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STATISTICAL REVIEW AND EVALUATION

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1 EXECUTIVE SUMMARY

Gilead submitted four pivotal Phase 3 trials in this NDA to support the use of a Sofosbuvir (SOF)-involved treatment regimen for the treatment of subjects infected with genotype 1, 2, 3, 4, 5, or 6 hepatitis C virus (HCV). The four studies had different patient populations but the same primary efficacy endpoint which was the SVR12 rate defined as the proportion of subjects who had HCV RNA below the lower limit of quantitation (LLOQ) 12 weeks after the end of treatment. Study US-334-0110 (i.e. Study 110) evaluated 12 weeks of SOF in combination with a Pegylated Interferon (PEG) and Ribavirin (RBV) in treatment-naive subjects with genotype 1, 4, 5 or 6 HCV infection. Study P7977-1231 (i.e., Study 1231) assessed 12 weeks of SOF plus RBV for the treatment of the HCV genotype 2 or 3 treatment-naïve subjects. Study US-334-0107 (i.e., Study 107) evaluated 12 weeks of SOF combined with RBV in the subjects with genotype 2 or 3 HCV infection who were interferon (IFN) intolerant, IFN ineligible or unwilling to take IFN. Study US-334-0108 (i.e., Study 108) investigated 12 and 16 weeks of SOF plus RBV in treatment-experienced subjects with genotype 2 or 3 HCV infection.

Study 110 demonstrated the efficacy of 12 weeks of SOF combined with PEG and RBV in treatment-naïve subjects with genotype 1 or 4 HCV infection. However, there were only seven HCV genotype 5 or 6 subjects in the study, and the sample size was too small to draw conclusions for these two genotypes.

The SVR12 rates appeared different between the HCV genotypes 2 and 3 subjects based on the results in Studies 1231, 107 and 108. The data from the three studies indicated that 12 weeks of SOF in combination with RBV had adequate efficacy for the treatment of the HCV genotype 2 subjects who were treatment-naïve, treatment-experienced, IFN intolerant, IFN ineligible or unwilling to take IFN. However, the data also suggested that 12 weeks of treatment may be too short for the genotype 3 patients.

Study 108 was the only trial consisting of an arm with the SOF-containing regimen longer than 12 weeks, i.e., 16-week SOF+RBV. This study demonstrated that 16 weeks of SOF+RBV treatment may be sufficient to treat the HCV genotype 3 treatment-experienced subjects because the regimen resulted in a 62% SVR12 rate which was significantly better than the pre-defined 25% historical rate. However, the relapse rate in the 16-week arm was still as high as 38% even though it was much lower than 66% in the 12-week arm. This suggested that the efficacy could potentially be further improved with treatment duration longer than 16 weeks.

Study 1231 suggested the 12-week SOF+RBV regimen was insufficient for the treatment of the HCV genotype 3 treatment-naïve subjects because the treatment regimen had a lower SVR12 rate than the 24 weeks of PEG+RBV treatment (i.e., 56% vs. 63%). Meanwhile, Study 108 revealed that the 16 weeks of SOF+RBV treatment had a SVR12 rate twice as high as the rate for the 12 week of SOF+RBV among the treatment-experienced subjects with genotype 3 HCV infection (i.e., 62% vs. 30%). Therefore, the applicant conducted a bridging analysis to estimate the SVR12 rate for 16 weeks of SOF+RBV in the treatment of HCV genotype 3 treatment-naïve subjects using the genotype 3 data in Studies 1231 and 108. The bridging analysis was based on

the assumption that the odds ratio (OR) between the 12-week and 16-week SOF+RBV among the HCV genotype 3 treatment-naïve subjects was the same as the OR for the HCV genotype 3 treatment-experienced subjects seen in Study 108. The results suggested that the 16-week SOF+RBV regimen would lead to approximately 80% SVR12 rate in HCV genotype 3 treatment-naïve subjects, which was higher than the 56% SVR12 rate for the 12-week SOF+RBV observed in Study 1231. Also, it was anticipated that a longer duration would result in a better SVR12 rate for the genotype 3 subjects from the clinical perspective. The clinically recommended treatment duration for the genotype 3 treatment-naïve subjects was 16 weeks. However, there was no data to validate the assumption of the same ORs between genotype 3 treatment-naïve and treatment-experienced subjects in the bridging analysis. Therefore, it is difficult to recommend the optimal treatment duration for the genotype 3 subjects from the statistical perspective.

