	0	0	1 (0.9%)	1 (0.9%)
Response to Prior HCV trt				
Relapse/breakthrough	60 (55.0%)	65 (58.6%)	60 (55.0%)	60 (54.1%)
Non-responder	49 (45.0%)	46 (41.4%)	49 (45.0%)	51 (45.9%)
Prior HCV treatment history and response to prior HCV treatment				
Peg-IFN + RBV	21 (19.3%)	23 (20.7%)	25 (22.9%)	32 (28.8%)
Relapse/breakthrough				
Non-responder	17 (15.6%)	12 (10.8%)	19 (17.4%)	16 (14.4%)
Null	5 (4.6%)	12 (10.8%)	14 (12.8%)	11 (9.9%)
Partial				
PI + Peg-IFN + RBV	39 (35.8%)	42 (37.8%)	35 (32.1%)	28 (25.2%)
Relapse/breakthrough	27 (24.8%)	22 (19.8%)	15 (13.8%)	23 (20.7%)
Non-responder				
Other	0	0	0	0
Relapse/breakthrough	0	0	1 (0.9%)	1 (0.9%)
Non-responder				

Sources: Tables 8-4 and 8-5 in Internal Clinical Study Reports for the ION-2 study

3.2.2.4 Results and Conclusions

A. Primary Efficacy Endpoint

Table 14 presents the applicant's results for the primary efficacy endpoint of SVR12 rate in the ION-2 study. The SVR12 rates were close to 100% for the two 24-week arms. The SVR12 rates for the 12-week SOF/LDV and 12-week SOF/LDV+RBV groups were 93.6% and 96.4%, respectively. The SVR12 rates for all treatment groups were statistically superior to the historical rate of 25% (p-values based on one-sample binomial test < 0.001). The differences in SVR12 rates between the 12 and 24 week arms were explained almost wholly by the relapse rates. The statistical reviewer conducted similar exploratory analyses for relapse to those for the ION-1 and ION-3 studies and present the results in Sections C and 4.

Table 14: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in ION-2 (All Treated)

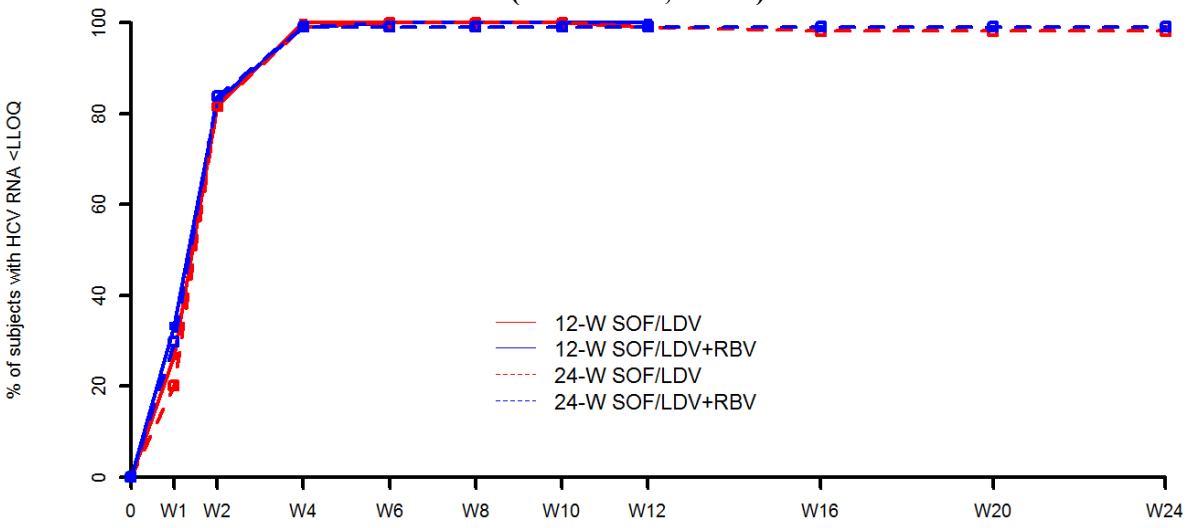
	SOF/LDV 12 Weeks (N=109)	SOF/LDV +RBV 12 Weeks (N=111)	SOF/LDV 24 Weeks (N=109)	SOF/LDV +RBV 24 Weeks (N=111)
SVR12 rate (# of responders/N) [95% CI]	93.6% (102/109) [87.2%, 97.4%]	96.4% (107/111) [91.0%, 99.0%]	99.1% (108/109) [95.0%, 100.0%]	99.1% (110/111) [95.1%, 100%]
Outcome for subjects without SVR12				
On-treatment virologic failure	0% (0/109)	0% (0/111)	0% (0/109)	0.9% (1/111)
Relapse	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/111)
Other	0% (0/109)	0% (0/111)	0.9% (1/109)	0% (0/111)

Sources: Tables 9-1 and 9-2 in Internal Clinical Study Report for the ION-2 study

B. Key Secondary Efficacy Endpoints

Similar to the TN subjects in the ION-1 and ION-3 studies, the HCV virus was rapidly suppressed below LLOQ within four weeks after the subjects received the study medications for almost all subjects. The high virologic response was maintained by the end of treatment (Figure 2).

Figure 2: Reviewer's Results for On-Treatment Virologic Response by Treatment Groups in ION-2 (All Treated, NC=F)



All post-treatment relapse occurred within four weeks after the end of treatment except for one subject in the 12-week SOF/LDV arm who relapsed between four and 12 weeks after the end of treatment (Table 15). The SVR4 and 12 rates were identical in the 12-week SOF/LDV+RBV and

24-week SOF/LDV+RBV arms, while the SVR12 rates were slightly lower than the SVR4 rate in the 12-week SOF/LDV group due to one relapse and in the 24-week SOF/LDV group due to patient's withdrawal of consent (Table 16).

Table 15: Reviewer's Results for Relapse Rates in ION-2 (All Treated)

	SOF/LDV 12 Weeks (N=109)	SOF/LDV +RBV 12 Weeks (N=111)	SOF/LDV 24 Weeks (N=109)	SOF/LDV +RBV 24 Weeks (N=111)
Number of virologic responders at end of treatment	108	111	109	110
Relapse				
By 4 weeks post-treatment	5.6% (6/108)	3.6% (4/111)	0% (0/109)	0% (0/110)
By 12 weeks post-treatment	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/110)

Table 16: Reviewer's Results for SVR Rates in ION-2 (All Treated)

	SOF/LDV 12 Weeks (N=109)	SOF/LDV +RBV 12 Weeks (N=111)	SOF/LDV 24 Weeks (N=109)	SOF/LDV +RBV 24 Weeks (N=111)
SVR4	94.5% (103)	96.4% (107)	100% (109)	99.1% (110)
Achieving SVR12	93.6% (102)	96.4% (107)	99.1% (108)	99.1% (110)
Not achieving SVR12	0.9% (1)	0% (0)	0.9% (1)	0% (0)
Relapse between post-trt WKs 4 and 12	0.9% (1)	0% (0)	0% (0)	0% (0)
Missing post-trt WK12 data due to discontinuation	0% (0)	0% (0)	0.9% (1)	0% (0)

Two hundred and six subjects out of the 219 (94%) had both SVR12 and SVR24 data available. All of the 205 subjects achieving SVR12 achieved SVR24 (Table 17).

Table 17: Applicant's Results for Concordance between SVR12 and SVR12 in ION-2 (All Treated)

	12-week SOF/LDV SVR24		12-week SOF/LDV+RBV SVR24	
	Yes	**No**	**Yes**	**No**
SVR12				
Yes	98	0	107	0
No	0	1	0	0

Source: Table 9-4 in Internal Clinical Study Reports for the ION-2 study

C. Exploratory Analysis for Relapse in TE Subjects

The exploratory analyses for relapse similar to those done for the ION-1 and ION-3 studies were conducted for the TE subjects in the ION-2 study. The results are displayed in the following sections and Section 4.2.