One statistical issue was the apparent treatment differences between the HCV genotypes 2 and 3 subjects. In the reviewer's opinion, the observed differences in the SVR12 rates between genotypes 2 and 3 subjects, in particular for the difference in the SOF+RBV treatment regimens in Studies 1231, 107 and 108, were not due to the chance. It was expected that the HCV genotype would have an impact on the SVR12 rate beforehand. Therefore, HCV genotype was one of the stratification factors in the randomization for Studies 1231 and 108, and the subgroup analysis by HCV genotype was one of the pre-defined subgroup analyses in the statistical analysis plan (SAP) in each study. In Study 1231, the 12-week SOF+RBV regime was compared to the 24 weeks PEG+RBV regime and the treatment-by-genotype interaction was significant (p-value = 0.0002). The difference in the SVR12 rate between genotypes 2 and 3 was greater in the 12-week SOF+RBV treatment arm than in the 24-week PEG+RBV treatment arm. In the 12-week SOF+RBV group, 97% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001). On the other hand, 78% and 63% of genotypes 2 and 3 subjects, respectively, achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326). Study 107 compared 12-weeks of SOF+RBV against placebo where no placebo subjects achieved SVR12. In the 12-week SOF+RBV group, the HCV genotype 2 subjects had a significantly higher SVR12 rate than the HCV genotype 3 subjects (i.e., 93% vs. 61%, p-value < 0.0001). In Study 108 where two durations of SOF+RBV were evaluated, the difference in SVR12 rates between the genotypes 2 and 3 subjects were significant within each duration group. In the 12-week SOF+RBV group, 83% of the HCV genotype 2 subjects achieved SVR12 compared with 30% of the HCV genotype 3 subjects (p-value < 0.0001). In the 16-week SOF+RBV group, the SVR12 rates were 89% and 62% for the genotypes 2 and 3 subjects, respectively (p-value = 0.0052). The collective evidence from the three studies strongly suggested that the HCV genotype 2 subjects did have a higher SVR rate than the HCV genotype 3 subjects. The small and consistent p-values could overcome the concern of the lack of a pre-specified plan to control Type 1 error.

Another major statistical issue was the appropriateness of the statistical methods in the applicant's bridging analyses to derive the SVR12 rate for the 16-week SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection based on the observed rates in Studies 1231 and 108. The applicant used the data from all HCV genotype 3 subjects in Studies 1231 and 108 to generate the logistic regression models. They estimated the model parameters using a Bayesian approach and derived the SVR12 rate for the 16 week SOF+RBV regimen in the genotype 3 treatment-naïve subjects based on the assumption that the OR of the 16-week SOF+RBV over

the 12-week SOF+RBV in the genotype 3 treatment-naïve subjects was the same as the OR in the genotype 3 treatment-experienced subjects. The reviewer conducted several analyses to test the sensitivity of the results to various methodologies. First, the reviewer used the maximum likelihood estimation (MLE) approach to estimate the model parameters. The reviewer obtained almost identical results to the applicant's results. Also, the reviewer estimated the SVR12 rate by extrapolating from the observed rates in Studies 1231 and 108 based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. The merit of the extrapolation was that it was relatively easy to follow. The reviewer obtained an 83% SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects based on the extrapolation, which was similar to the applicant's result. The reviewer also used relative risk (RR) and proportion difference (PD) to extrapolate the SVR rate. The estimated SVR12 rate was 76% based on RR and 88% based on PD. All of these post-hoc analyses suggested that 16 weeks of SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects would lead to a higher SVR12 rate than the observed 56% rate for the 12 weeks of SOF+RBV treatment seen in Study 1231. Again, the strong assumptions in the bridging analysis and the lack of Week 16 data made it difficult to determine the optimal treatment duration from the statistical point of view.

Another issue worth noting was the applicant's exclusion of subjects from the efficacy analysis sets in Studies 1231 and 108. There were nine subjects who were misclassified as having genotype 2 HCV infection by the LiPA method at screening but were subsequently found to have genotype 1 infection by population sequencing in the two studies. The LiPA method is currently used to determine the genotype in the clinical practice, whereas population sequencing is not. The applicant excluded these subjects from the efficacy analysis. The inclusion or exclusion of these subjects slightly affected the study results, and the reviewer included the subjects in the analysis in order to follow the intent-to-treat principle.

The final issue was the interpretation of the finding that the HCV genotype 1a treatment-naïve subjects had higher SVR12 rate than the genotype 1b subjects in Study 110 (i.e., 92% vs. 82%). Historically, the subjects infected with genotype 1a HCV are more difficult to treat compared to the subjects with genotype 1b HCV infection. The applicant attributed the observed treatment difference to the findings that the subjects with genotype 1a had a lower percentage of IL28B CC subjects, black subjects, non-cirrhotic subjects and had a lower mean age as compared to the subjects infected with genotype 1b HCV in the study. However, the reviewer compared the SVR12 rates between the two subgenotypes across the subgroups defined by the demographics and baseline characteristics, and found that the genotype 1a subjects had numerically higher SVR12 rate than the genotype 1b subjects in all subgroups. Therefore, the reviewer disagreed with the applicant's interpretation. However, the lack of a control group in the study made it difficult to definitively conclude whether the observed differences between the two subgenotypes were due to chance.

2 INTRODUCTION

2.1 Overview

SOF is a novel nucleotide analogue inhibitor of the HCV NS5B protein to prevent viral replication. It was initially developed by Pharmasset and then acquired by Gilead. The current standard of care (SOC) for the treatment of genotype 1 HCV infection is one protease inhibitor (PI) combined with PEG and RBV. The PIs are Telaprevir and Boceprevir which were approved in 2011. The current SOC improved response rates by 3 to 40% over the old SOC of PEG+RBV alone. However, the safety profile of the SOC is poor. PEG is well known to have many side effects. It is estimated that only 32% of subjects infected with HCV are considered eligible for PEG therapy. Meanwhile, the PIs lead to increased adverse drug reactions. The early phase studies for the SOF-involved regimens demonstrated that SOF in combination with PEG and RBV for 12 weeks was efficacious in treatment of genotype 1 HCV infection. Also the treatment regimen shortened the duration of PEG and RBV and therefore resulted in less adverse events. In contrast, the current SOC for genotype 2 or 3 HCV infection is 24 weeks of PEG and RBV. The early phase studies for SOF also revealed that the PEG-free SOF+RBV regimens resulted in higher cure rates but much less toxicities in treatment of genotype 2 or 3 HCV infection compared with the current SOC.

Since the SOF-containing treatment regimens were shown to be a safe and effective alternative to the current SOC regimens based on the data from the early phase studies, the regimens are considered to be breakthrough therapies. The Division granted Fast Track designation in August of 2010. In this NDA, the applicant submitted the interim clinical study reports for the four pivotal studies including the results of the primary efficacy analysis to support the SOF-involved treatment regimens for the indication of treatment of genotype 1, 2, 3, 4, 5, or 6 HCV infections. The NDA was granted a priority review and will be presented at an advisory committee meeting in October, 2013.

The statistical reviewer focused on reviewing the efficacy of the four Phase 3 trials. These studies had different study designs because they consisted of different patient populations. The summaries of the key elements in the study design in each study are displayed in Table 1.

2.2 Data Sources

The data were submitted electronically and are located in \\Cdsesub1\evsprod\NDA204671\0000. The proposed label discussed in Section 5.4 is located in \\Cdsesub1\evsprod\NDA204671\00004.