C1. Impact of Use of RBV on Relapse

The relapse rate was approximately 6.5% in the 12-week SOF/LDV group and 3.6% in the 12-week SOF/LDV+RBV group; and there was no relapse in the two 24-week treatment arms (Table 18). When the subjects were broken down into non-cirrhotic and cirrhotic, it was noticed that none of the non-cirrhotic subjects relapsed except four in the 12-week SOF/LDV arm. It was also noticed that the relapse rate in the 12-week SOF/LDV arm was slightly lower than the rate in the 12-week SOF/LDV+RBV arm. The use of RBV did not reduce the relapse rate in cirrhotic subjects.

Table 18: Reviewer's Results for SVR12 and Relapse Rates in ION-2 (All Treated)

	12-Week SOF/LDV (N=109)	**12-Week SOF/LDV+RBV (N=111)**	**24-Week SOF/LDV (N=109)**	**24-Week SOF/LDV+RBV (N=111)**
All Subjects				
SVR12	93.6 (102/109)	96.4% (107/111)	99.1% (108/109)	99.1% (110/111)
Relapse	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/111)
Subjects with cirrhosis				
SVR12	86.4% (19/22)	81.2% (18/22)	100% (22/22)	100% (22/22)
Relapse	13.6% (3/22)	18.2% (4/22)	0% (0/22)	0% (0/22)
Subjects without cirrhosis				
SVR12	95.4% (83/87)	100% (88/88)	98.8% (85/86)	98.9% (88/89)
Relapse	4.7% (4/86)	0% (0/88)	0% (0/86)	0% (0/88)

C2 Impact of Treatment Duration on Relapse

The comparison of relapse rates between the two treatment durations in the ION-2 study is summarized in Table 19 below. The 24-week treatment regimens led to significant reduction in the relapse rates compared to the 12-week treatment regimens as the 95% CIs as the differences in the relapse rates did not cover zero.

Table 19: Reviewer's Results for Comparison of Relapse Rates between Different Treatment Durations in ION-2 (All Treated)

	Proportion Difference in Relapse Rate	Exact 95% CI[1]
12-Week SOF/LDV vs. 24-Week SOF/LDV	6.5%	(2.7%, 13.0%)
12-Week SOF/LDV+RBV vs. 24-Week SOF/LDV+RBV	3.6%	(0.1%, 9.0%)
combination of 12-Week SOF/LDV and 12-Week SOF/LDV+RBV vs. combination of 24-Week SOF/LDV and 24-Week SOF/LDV+RBV	5.0%	(2.7%, 8.9%)

[1]based on inverting a two-sided test

3.3 Evaluation of Safety

The statistical reviewer did not evaluate the safety data. For a detailed safety evaluation, please refer to Dr. Sarah Connelly's review report.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the subgroup analyses for the SVR12 and relapse rates. The subgroup analyses for the SVR12 rate were pre-specified, while the subgroup analyses for the relapse rate were post hoc due to clinical interest.

4.1 Subgroup Analyses for SVR12 Rate

Both the applicant and the reviewer performed the subgroup analyses the primary efficacy endpoint of SVR12 rate. This section displays the reviewer's results. One difference in the subgroup analyses between the reviewer and the applicant was that, in the ION-1 and ION-3 studies, the applicant's analyses included one GT4 subject in the ION-1 study and excluded the five subjects with updated SVR12 data in the two studies. These affected the subgroup analyses results for the 12-week SOF/LDV and 12-week SOF/LDV+RBV treatment groups in the ION-1 study and 12-week SOF/LDV treatment group in the ION-3 study. Another difference was that, in the subgroup analyses by cirrhosis status in the ION-1 and ION-2 studies, the reviewer excluded the subjects with missing cirrhotic status from the analyses but the applicant treated them as non-cirrhotic subjects. The reviewer's results are displayed in Table 31 to Table 34 in Appendix 6.

4.1.1 Gender, Race, Age, and Geographic Region

All treatment groups in the three studies had at least 93% SVR12 rates. Table 31 and Table 33 summarize the subgroup analyses by gender (male, female), race (Africa American, non-Africa American), age (< 65, ≥ 65 years old), and geographic region (US, non-US). In the ION-1 study for the TN subjects, the SVR12 rates for the two 12-week regimens in all the subgroups were

above 95%. In the ION-3 study for the TN subjects, the SVR12 rates for the three treatment arms in all the subgroups were greater than or approximately equal to 90%. In the ION-2 study for the TE subjects, the SVR12 rates for all treatment groups in all subgroups were above 90% except for the subjects with age ≥ 65 years for the 12-week SOF/LDV+RBV group. The SVR12 rate was 85.7% in that subgroup. However, the sample size in the subgroup was only 7 subjects and too small to be informative.

4.1.2 Baseline Characteristics

In all three studies, these subgroups by baseline characteristics included baseline BMI (< 30, ≥ 30 kg/m^2), HCV genotype (1a, 1b), IL28B (CC, non-CC), baseline HCV RNA (< 800,000, ≥ 800,000 IU/mL), baseline ALT (≤ 1.5 x ULN, > 1.5 x ULN). Since the ION-1 and ION-2 studies recruited cirrhotic subjects, the subgroup analysis by baseline cirrhotic status (absence, presence) was also conducted. Furthermore, the ION-2 study enrolled the TE subjects, and therefore the additional subgroup analyses by the prior HCV treatment (PR, PI+PR) and by response to prior HCV treatment (relapser/breakthrough, nonresponder) were performed.

In the ION-1 study, the two 12-week regimens resulted in above 94% SVR12 rates in all subgroups even in the cirrhotic and IL28B non-CC subgroups. In the ION-3 study, the SVR12 rates were consistently high in all subgroups as well.

In the ION-2 study, among the cirrhotic subjects, the SVR12 rates for the 12 weeks regimens appeared lower than the 24 weeks regimens. Specifically, the SVR12 rate was 86.4% with 95% CI of (65.1%, 97.1%) for the 12-week SOF/LDV, 81.8% with 95% CI of (59.7%, 94.8%) for the 12-week SOF/LDV+RBV, and 100% for both 24-week regimens. Other than baseline cirrhosis, the traditional baseline predictors including African-American, genotype 1a, high viral load, non-CC IL28 allele had no impact on SVR12 rates.

4.2 Subgroup Analyses for Relapse Rate

As mentioned in Section 3, it was of clinical interest to identify a subgroup that may benefit from the longer treatment duration based on the relapse rate. The reviewer conducted the subgroup analyses for the relapse rate for the TN subjects in the ION-3 study and the TE subjects in the ION-2 study respectively. The results are shown in the following sections.

4.2.1 Subgroup Analyses for Relapse Rate in TN Subjects in ION-3 Study

The subgroup analysis for relapse was performed in the ION-3 study to identify any subset of TN non-cirrhotic subjects who could benefit from a longer treatment duration. The subgroups were defined by patient demographics and baseline HCV disease characteristics including age, body weight, gender, race, body mass index (BMI), HCV subtype, IL28B status, baseline HCV viral load and ALT. The 8-week SOF/LDV and 8-week SOF/LDV+RBV arms had similar relapse rates in the subgroups (Table 20). Therefore, the two arms were pooled together to compare with the 12-week SOF/LDV group and the results are presented in the next two paragraphs.

Table 20: Reviewer's Results for Subgroup Relapse Rates for 8-Week Treatment Arms in ION-3 (All Treated)

	8-Week SOF/LDV (N=215)	8-Week SOF/LDV+RBV (N=216)
# of responders at end of treatment	215	214
Age		
< 50 years	3.4% (2/59)	0% (0/70)
≥ 50 years	5.8% (9/156)	6.3% (9/144)
Weight[1]		
< 82 kg	3.8% (4/106)	3.5% (4/116)
≥ 82 kg	6.4% (7/109)	5.1% (5/98)
Sex		
Female	1.2% (1/85)	1.0% (1/98)
Male	7.7% (10/130)	6.9% (8/116)
Race		
White	4.9% (8/164)	2.9% (5/174)
Black	6.7% (3/45)	11.1% (4/36)
Other	0% (0/6)	0% (0/4)
BMI		
< 30 kg/m^2	5.3% (8/151)	4.7% (7/150)
≥ 30 kg/m^2	4.7% (3/64)	3.1% (2/64)
Genotype		
GT1a	5.9% (10/171)	4.1% (7/170)
GT1b	2.3% (1/44)	4.6% (2/44)
IL28B		
CC	3.6% (2/56)	0% (0/59)
Non-CC	5.7% (9/159)	5.8% (9/155)
Baseline HCV viral load		
< 1.5M copies/mL	0% (0/52)	0% (0/62)
≥ 1.5M copies/mL	6.8% (11/163)	5.9% (9/152)
< 6M copies/mL	1.6% (2/123)	2.2% (3/137)
≥ 6M copies/mL	9.8% (9/92)	7.8% (6/77)
Baseline ALT		
≤ 1.5 x ULN	5.5% (7/128)	2.5% (3/121)
> 1.5 x ULN	4.6% (4/87)	6.5% (6/93)

[1]The median weight of all treated subjects in the study was approximately 82 kg.

The baseline viral load is usually considered as one of the most important baseline prognostic factors associated with relapse. Comparisons of the relapse rates in the combined 8-week groups and the 12-week SOF/LDV using different cutoffs for the baseline viral load were explored to assess the relapse rate by different baseline viral load cutoffs (Table 21). It was determined that no relapse occurred in all treatment arms among the subjects with the baseline viral load < 1.5 million IU/mL while the difference in relapse rates between the two treatment durations was 4.4% in the subjects with the baseline viral load ≥ 1.5 million IU/mL. It was also determined that the

difference comparing the relapse rates between the 8 and 12 week treatment durations in the subjects with low and high baseline viral load was greatest when the baseline viral load was categorized as < or ≥ 6 million IU/mL. However, none of the statistical interaction tests between treatment duration and subgroups defined by different thresholds of baseline viral load were significant, and the 95% CIs for the difference in relapse rates between the two treatment durations with low and high baseline viral loads overlapped.

Table 21: Reviewer's Results for Relapse Rates by Baseline Viral Load for 8-Week and 12-Week Regimens in ION-3 (All Treated)

	8-Week SOF/LDV & SOF/LDV+RBV (N=431)	12-Week SOF/LDV (N=216)	Proportion Difference (Exact 95% CI[1])	P-value for Interaction based on Zelen's Test
Baseline viral load (IU/mL)				
< 1 million	0% (0/99)	0% (0/51)	0% (-7.8%, 3.8%)	not significant
≥ 1 million	5.9% (20/339)	1.8% (3/165)	4.1% (0.2%, 7.5%)	
< 1.5 million	0% (0/114)	0% (0/60)	0% (-3.3%, 6.7%)	not significant
≥ 1.5 million	6.4% (20/315)	1.9% (3/156)	4.4% (0.3%, 8.1%)	
< 2 million	1.4% (2/146)	1.4% (1/72)	0% (-6.6%, 3.7%)	0.34
≥ 2 million	6.4% (18/283)	1.4% (2/144)	5.0% (0.9%, 8.8%)	
< 2.5 million	1.9% (3/160)	1.2% (1/83)	0.7% (-4.9%, 4.4%)	0.46
≥ 2.5 million	6.3% (17/269)	1.5% (2/133)	4.8% (0.5%, 8.8%)	
< 3 million	1.7% (3/179)	1.1% (1/94)	0.6% (-4.3%, 4.0%)	0.46
≥ 3 million	6.8% (17/250)	1.6% (2/122)	5.2% (0.6%, 9.4%)	
< 3.5 million	1.5% (3/195)	1.0% (1/98)	0.5% (-4.2%, 3.6%)	0.44
≥ 3.5 million	7.3% (17/234)	1.7% (2/118)	5.6% (0.7%, 10.1%)	
< 4 million	1.9% (4/213)	0.9% (1/107)	0.9% (-3.6%, 4.2%)	0.53
≥ 4 million	7.4% (16/216)	1.8% (2/109)	5.6% (0.4%, 10.3%)	
< 5 million	2.1% (5/243)	0.8% (1/123)	1.2% (-2.7%, 4.1%)	1.0
≥ 5 million	8.1% (15/186)	2.2% (2/93)	5.9% (-0.1%, 11.4%)	
< 6 million	1.9% (5/260)	1.5% (2/131)	0.4% (-3.7%, 3.2%)	0.20
≥ 6 million	8.9% (15/169)	1.2% (1/85)	7.7% (1.9%, 13.3%)	
< 7 million	2.8% (8/286)	1.4% (2/145)	1.4% (-2.3%, 4.3%)	0.55
≥ 7 million	8.4% (12/143)	1.4% (1/71)	7.0% (0.2%, 13.2%)	
< 8 million	3.6% (11/306)	1.3% (2/151)	2.3% (-1.4%, 5.4%)	1.0
≥ 8 million	7.3% (9/123)	1.5% (1/65)	5.8% (-2.3%, 12.4%)	
< 9 million	3.8% (12/318)	1.3% (2/158)	2.5% (-1.3%, 5.6%)	1.0
≥ 9 million	7.2% (8/111)	1.7% (1/58)	5.5% (-2.9%, 12.4%)	
< 10 million	3.6% (12/332)	1.2% (2/166)	2.4% (-1.2%, 5.3%)	1.0
≥ 10 million	8.3% (8/97)	2.0% (1/50)	6.2% (-3.1%, 13.9%)	

[1]based on inverting a two-sided test

Table 22 summarizes the differences in relapse rates between the combined 8-week treatment arms and the 12-week SOF/LDV in the subgroups defined by demographics and baseline characteristics other than the baseline HCV viral load. The longer treatment duration resulted in numerically

lower relapse rates in almost all subgroups. The differences were more apparent in subjects with age ≥ 50 years, male subjects, and subjects with GT1a infection. However, there were no statistically significant interactions between treatment duration and subgroups.

Table 22: Reviewer's Results for Subgroup Relapse Rates for 8-Week and 12-Week Regimens in ION-3 (All Treated)

	8-Week SOF/LDV & 8-Week SOF/LDV+RBV (N=431)	12-Week SOF/LDV (N=216)	Proportion Difference (Exact 95% CI[1])	P-value for interaction based on Zelen's test
# of responders at end of treatment	429	216		
Age				0.34
< 50 years	1.6% (2/129)	1.6% (1/63)	-0.04% (-7.5%, 4.2%)	
≥ 50 years	6.0% (18/300)	1.3% (2/153)	4.7% (0.9%, 8.3%)	
Weight				1.0
< 82 kg	3.6% (8/222)	0.9% (1/112)	2.7% (-1.8%, 6.3%)	
≥ 82 kg	5.8% (12/207)	1.9% (2/104)	3.9% (-1.9%, 8.5%)	
Sex				1.0
Female	1.1% (2/183)	0% (0/88)	1.1% (-3.2%, 4.0%)	
Male	7.3% (18/246)	2.3% (3/128)	5.0% (0.04%, 9.4%)	
Race				1.0
Black	8.6% (7/81)	2.4% (1/42)	6.3% (-5.0%, 15.0%)	
Other	3.7% (13/348)	1.2% (2/174)	2.6% (-0.9%, 5.5%)	
BMI				1.0
< 30 kg/m^2	5.0% (15/301)	1.9% (3/159)	3.1% (-1.0%, 6.6%)	
≥ 30 kg/m^2	3.9% (5/128)	0% (0/57)	3.9% (-2.7%, 8.9%)	
Genotype				0.45
GT1a	4.9% (17/341)	1.2% (2/172)	3.8% (0.5%, 6.9%)	
GT1b	3.4% (3/88)	2.3% (1/44)	1.1% (-9.3%, 7.8%)	
IL28B				1.0
CC	1.7% (2/115)	0% (0/56)	1.7% (-4.9%, 6.2%)	
Non-CC	5.7% (18/314)	1.9% (3/160)	3.9% (-0.5%, 7.5%)	