Table 1: List of All Phase 3 Studies Included in Review Report

Study Number	Phase and Design	Study Population	Treatment Arms and Number of Randomized/Enrolled Subjects per Arm	Follow-up Period	Primary Hypothesis
P7977-1231 (Study 1231) (Fission)	phase 3, multicenter, open-label, randomized, active-controlled, non-inferiority	treatment-naïve subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week SOF and ribavirin (SOF+RBV), N=263 Arm 2: 24-week pegylated interferon and ribavirin (PEG+RBV), N=264	48 weeks	The SVR12 rate in the12-week SOF+RBV treatment arm was non-inferior to the 24-week PEG+RBV by 15%.
GS-US-334-0107 (Study 107) (Positron)	phase 3, multicenter, randomized, double-blind, placebo-controlled	subjects with chronic genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible or unwilling to take IFN	Arm 1: 12-week SOF+RBV, N=207 Arm 2: placebo, N=71	24 weeks	The SVR12 rate for the 12-week SOF+RBV was superior to placebo.
GS-US-334-0108 (Study 108) (Fusion)	phase 3, multicenter, randomized, double-blind, historical control	treatment-experienced subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week SOF+RBV, N=103 Arm 2: 16-week SOF+RBV, N=99	24 weeks	The SVR12 rate in each of the two treatment arms was no worse than 25%.
GS-US-334-0110 (Study 110) (Neutrino)	phase 3, multicenter, open-label, single-arm, historical control	treatment-naïve subjects with chronic genotype 1, 4, 5 or 6 HCV infection	12-week SOF+PEG+RBV, N=328	24 weeks	The SVR12 rate in the study arm was greater than 60%.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Prior to the NDA submission, the applicant provided the SAP for each study, and each was reviewed. In addition, the reviewers requested sample datasets before the NDA submission and identified data issues which were clarified with the applicant before the submission. In general, the data in this NDA was of high quality, which made it possible for the statistical reviewer to reproduce the applicant's efficacy results easily.

3.2 Evaluation of Efficacy

Because the four studies had different patient populations and primary hypotheses, the reviewer will present the review results for each study individually in the following sections.

3.2.1 Study 1231

3.2.1.1 Study Design and Endpoints

The study was a phase 3, randomized, multicenter, open-label active-controlled, non-inferiority trial conducted among the treatment-naïve subjects with chronic genotype 2 or 3 HCV infection. It aimed to evaluate the efficacy and safety of 12 weeks of SOF in combination with RBV compared with the current SOC, i.e., 24 weeks of PEG plus RBV. The primary hypothesis was that the 12-week SOF+RBV treatment was non-inferior to the 24-week PEG+RBV regimen in the primary efficacy endpoint of SVR12 rate by 15%. Of note, the 15% non-inferiority margin was pre-specified in the protocol. Based on the literature review, the applicant assumed that the SVR rate for the 24-week PEG/weight-based RBV was 70% and that the monotherapy RBV treatment effect was small, and therefore they proposed the non-inferiority margin of 15%. The review team agreed with the margin based on clinical judgment.

The subjects enrolled in the study had chronic genotype 2 or 3 HCV infection, were males or nonpregnant, nonlactating females, were naïve to HCV antiviral treatment, were at least 18 years old, and had a body mass index (BMI) ≤ 18 kg/m^2. Subjects had HCV RNA levels $\geq 10^4$ IU/mL at screening.

The eligible subjects were randomized in a1:1 ratio to either of the following 2 treatment groups:

1) 12-week SOF+RBV: SOF 400 mg plus RBV 1000 to 1200 mg (based on baseline body weight) daily for 12 weeks;
2) 24-week PEG+RBV: PEG 180 ug weekly plus RBV 800 mg daily for 24 weeks

The randomization was stratified by genotype (2 or 3), screening HCV RNA levels (< 6 $\log_{10}$ IU/mL or ≥ 6 $\log_{10}$ IU/mL), and cirrhosis at baseline (present or absent).

All subjects who received at least 1 dose of study medication were followed for 24 weeks after discontinuation or completion of the assigned treatments. Table 35 in Appendix 6.1 provides the study procedures and assessments.

The primary efficacy endpoint was the SVR12 rate defined as the proportion of subjects with HCV RNA < LLOQ 12 weeks after the last dose of study drug.

The secondary efficacy endpoints included the following:

- proportion of subjects with sustained virologic response 24 weeks after stopping therapy, defined as HCV RNA < LLOQ 24 weeks after stopping treatment (i.e., SVR24)
- proportion of subjects with HCV RNA below LLOQ at each visit
- proportion of subjects with ALT normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at each visit) at each visit
- HCV RNA (log10 IU/mL) and change from baseline in HCV RNA (log10 IU/mL) through Week 12
- time to first HCV RNA < LLOQ while on treatment
- time to first HCV RNA < LLOQ target not detected while on treatment
- virologic failure and relapse

The definition of on-treatment virologic failure was as follows:

- 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 value); or
- 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); or
- non-response (HCV RNA persistently ≥ LLOQ through 12 weeks of treatment).