[1]based on inverting a two-sided test

Furthermore, the relation between early viral kinetics and relapse was evaluated. By viral kinetics, we mean virologic responses at the early visits including Weeks 2 and 4. Two criteria were used to determine virologic response – one was whether HCV RNA target was detected or not, and another one was whether HCV RNA was below or above LLOQ. There were two ways to examine the relation between the early viral kinetics and relapse. The first approach was based on the positive predictive value (PPV) (i.e., the proportion of subjects with early viral response who did not relapse) and the negative predictive value (NPV) (i.e., the proportion of subjects without early viral response who relapsed), which has been conventionally used to assess the relation between the early viral kinetics and the treatment outcome. The early viral load can be used to predict the treatment outcome when both PPV and NPV are reasonably high (Davis, Hepatology 2002). In other words, if the early viral load is a good predictor for the treatment outcome, then the early viral response status should be fairly consistent with the long-term treatment response

status. As shown in Table 23, the early viral responses had high PPVs but low NPVs. The high PPVs suggested that there were high proportions of subjects with early viral response who did not relapse later. Therefore, early virologic response could predict the long-term treatment responders. However, the low NPVs implied that there were high proportions of subjects without early viral response who did not relapse later, and therefore lack of early viral response could not predict relapse.

Table 23: Reviewer's Results for Relapse Rates by Early Viral Response with Positive Predictive Values and Negative Predictive Values in ION-3 (All Treated)

	8-Week SOF/LDV (N=215)	8-Week SOF/LDV+RBV (N=216)	12-Week SOF/LDV (N=216)
Positive predictive value based on HCV RNA target detected status[1]			
Week 2	98.4% (63/64)	97.9% (93/95)	98.7% (79/80)
Week 4	96.1% (172/179)	95.6% (173/181)	98.9% (177/179)
Negative predictive value based on HCV RNA target detected status[2]			
Week 2	6.6% (10/151)	5.9% (7/119)	1.5% (2/136)
Week 4	11.1% (4/36)	3.0% (1/33)	2.7% (1/37)
Positive predictive value based on HCV RNA LLOQ status[3]			
Week 2	94.7% (180/190)	95.4% (186/195)	98.5% (194/197)
Week 4	94.9% (204/215)	95.7% (202/211)	98.7% (213/216)
Negative predictive value based on HCV RNA LLOQ status[4]			
Week 2	4.0% (1/25)	0% (0/19)	0% (0/19)
Week 4	0/0	0% (0/3)	0/0

[1]proportion of subjects with HCV RNA target not detected who did not relapse
[2]proportion of subjects with HCV RNA target detected who relapsed
[3]proportion of subjects with HCV RNA < LLOQ who did not relapse
[4]proportion of subjects with HCV RNA ≥ LLOQ who relapsed

Another approach to investigate the relation between early viral response and relapse was to evaluate the interactions between treatment duration and the subgroups defined by the early viral response, the same analyses for demographics and baseline characteristics shown in previous section. The two 8-week arms were combined in the analyses since they had similar relapse rates in all subgroups except for couple with small sample sizes. There were no statistically significant interactions between treatment duration and the subgroups by early viral response (Table 24). In conclusion, there was no obvious relation between early viral kinetics and relapse.

Table 24: Reviewer's Results for Relapse Rates by Early Viral Response in ION-3 (All Treated)

	8-Week SOF/LDV & SOF/LDV +RBV (N=431)	12-Week SOF/LDV (N=216)	Proportion Difference (Exact 95% CI[1])	P-value for Interaction based on Zelen's Test
Week 2				0.44
HCV RNA target not detected	1.9% (3/159)	1.3% (1/80)	0.6% (-5.1%, 4.4%)	
HCV RNA target detected	6.3% (17/270)	1.5% (2/136)	4.8% (0.6%, 8.8%)	
Week 4				1.0
HCV RNA target not detected	4.2% (15/360)	1.1% (2/179)	3.1% (-0.8%, 5.9%)	
HCV RNA target detected	7.2% (5/69)	2.7% (1/37)	4.5% (-7.5%, 13.9%)	
Week 2				1.0
HCV RNA < LLOQ	4.9% (19/385)	1.5% (3/197)	3.4% (0.2%, 6.4%)	
HCV RNA ≥ LLOQ	2.3% (1/44)	0% (0/19)	2.3% (-15.4%, 11.9%)	
Week 4				not significant
HCV RNA < LLOQ	4.7% (20/426)	1.3% (3/216)	3.3% (0.2%, 6.0%)	
HCV RNA ≥ LLOQ	0% (0/3)	0% (0/0)	n/a	

4.2.2 Subgroup Analyses for Relapse Rate in TE Subjects in ION-2 Study

The subgroup analyses similar to those for the TN in the ION-3 study were carried out. Two more baseline characteristics were taken into account here, i.e., baseline cirrhotic status and previous HCV treatment history. Table 25 shows the relapse rates for the subgroups in each treatment arm. Sample sizes in some subgroups were too small to be informative. Overall there was no apparent difference in the relapse rates in any subgroup with reasonable sample sizes between the 12-week SOF/LDV and 12-week SOF/LDV+RBV groups.

Table 25: Reviewer's Results for Subgroup Relapse Rate in ION-2 (All Treated)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
# of responders at end of treatment	108	111	109	110
Age				
< 50 years	0% (0/16)	0% (0/15)	0% (0/15)	0% (0/26)
≥ 50 years	7.6% (7/92)	4.2% (4/96)	0% (0/94)	0% (0/84)
Weight				
< 83 kg	7.7% (4/52)	3.6% (2/55)	0% (0/52)	0% (0/57)
≥ 83 kg	5.4% (3/56)	3.6% (2/56)	0% (0/57)	0% (0/53)
Sex				
Female	5.9% (2/34)	0% (0/40)	0% (0/35)	0% (0/43)
Male	6.8% (5/74)	5.6% (4/71)	0% (0/74)	0% (0/67)

(to be continued)

Table 25: Reviewer's Results for Subgroup Relapse Rate in ION-2 (All Treated) (Continued)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
Race				
White	8.3% (7/84)	3.2% (3/94)	0% (0/17)	0% (0/20)
Black	0% (0/23)	6.3% (1/16)	0% (0/91)	0% (0/88)
Other	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/2)
BMI				
< 30 kg/m^2	7.7% (5/65)	4.1% (3/74)	0% (0/75)	0% (0/81)
≥ 30 kg/m^2	4.7% (2/43)	2.7% (1/37)	0% (0/34)	0% (0/29)
Genotype				
GT1a	4.7% (4/85)	4.6% (4/88)	0% (0/85)	0% (0/87)
GT1b	13.0% (3/23)	0% (0/23)	0% (0/24)	0% (0/23)
Cirrhosis[1]				
Yes	13.6% (3/22)	18.2% (4/22)	0% (0/22)	0% (0/22)
No	4.7% (4/86)	0% (0/88)	0% (0/86)	0% (0/88)
IL28B				
CC	0% (0/10)	0% (0/11)	0% (0/16)	0% (0/17)
Non-CC	7.1% (7/98)	4.0% (4/100)	0% (0/93)	0% (0/93)
Baseline HCV viral load				
< 800K copies/mL	16.7% (1/6)	0% (0/13)	0% (0/16)	0% (0/15)
≥ 800K copies/mL	5.9% (6/102)	4.1% (4/98)	0% (0/93)	0% (0/95)
Baseline ALT				
≤ 1.5 x ULN	5.5% (3/55)	5.0% (3/60)	0% (0/49)	0% (0/61)
> 1.5 x ULN	7.6% (4/53)	2.0% (1/51)	0% (0/60)	0% (0/49)
Prior HCV treatment				
PR	7.0% (3/43)	4.3% (2/47)	0% (0/58)	0% (0/58)
PI+PR	6.2% (4/65)	3.1% (2/64)	0% (0/50)	0% (0/51)
Response to prior HCV trt				
Relapse/Breakthrough	5.1% (3/59)	3.1% (2/65)	0% (0/59)	0% (0/60)
Nonresponder	8.2% (4/49)	4.4% (2/46)	0% (0/50)	0% (0/48)

[1]Subjects with missing cirrhotic status were excluded from the analyses.