Relapse was defined as a subject with 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.

3.2.1.2 Statistical Methodologies

A. Efficacy Analysis

The efficacy analysis was performed on the full analysis set (FAS) which included subjects with genotype 2, 3 or mixed 2/3 HCV infection who were randomized into the study and received at least one dose of study medication. Subjects with baseline NS5B sequencing that determined the HCV infection was not genotype 2 or 3 were excluded from the FAS.

In the analysis of the primary efficacy endpoint of the SVR12 rate, a closed testing procedure was used. The non-inferiority of SOV+RBV to PEG+RBV was tested first. If the lower limit of the 2-sided 95% CI on the treatment difference (SOF+RBV group minus PEG+RBV group) in the SVR12 rates was > -15%, then it was concluded that SOF+RBV was non-inferior to PEG+RBV. If the non-inferority null hypothesis was rejected, then the p-value associated with the test of superiority was calculated. Superiority would have been demonstrated if the 2-sided p-value was < 0.05.

The point estimate and the 95% CI of the treatment difference in the response rates were constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions to assess non-inferiority. If the null hypothesis for noninferiority was rejected, a Cochran-Mantel-Haenszel (CMH) test stratified by HCV genotype, baseline HCV RNA and cirrhosis status was applied to evaluate the superiority of SOF+RBV group over PEG+RBV.

The point estimates and the 95% exact CIs for the SVR12 rates within each treatment group were calculated based on the Clopper-Pearson method.

For the secondary efficacy endpoints with binary outcome, the proportion and the 95% exact CI using the Clopper-Pearson method were calculated in each treatment group at each scheduled visit.

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 visit windows during the treatment period were calculated from the first dose of study drug (i.e., study day = collection date – date of the first dose; +1 if result is ≥0), while the windows after treatment were from the last study drug dosing date (i.e., follow-up day = collection data – last dose date). The detailed visit windows for all schedule visits are as shown in Table 36 and Table 37 in Appendix 6.1.

C. Handling Missing Data or Dropouts

The applicant described their approach to handling missing data as follows:

> A missing data point for a given study visit may have been due to 1 of the following reasons:
> A visit occurred in the window, but data were not collected or were unusable.
> A visit did not occur in the window.
> A subject permanently discontinued from the study before reaching the visit window.
>
> Values for the missing data (including all safety and health-related quality of life data) were not imputed, with the exception of HCV RNA data.
>
> For the analyses of categorical HCV RNA data, if a data point was missing and was preceded and followed in time by values that were "< LLOQ TND" then the missing data point was set to "< LLOQ TND." If a data point was missing and preceded and followed by values that were "< 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 was set to "< LLOQ detected;" otherwise the data point was considered a failure (ie, ≥ LLOQ detected).

Subjects with missing data due to premature discontinuation of the study had missing data imputed up to the time of their last dose (for on-treatment displays). If study days associated with the last dosing date was greater than the lower bound of a visit window, and the value at the visit was missing, then the value was imputed. If the study days associated with the last dosing date were less than the lower bound of a visit window then the on-treatment value at that visit remained missing. If no HCV RNA values were obtained after the last dose of study drug, the subject was considered a treatment failure for SVR endpoints. However, subjects who were successful for SVR12 and had no further HCV RNA measurements collected were 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 was bracketed by prior and subsequent values of "< LLOQ TND," preceded and followed by "< LLOQ detected," preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected" were set to 24 IU/mL.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows the patient disposition for Study 1231. A total of 527 subjects from 90 study sites in the United States (including Puerto Rico), Australia, New Zealand, Canada, Sweden, Italy and Netherlands were randomized into the study with 263 subjects in the 12-week SOF+RBV group and 264 subjects in the 24-week PEG+RBV group.

Among the randomized subjects who were treated with at least one dose of study medicine (referred to as All Treated hereafter), the percentage of the subjects who discontinued study drug in the 24-week PEG+RBV group was 22%, which was about 5 times as high as the 4% in the 12-week SOF+RBV group. This difference was predominately driven by the lower rate of discontinuations due to AEs or efficacy failure in the 12-week SOF+RBV arm. Specifically, 1% and 0.4% of the subjects treated with SOF+RBV discontinued study drug due to AE and efficacy failure, respectively; while 11% and 7% of the subjects receiving the PEG+RBV treatment discontinued study drug due to AE and efficacy failure, respectively.