Because the two 12-week treatment arms had similar relapse patterns and the two 24-week treatment arms had no relapses, and because combining the two 12-week arms and the two 24-week arms provided larger sample sizes, the subgroup analyses compared the relapse rate for the combined 12-week arms against the relapse rate for the combined 24-week arms (Table 26). There was no apparent interaction between the treatment duration and any subgroup except possibly for the subgroup defined by cirrhosis. Among the non-cirrhotic subjects, the relapse rate for the 24-week treatment was 2.3% lower than the 12-week treatment. On the other hand, the 24-week treatment reduced relapse rate as much as 15.9% compared to the 12-week treatment in the cirrhotic subjects. The 95% CIs for the difference between the two treatment durations in the cirrhotic and non-cirrhotic subjects did not overlap. Zelen's exact test for the interaction was not conducted because the relapse rates were zero in the two 24-week treatment arms and was therefore not defined.

Table 26: Reviewer's Results for Subgroup Relapse Rates for 8-Week and 12-Week Regimens in ION-2 (All Treated)

	12-Week SOF/LDV & SOF/LDV+RBV (N=220)	24-Week SOF/LDV & SOF/LDV+RBV (N=220)	Proportion Difference (Exact 95% CI[1])
# of responders at end of treatment	219	219	
Age			
< 50 years	0% (0/31)	0% (0/41)	0% (-8.9%, 13.0%)
≥ 50 years	5.9% (11/188)	0% (0/178)	5.9% (3.2%, 10.4%)
Weight			
< 83 kg	5.6% (6/107)	0% (0/109)	5.6% (1.9%, 12.2%)
≥ 83 kg	4.5% (5/112)	0% (0/110)	4.5% (0.9%, 10.3%)
Sex			
Female	2.7% (2/74)	0% (0/78)	2.7% (-2.1%, 10.2%)
Male	6.2 (9/145)	0% (0/141)	6.2% (3.1%, 11.7%)
Race			
Black	2.6% (1/39)	0% (0/37)	2.6% (-7.3%, 14.1%)
Other	5.6% (10/180)	0% (0/182)	5.6% (2.9%, 10.0%)
BMI			
< 30 kg/m^2	5.8% (8/139)	0% (0/156)	5.8% (2.8%, 11.2%)
≥ 30 kg/m^2	3.8% (3/80)	0% (0/63)	3.8% (-2.4%, 10.7%)
Sub-genotype			
GT1a	4.6% (8/173)	0% (0/172)	4.6% (2.2%, 9.0%)
GT1b	6.5% (3/46)	0% (0/47)	6.5% (-1.5%, 18.6%)
Cirrhosis[2]			
No	2.3% (4/174)	0% (0/174)	2.3% (0.1%, 6.0%)
Yes	15.9% (7/44)	0% (0/44)	15.9% (6.5%, 29.8%)
IL28B			
CC	0% (0/21)	0% (0/33)	0% (-10.4%, 16.7%)
Non-CC	5.6% (11/198)	0% (0/186)	5.6% (3.0%, 9.9%)
Baseline HCV viral load			
< 800K copies/mL	5.3% (1/19)	0% (0/31)	0% (-6.1%, 26.4%)
≥ 800K copies/mL	5.0% (10/200)	0% (0/188)	5.0% (2..6%, 9.0%)

[1]based on inverting a two-sided test
[2]Subjects with missing cirrhotic status were excluded from the analyses.

(to be continued)

Table 26: Reviewer's Results for Subgroup Relapse Rates for 8-Week and 12-Week Regimens in ION-2 (All Treated) (Continued)

	12-Week SOF/LDV & SOF/LDV+RBV (N=220)	24-Week SOF/LDV & SOF/LDV+RBV (N=220)	Proportion Difference (Exact 95% CI[1])
Baseline ALT			
≤ 1.5 x ULN	5.2% (6/115)	0% (0/110)	5.2% (1.6%, 11.3%)
> 1.5 x ULN	4.8% (5/104)	0% (0/109)	4.8% (1.2%, 11.1%)
Previous HCV trt history			
Peg-IFN + RBV	5.6% (5/90)	0% (0/116)	5.6% (1.9%, 12.8%)
PI + Peg-IFN + RBV	4.7% (6/129)	0% (0/101)	4.7% (0.8%, 10.1%)
Response to Prior HCV trt			
Relapse/breakthrough	4.0% (5/124)	0% (0/119)	4.0% (0.8%, 9.3%)
Non-responder	6.3% (6/95)	0% (0/98)	6.3% ((2.2%, 13.7%)

[1]based on inverting a two-sided test

Similar analyses performed for TN subjects in the ION-3 study to evaluate the relation between early viral kinetics and relapse were carried out for TE subjects in the ION-2 study. Table 27 displays the relapse rates by early viral kinetics with PPVs and NPVs. Like the ION-3 study, there were high PPVs but low NPVs in particular for the 24-week arms where no relapse occurred. Therefore, early virologic response could predict the long-term treatment responders because of high PPVs. However, lack of early viral response could not predict relapse due to low NPVs.

Table 27: Reviewer's Results for Relapse Rates by Early Viral Response with Positive Predictive Values and Negative Predictive Values in ION-3 (All Treated)

	12-Week SOF/LDV	12-Week SOF/LDV+RBV	24-Week SOF/LDV	24-Week SOF/LDV+RBV
Positive predictive value based on HCV RNA target detected status[1]				
Week 2	93.3% (28/30)	100% (33/33)	100% (25/25)	100% (33/33)
Week 4	95.4% (83/87)	97.8% (88/90)	100% (87/87)	100% (91/91)
Negative predictive value based on HCV RNA target detected status[2]				
Week 2	6.4% (5/78)	5.1% (4/78)	0% (0/84)	0% (0/77)
Week 4	14.3% (3/21)	9.5% (2/21)	0% (0/22)	0% (0/19)
Positive predictive value based on HCV RNA LLOQ status[3]				
Week 2	96.6% (85/88)	98.9% (91/92)	100% (89/89)	100% (93/93)
Week 4	93.5% (101/108)	97.3% (107/110)	100% (108/108)	100% (110/110)
Negative predictive value based on HCV RNA LLOQ status[4]				
Week 2	20% (4/20)	15.8% (3/19)	0% (0/20)	0% (0/17)
Week 4	0/0	100% (1/1)	0% (0/1)	0/0

[1]proportion of subjects with HCV RNA target not detected who did not relapse
[2]proportion of subjects with HCV RNA target detected who relapsed
[3]proportion of subjects with HCV RNA < LLOQ who did not relapse
[4]proportion of subjects with HCV RNA ≥ LLOQ who relapsed

Like the ION-3 study, the subgroup analyses to compare the relapse rate for the pooled 12-week arms versus the relapse rate for the pooled 24-week arms were conducted to examine the relation between early viral load and the relapse rate as well. The subgroup analyses indicated that the interaction between treatment duration and the subgroup by HCV RNA LLOQ status at Week 2 may be significant since the 95% CIs for the difference for the difference between the two treatment durations in the subjects with HCV RNA < LLOQ at Week 2 and the subjects with HCV RNA ≥ LLOQ at Week 2 did not overlap (Table 28). Further analyses that broke down the subjects as cirrhotic and non-cirrhotic subjects indicated that the differences in relapse rate in the subgroups were more obvious among cirrhotic subjects compared with the non-cirrhotic subjects (Table 29 and Table 30). However, no interactions were significant in the cirrhotic subjects because of small sample sizes.