Furthermore, the percent of the subjects that withdrew from the study in the 12-week SOF+RBV arm was about 8%, compared with 20% in the 24-week PEG+RBV arm. The major reason for the difference was that none of the subjects in the 12-week SOF+RBV group discontinued the study due to efficacy failure, but 12% in the 24-week PEG+RBV group discontinued due to efficacy failure.

Table 2: Patient Disposition in Study 1231

	12-Week SOF+RBV	24-Week PEG+RBV
Number of screened	677	
Number of randomized	263	264
Number of randomized and treated	256 (100%)	243 (100%)
Discontinued study drug	11 (4%)	54 (22%)
Adverse event	3 (1%)	26 (11%)
Efficacy failure	1 (<1%)	17 (7%)
Death	1 (<1%)	0
Lost to follow-up	2 (1%)	5 (2%)
Consent withdrawn	1 (<1%)	2 (1%)
Other	3 (1%)	4 (2%)
Discontinued study	20 (8%)	48 (20%)
Efficacy failure	0	28 (12%)
Death	1 (<1%)	1 (<1%)
Initiated non-protocol HCV treatment	4 (2%)	0
Lost to follow-up	6 (2%)	9 (4%)
Consent withdrawn	4 (2%)	6 (3%)
Other	5 (2%)	4 (2%)

Source: Table 8-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

The demographics and baseline characteristics for the randomized and treated subjects were well balanced between the two treatment arms (Table 38 in Appendix 6.1). Among the All Treated subjects, the mean (SD) age was approximately 48 (11) years old. The majority of the subjects were male (66%), white (87%), and non-Hispanic (86%). Most subjects were enrolled in U.S. sites (63%).

The baseline disease characteristics were comparable between the two treatment groups (Table 39 in Appendix 6.1). Among the All Treated subjects, the majority (72%) had genotype 3 HCV infection. Approximately 80% of the subjects did not have cirrhosis at baseline. Approximately 57% of the subjects had non-CC IL28B alleles. The mean (SD) of the baseline HCV RNA was 6 (0.8) $\log_{10}$IU/mL with 57% of the subjects having baseline HCV RNA $\geq 6\log_{10}$IU/mL. Approximately 80% of the subjects had baseline ALT above the upper limit of normal range (ULN).

Of note, three subjects in the SOF+RBV arm were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by population sequencing. According to the intent-to-treat principle, these subjects should be included in the efficacy analysis. However, the applicant excluded them. There will be further discussion in Section 3.2.1.4 below.

3.2.1.4 Results and Conclusions

A. Primary Efficacy Endpoint

The applicant's results demonstrated that the SVR12 rates in both treatment groups were around 67% and that the rate in the SOF+RBV group was non-inferior to that in the PEG+RBV group (Table 3).

The applicant's FAS excluded three subjects who were misclassified as having genotype 2 HCV infection by LiPA at screening but were subsequently found to have genotype 1 infection by the population sequencing. In clinical practice, the LiPA assay is used to determine the HCV genotype, whereas the population sequencing is never utilized. Therefore, in the reviewer's opinion, the LiPA assay results should be used to determine HCV genotype, and these three subjects should be included in the analysis in order to follow the intent-to-treat principle. The reviewer conducted the analyses based on the All Treated population including the three subjects with misclassified genotype. Table 4 summarizes the reviewer's results. The inclusion or exclusion of the three subjects had little impact on the results.

Table 3: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 1231 (FAS)

	12-Week SOF+RBV (N=253)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
SVR12 rate (number of subjects with SVR12)	67% (170)	67% (162)	0.3% (-7.5%, 8%)

Source: Table 9-1 in Study GS-US-334-1231 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI are calculated based on Mantel-Haenszel proportions stratified by HCV genotype, cirrhosis status at baseline, and HCV RNA level at screening.