Table 28: Reviewer's Results for Relapse Rates by Early Viral Response for All Subjects in ION-2 (All Treated)

	12-Week SOF/LDV & SOF/LDV+RBV (N=219)	24-Week SOF/LDV & SOF/LDV+RBV (N=219)	Proportion Difference (Exact 95% CI[1])
Week 2			
HCV RNA target not detected	3.2% (2/63)	0% (0/58)	3.2% (-3.2%, 11.1%)
HCV RNA target detected	5.8% (9/156)	0% (0/161)	5.8% (2.9%, 10.9%)
Week 4			
HCV RNA target not detected	3.4% (6/177)	0% (0/178)	3.4% (1.1%, 7.4%)
HCV RNA target detected	11.9% (5/42)	0% (0/41)	11.9% (2.5%, 26.2%)
Week 2			
HCV RNA < LLOQ	2.2% (4/180)	0% (0/182)	2.2% (0.1%, 5.8%)
HCV RNA ≥ LLOQ	18.0% (7/39)	0% (0/37)	18.0% (7.0%, 33.4%)
Week 4			
HCV RNA < LLOQ	4.6% (10/218)	0% (0/218)	4.6% (2.4%, 8.5%)
HCV RNA ≥ LLOQ	100% (1/1)	0% (0/1)	100% (-55.3%, 100.0%)

[1]based on inverting a two-sided test

Table 29: Reviewer's Results for Relapse Rates by Early Viral Response for Cirrhotic Subjects in ION-2 (All Treated)

	12-Week SOF/LDV & SOF/LDV+RBV (N=219)	24-Week SOF/LDV & SOF/LDV+RBV (N=219)	Proportion Difference (Exact 95% CI)[1]
Week 2			
HCV RNA target not detected	9.1% (1/11)	0% (0/9)	9.1% (-24.7%, 40.2%)
HCV RNA target detected	18.2% (6/33)	0% (0/35)	18.2% (6.5%, 35.4%)
Week 4			
HCV RNA target not detected	8.8% (3/34)	0% (0/35)	8.8% (-2.0%, 23.6%)
HCV RNA target detected	40.0% (4/10)	0% (0/10)	40.0% (4.4%, 7.0%)
Week 2			
HCV RNA < LLOQ	7.1% (2/28)	0% (0/30)	7.1% (-5.0%, 23.3%)
HCV RNA ≥ LLOQ	31.3% (5/16)	0% (0/14)	31.3% (5.8%, 57.6%)
Week 4			
HCV RNA < LLOQ	14.0% (6/43)	0% (0/43)	14.0% (4.5%, 28.0%)
HCV RNA ≥ LLOQ	100% (1/1)	0% (0/1)	100.0% (-55.3%, 100.0%)

[1]based on inverting a two-sided test

Table 30: Reviewer's Results for Relapse Rates by Early Viral Response for Non-Cirrhotic Subjects in ION-2 (All Treated)

	12-Week SOF/LDV & SOF/LDV+RBV (N=219)	24-Week SOF/LDV & SOF/LDV+RBV (N=219)	Proportion Difference (Exact 95% CI[1])
Week 2			
HCV RNA target not detected	2.0% (1/51)	0% (0/49)	2.0% (-5.5%, 10.8%)
HCV RNA target detected	2.4% (3/123)	0% (0/125)	2.4% (-0.6%, 7.3%)
Week 4			
HCV RNA target not detected	2.1% (3/142)	0% (0/143)	2.1% (-0.5%, 6.3%)
HCV RNA target detected	3.1% (1/32)	0% (0/31)	3.1% (-8.6%, 17.2%)
Week 2			
HCV RNA < LLOQ	1.3% (2/151)	0% (0/151)	1.3% (-1.2%, 5.0%)
HCV RNA ≥ LLOQ	8.7% (2/23)	0% (0/23)	8.7% (-7.5%, 28.3%)
Week 4			
HCV RNA < LLOQ	3.4% (4/174)	0% (0/174)	3.4% (0.01%, 6.0%)
HCV RNA ≥ LLOQ	0/0	0/0	n/a

[1]based on inverting a two-sided test

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was not statistical issue.

5.2 Collective Evidence

Three Phase 3 studies had different patient populations and treatment durations of SOF/LDV-containing regimens. The treatment regimens in all studies rapidly suppressed the HCV virus. Nearly all subjects achieved HCV RNA < LLOQ within four weeks after receiving the treatments, and the high response rate maintained through the end of the treatment regardless of treatment duration. Almost no subject experienced on-treatment virologic failure in any of the three studies. A small proportion of subjects relapsed and the relapses usually occurred by four weeks after the end of study treatment. Above 93% SVR12 rates were observed in all regimens.

The ION-1 study demonstrated that the SVR12 rate for the 12-week SOF/LDV either without or with RBV was greater than 97% in the TN subjects including cirrhotic and non-cirrhotic subjects. Both rates were statistically significantly superior to the pre-specified 60% historical rate. There was only one relapse in the two treatment groups. The use of RBV did not appear to affect the SVR12 rate.

In the ION-3 study, the 8-week and 12-week regimens resulted in at least 93% SVR12 rates in the non-cirrhotic TN subjects. The use of RBV did not show to have an impact on SVR12 rate in the study. There was no statistically significant difference in SVR12 rates between the 8-week and 12-week treatment durations. Relapse was the main reason for subjects not achieving SVR12 in the 8-week regimens, whereas discontinuation of study was the main attributor for non-response of

SVR12 in the 12-week regimen. Relapse was one of the key pre-specified secondary efficacy endpoints. The relapse rate for 8 weeks of SOF/LDV without RBV (5%) was similar to the rate for 8 weeks of SOF/LDV with RBV (4%), which suggested that the use of RBV did not have an impact on relapse. The exploratory analyses to compare the pooled relapse rate for 8 weeks SOF/LDV with and without RBV versus 12 weeks of SOF/LDV revealed that the 12-week duration reduced the relapse rate by approximately 3% (95% CI: 0.2%, 6.0%) in comparison to the 8-week duration. Meanwhile, the 8 weeks and 12 weeks of SOF/LDV had similar safety profiles.

The ION-2 study for the TE subjects showed that the 12 weeks of SOF/LDV without or with RBV led to approximately 95% SVR12 rates and 24 weeks of SOF/LDV without or with RBV had the SVR12 rates of at least 99%. The relapse rates for the two12-week regimens were 4% to 6%, whereas no relapse occurred in the two 24-week treatment regimens. The difference in SVR12 rates between the 12-week and 24-week regimens were almost entirely explained by the relapse rate. The study suggested that the use of the RBV had a minimal impact on the SVR12 or relapse rate. The pre-specified subgroup analysis demonstrated that the SVR12 rates for the two 24-week regimens had 100% SVR12 rates compared to 86% rate for 12 weeks of SOF/LDV and 82% for 12 weeks of SOF/LDV plus RBV among the cirrhotic TE subjects. The subgroup analyses also demonstrated that all SVR12 rates for the four regimens were above 95% among the non-cirrhotic TE subjects. Further exploratory analyses for relapse rates showed that, compared to the pooled 12-week arms, the relapse rate for the pooled 24-week arms were approximately 16% lower in the cirrhotic subjects and only 2% lower in the non-cirrhotic subjects. The 95% CI for the differences in the relapse rates between the treatment duration in the cirrhotic subjects did not overlap the 95% CI for the non-cirrhotic subjects.

5.3 Conclusions and Recommendations

Based on the totality evidence in three studies, the statistical reviewer concludes that 12 weeks of SOF/LDV was the optimal treatment regimen for the cirrhotic and non-cirrhotic GT1 TN subjects and non-cirrhotic GT1 TE subjects and that 24 weeks of SOF/LDV was the optimal regimen for the cirrhotic GT1 TE subjects.

6 APPENDICES

Table 31: Reviewer's Results for SVR12 Rates by Demographics in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=213[1])	**SOF/LDV +RBV 12 Weeks (N=217)**	**SOF/LDV 8 Weeks (N=215)**	**SOF/LDV +RBV 8 Weeks (N=216)**	**SOF/LDV 12 Weeks (N=216)**
Age (years)					
< 65	98.5% (196/198)	96.9% (189/195)	94.4% (185/196)	93.1% (189/203)	96.0% (191/199)
[95% CI]	[96.4%, 99.9%]	[93.4%, 98.9%]	[90.2%, 97.2%]	[88.7%, 96.2%]	[92.2%, 98.3%]
≥ 65	100% (15/15)	100% (22/22)	89.5% (17/19)	92.3% (12/13)	100% (17/17)
[95% CI]	[78.2%, 100.0%]	[84.6%, 100.0%]	[66.9%, 98.7%]	[64.0%, 99.8%]	[80.5%, 100.0%]
Gender					
Male	98.4% (124/126)	96.9% (124/128)	91.5% (119/130)	90.6% (106/117)	96.9% (124/128)
[95% CI]	[94.4%, 99.8%]	[92.2%, 99.1%]	[85.4%, 95.7%]	[83.8%, 95.2%]	[92.2%, 99.1%]
Female	98.9% (86/87)	97.8% (87/89)	97.6% (83/95)	96.0% (95/99)	95.5% (84/88)
[95% CI]	[93.8%, 100.0%]	[92.1%, 99.7%]	[91.8%, 99.7%]	[90.0%, 98.9%]	[88.8%, 98.8%]
Race					
African-American	100% (24/24)	100% (26/26)	91.1% (41/45)	88.9% (32/36)	97.6% (41/42)
[95% CI]	[85.8%, 100.0%]	[86.8%, 100.0%]	[78.8%, 97.5%]	[73.9%, 96.9%]	[87.4%, 99.9%]
Non-African-American	98.4% (186/189)	96.8% (184/190)	94.7% (161/170)	93.9% (169/180)	96.0% (167/174)
[95% CI]		[93.3%, 98.8%]	[90.2%, 97.6%]	[89.3%, 96.9%]	[91.9%, 98.4%]
Geographic region			n/a	n/a	n/a
US	97.6% (122/125)	97.5% (115/118)			
[95% CI]	[93.2%, 99.5%]	[92.7%, 99.5%]			
Non-US	100% (88/88)	97.0% (96/99)			
[95% CI]	[95.9%, 100.0%]	[91.4%, 99.4%]			

[1]Excluding one GT4 subject

Table 32: Reviewer's Results for SVR12 Rates by Baseline Characteristics in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	SOF/LDV 12 Weeks (N=213[1])	SOF/LDV +RBV 12 Weeks (N=217)	SOF/LDV 8 Weeks[2] (N=215)	SOF/LDV +RBV 8 Weeks[2] (N=216)	SOF/LDV 12 Weeks (N=216)
BMI (kg/m^2)					
< 30	98.3% (172/175)	97.1% (166/171)	93.4% (141/151)	91.4% (139/152)	95.6% (152/159)
[95% CI]	[95.1%, 99.7%]	[93.3%, 99.0%]	[88.2%, 96.8%]	[85.8%, 95.4%]	[91.1%, 98.2%]
≥ 30	100% (38/38)	97.8% (45/46)	95.3% (61/64)	96.9% (62/64)	98.3% (56/57)
[95% CI]	[90.8%, 100.0%]	[88.5%, 99.9%]	[86.9%, 99.0%]	[89.2%, 99.6%]	[90.6%, 100.0%]
HCV genotype					
1a	97.9% (142/145)	96.6% (143/148)	93.0% (159/171)	92.4% (159/172)	95.9% (165/172)
[95% CI]	[94.1%, 99.6%]	[92.3%, 98.9%]	[88.1%, 96.3%]	[87.4%, 95.9%]	[91.8%, 98.4%]
1b	100% (67/67)	98.5% (67/68)	97.7% (42/43)	95.5% (42/44)	97.7% (43/44)
[95% CI]	[94.6%, 100.0%]	[92.1%, 100.0%]	[87.7%, 99.9%]	[84.5%, 99.4%]	[88.0%, 99.9%]
IL28 B					
CC	100% (55/55)	97.4% (74/76)	96.4% (54/56)	95.0% (57/60)	96.4% (54/56)
[95% CI]	[93.5%, 100.0%]	[90.8%, 99.7%]	[87.7%, 99.6%]	[86.1%, 99.0%]	[87.7%, 99.6%]
Non-CC	98.1% (155/158)	97.2% (137/141)	93.1% (148/159)	92.3% (144/156)	96.3% (154/160)
[95% CI]	[94.6%, 99.6%]	[92.9%, 99.2%]	[88.0%, 96.5%]	[86.9%, 96.0%]	[92.0%, 98.6%]
Cirrhosis			n/a	n/a	n/a
Yes	94.1% (32/34)	100% (33/33)			
[95% CI]	[80.3%, 99.3%]	[89.4%, 100.0%]			
No	99.4% (176/177)	96.7% (177/183)			
[95% CI]	[96.9%, 100.0%]	[93.0%, 98.8%]			
Baseline HCV RNA (IU/mL)					
< 800,000	100% (45/45)	93.2% (41/44)	97.1% (33/34)	95.6% (43/45)	95.5% (42/44)
[95% CI]	[92.1%, 100.0%]	[81.3%, 98.6%]	[84.7%, 99.9%]	[84.9%, 99.5%]	[84.5%, 99.4%]
≥ 800,000	98.2% (165/168)	98.3% (170/173)	93.4% (169/181)	92.4% (158/171)	96.5% (166/172)
[95% CI]	[94.9%, 99.6%]	[95.0%, 99.6%]	[88.7%, 96.5%]	[87.4%, 95.9%]	[92.6%, 98.7%]
Baseline ALT					
≤ 1.5 x ULN	98.9% (92/93)	96.9% (95/98)	93.8% (120/128)	95.9% (116/121)	97.4% (114/117)
[95% CI]	[94.2%, 100.0%]	[91.3%, 99.4%]	[88.1, 97.3%]	[90.6%, 98.6%]	[92.7%, 99.5%]
> 1.5 x ULN	98.3% (118/120)	97.5% (116/119)	94.3% (82/87)	89.5% (85/95)	95.0% (94/99)
[95% CI]	[94.1%, 99.8%]	[92.8%, 99.5%]	[87.1%, 98.1%]	[81.5%, 94.8%]	[88.6%, 98.3%]

[1]Excluding one GT4 subject

Table 33: Reviewer's Results for SVR12 Rates by Demographics in ION-2 (All Treated)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
Age (years)				
< 65	93.1% (94/101)	97.1% (101/104)	99.0% (99/100)	99.0% (103/104)
[95% CI]	[86.2%, 97.2%]	[91.8%, 99.4%]	[94.6%, 100.0%]	[94.8%, 100.0%]
≥ 65	100% (8/8)	85.7% (6/7)	100% (9/9)	100% (7/7)
[95% CI]	[63.1%, 100.0%]	[42.1%, 99.6%]	[66.4%, 100.0%]	[59.0%, 100.0%]
Gender				
Male	93.2% (69/74)	94.4% (67/71)	98.6% (73/74)	98.5% (67/68)
[95% CI]	[84.9%, 97.8%]	[86.2%, 98.4%]	[92.7%, 100.0%]	[92.1%, 100.0%]
Female	94.3% (33/35)	100% (40/40)	100% (35/35)	100% (43/43)
[95% CI]	[80.8%, 99.3%]	[91.2%, 100.0%]	[90.0%, 100.0%]	[91.8%, 100.0%]
Race				
African-American	100% (24/24)	93.8% (15/16)	94.1% (16/17)	100% (20/20)
[95% CI]	[85.8%, 100.0%]	[69.8%, 99.8%]	[71.3%, 99.9%]	[83.2%, 100.0%]
Non-African-American	91.8% (78/85)	96.8% (92/95)	100% (92/92)	98.9% (90/91)
[95% CI]	[83.8%, 96.6%]	[91.0%, 99.3%]	[96.1%, 100.0%]	[94.0%, 100.0%]

Table 34: Reviewer's Results for SVR12 Rates by Baseline Characteristics in ION-2 (All Treated)

	12-Week SOF/LDV (N=109)	12-Week SOF/LDV+RBV (N=111)	24-Week SOF/LDV (N=109)	24-Week SOF/LDV+RBV (N=111)
BMI (kg/m^2)				
< 30	92.4% (61/66)	95.9% (71/74)	98.7% (74/75)	98.8% (81/82)
[95% CI]	[83.2%, 97.5%]	[88.6%, 99.2%]	[92.8%, 100.0%]	[93.4%, 100.0%]
≥ 30	95.3% (41/43)	97.3% (36/37)	100% (34/34)	100% (29/29)
[95% CI]	[84.2%, 99.4%]	[85.8%, 99.9%]	[89.7%, 100.0%]	[88.1%, 100.0%]
HCV genotype				
1a	95.3% (82/86)	95.5% (84/88)	98.8% (84/85)	98.9% (87/88)
[95% CI]	[88.5%, 98.7%]	[88.8%, 98.7%]	[93.6%, 100.0%]	[93.8%,, 100.0%]
1b	87.0% (20/23)	100% (23/23)	100% (24/24)	100% (23/23)
[95% CI]	[66.4%, 97.2%]	[85.2%, 100.0%]	[85.8%, 100.0%]	[85.2%, 100.0%]
IL28 B				
CC	100% (10/10)	100% (11/11)	100% (16/16)	94.4% (17/18)
[95% CI]	[69.2%, 100.0%]	[71.5%, 100.0%]	[79.4%, 100.0%]	[72.7%, 99.9%]
Non-CC	92.9% (92/99)	96.0% (96/100)	98.9% (92/93)	100.0% (93/93)
[95% CI]	[86.0%, 97.1%]	[90.1%, 98.9%]	[94.2%, 100.0%]	[96.1%, 100.0%]
Cirrhosis[1]				
Yes	86.4 (19/22)	81.8% (18/22)	100% (22/22)	100% (22/22)
[95% CI]	[65.1%, 97.1%]	[59.7%, 94.8%]	[84.6%, 100.0%]	[84.6%, 100.0%]
No	95.4% (83/87)	100% (88/88)	98.8% (85/86)	98.9% (88/89)
[95% CI]	[88.6%, 98.7%]	[95.9%, 100.0%]	[93.7%, 100.0%]	[93.9%, 100.0%]
Prior HCV trt history				
PI+PR	93.9% (62/66)	96.9% (62/64)	98.0% (49/50)	100% (51/51)
[95% CI]	[85.2%, 98.3%]	[89.2%, 99.6%]	[89.4%, 99.9%]	[93.0%, 100.0%]
PR	93.0% (40/43)	95.7% (45/47)	100% (58/58)	98.3% (58/59)
[95% CI]	[80.9%, 98.5%]	[85.5%, 99.5%]	[93.8%, 100.0%]	[90.9%, 100.0%]
Response to prior HCV trt				
Relapse/breakthrough	95.0% (57/60)	96.9% (63/65)	100% (60/60)	98.3% (59/60)
[95% CI]	[86.1%, 99.0%]	[89.3%, 99.6%]	[94.0%, 100.0%]	[91.1%, 100.0%]
Nonresponse	91.8% (45/49)	95.7% (44/46)	98.0% (48/49)	100% (51/51)
[95% CI]	[80.4%, 97.7%]	[85.2%, 99.5%]	[89.1%, 99.9%]	[93.0%, 100.0%]
Baseline HCV RNA (IU/mL)				
< 800,000	83.3% (5/6)	100% (13/13)	100% (16/16)	100% (15/15)
[95% CI]	[35.9%, 99.6%]	[75.3%, 100.0%]	[79.4%, 100.0%]	[78.2%, 100.0%]
≥ 800,000	94.2% (97/103)	95.9% (94/98)	98.9% (92/93)	99.0% (95/96)
[95% CI]	[87.8%, 97.8%]	[89.9%, 98.9%]	[94.2%, 100.0%]	[94.3%, 100.0%]
Baseline ALT				
≤ 1.5 x ULN	94.6% (53/56)	95.0% (57/60)	98.0% (48/49)	98.4% (61/62)
[95% CI]	[85.1%, 98.9%]	[86.1%, 99.0%]	[89.1%, 99.9%]	[91.3%, 100.0%]
> 1.5 x ULN	92.5% (49/53)	98.0% (50/51)	100% (60/60)	100% (49/49)
[95% CI]	[81.8%, 97.9%]	[89.6%, 100.0%]	[94.0%, 100.0%]	[92.7%, 100.0%]

[1]Subjects with missing cirrhotic status were excluded from the analyses.

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

/s/

XIAOJING K QI
07/09/2014

TSAE YUN D LIN
07/10/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:
205834

Applicant:
Gilead Science

Stamp Date:
Feb. 10, 2014

Drug Name:
Ledipasvir/Sofosbuvir fixed dose combination (LDV/SOF FDC)

NDA/BLA Type:
NDA, Priority Review

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **No issues.**

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Patient population	Treatment arms/ Sample size	Primary efficacy endpoint/ hypothesis	Sponsor's findings
ION-1 (GS-US-337-0102)	phase 3, multicenter, randomized, open-label Of note, the study consisted of two parts: Part A and Part B. The sponsor originally planned to use SVR4 for subjects in Part A to determine whether to terminate the 12-week arms.	treatment-naïve subjects with genotype 1 (GT1) HCV infection Note: Approximately 16% of the subjects had cirrhosis at baseline.	• 12-week LDV/SOF, n=214 • 12-week LDV/SOF +RBV, n=217 • 24-week LDV/SOF, n=217 • 24-week LDV/SOF +RBV, n=217 Of note, the sponsor did not provide the SVR12 rates for the two 24-week arms in this NDA submission.	The primary efficacy endpoint was SVR12 rate, defined as the proportion of subjects achieving HCV RNA < LLOQ 12 weeks after discontinuation of all study drugs. The primary efficacy hypothesis was that the SVR12 rate in each treatment arm was superior to the historical rate of 60%.	The SVR12 rates were as follows: • 12-week LDV/SOF: 98% (95% CI: 95%, 99%); • 12-week LDV/SOF +RBV: 97% (95% CI: 94%, 99%). Both rates were statistically superior to the historical control rate of 60%.
ION-3 (GS-US-337-0108)	phase 3, multicenter, randomized, open-label	treatment-naïve subjects with GT1 HCV infection Note: The study did not enroll any cirrhotic subjects. The 8-week regimens were not evaluated in the treatment-naïve, cirrhotic subjects.	• 8-week SOF/LDV, n=215 • 8-week SOF/LDV+RBV, n=216 • 12-week SOF/LDV, n=216	same as ION-1	The SVR12 rates were as follows: • 8-week SOF/LDV: 94% (95% CI: 90%, 97%); • 8-week SOF/LDV+RBV: 93% (95% CI: 89%, 96%); • 12-week SOF/LDV: 95% (95% CI: 92%, 98%). Both rates were statistically superior to the historical control rate of 60%.
ION-2 (GS-US-337-0109)	phase 3, multicenter, randomized, open-label	treatment-experienced subjects with chronic GT1 HCV infection Note: Approximately 20% of the subjects had cirrhosis at baseline.	• 12-week SOF/LDV, n=109 • 12-week SOF/LDV+RBV, n=111 • 24-week SOF/LDV, n=109 • 24-week SOF/LDV+RBV, n=111	The primary efficacy endpoint was SVR12 rate. The primary efficacy hypothesis was that the SVR12 rate in each treatment arm was superior to the historical rate of 25%.	The SVR12 rates were as follows: • 12-week SOF/LDV: 94% (95% CI: 87%, 97%); • 12-week SOF/LDV+RBV: 96% (95% CI: 91%, 99%); • 24-week SOF/LDV: 99% (95% CI: 95%, 100%); • 24-week SOF/LDV+RBV: 99% (95% CI: 95% to 100%). All SVR12 rates were

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

					statistically significant greater than the historical control rate of 25%.

Karen Qi 03/10/2014

Reviewing Statistician Date

Fraser Smith 03/10/2014

Secondary Reviewer Date

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

/s/

XIAOJING K QI
03/12/2014

FRASER B SMITH
03/12/2014