Table 4: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
SVR12 rate (number of subjects with SVR12)	67% (171)	67% (162)	0.1% (-8%, 8%)

[1]based on the Wald asymptotic confidence limits

In addition, the SVR12 rates differed between genotypes 2 and 3 within each treatment group. In the 12-week SOF+RBV group, 95% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001 based on Chi-Square test). In contrast, 78% and 63% of genotypes 2

and 3 subjects achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326 based on Chi-Square test). Furthermore, there was a significant interaction between treatment and HCV genotype for SVR12 rate (p-value based on Breslow-Day test = 0.0002). The SOF+RBV group had a significantly higher SVR12 rate in genotype 2 subjects but numerically lower rate in the HCV genotype 3 subjects. Table 5 displays the applicant's results of the SVR rate by HCV genotype based on the FAS, while Table 6 presents the reviewer's results based on All Treated population. Specifically, the reviewer's analysis demonstrated that the SOF+RBV group had approximately 95% SVR12 rate compared to the 78% SVR12 rate in the PEG+RBV group among genotype 2 subjects (p-value for the treatment difference based on Chi-Squared test = 0.0035). In contrast, the SVR12 rate was 56% in the SOF+RBV group and 63% in the PEG+RBV group among the subjects with genotype 3 HCV infection. These results suggested that the 12 week SOF+RBV treatment was sufficient for the HCV genotype 2 treatment-naïve subjects but not for the HCV genotype 3 treatment-naïve subjects. The subgroup analyses for each genotype to evaluate the treatment effect within the individual genotype were conducted and are presented in Section 4.1.

Of note, patient demographics and the baseline disease characteristics were generally balanced between the two groups within each HCV genotype because genotype was one of the three stratified factors in randomization (Table 40 in Appendix 6.1). Also, the subgroup analysis by genotype was one of the subgroup analyses the applicant planned to conduct as described in their SAP.

Table 5: Applicant's Results for SVR12 Rate by HCV Genotype in Study 1231 (FAS)

	12-Week SOF+RBV	**24-Week PEG+RBV**	**12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]**
Genotype 2			
SVR12 rate (number of SVR12 / number of treated)	97% (68/70)	78% (52/67)	19% (7%, 31%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	56% (102/183)	63% (110/176)	-7% (-17%, 3%)

Source: Table 9-4 in Study GS-US-334-1231 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI are calculated based on Mantel-Haenszel proportions stratified by cirrhosis status at baseline and HCV RNA level at screening.

Table 6: Reviewer's Results for SVR12 Rate by HCV Genotype in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI[1])
Genotype 2[2]			
SVR12 rate (number of SVR12 / number of treated)	95% (69/73)	78% (52/67)	17% (6%, 28%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	56% (102/183)	63% (110/176)	-7% (-17%, 3%)

[1]based on the Wald asymptotic confidence limits
[2]including the 3 subjects who were found to have genotype 2 HCV infection by LiPA assay at screening but later found to have genotype 1 infection by the population sequencing

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

In the analysis of on-treatment virologic responses, the applicant utilized the observed approach, i.e., using all available data without imputing any missing data. Therefore, the analysis set no longer included all randomized and treated subjects. Also, the analysis excluded the subjects who discontinued study drug due to efficacy failure instead of considering them as nonresponders.

The reviewer performed a different analysis based on the All Treated population using the following rules to impute the missing data:

1) the subjects who prematurely discontinued the study drugs were considered as failures regardless of the reasons for discontinuation;

2) the viral load at the next visit was carried backwards to impute the intermittent missing value.

The reviewer's approach will be referred as noncomplete = failure (i.e., NC=F) hereafter. If there were few subjects discontinuing study treatment prematurely, then the reviewer's analysis would lead to similar results as the applicant's observed analysis. However, if there were many discontinuations such as seen in the PEG+RBV treatment group, then the NC=F approach would produce lower response rates.

Figure 1 and Table 7 show the on-treatment responses by genotype in each treatment arm based on the NC=F approach. The SOF+RBV treatment suppressed the viral load quickly. Almost all subjects in the SOF+RBV group achieved HCV RNA < LLOQ around four weeks after receiving the treatment regardless of genotype. The HCV genotype 2 subjects maintained the high response rates thereafter, while the response rates for the genotype 3 subjects dropped slightly at the end of the treatment period because some subjects discontinued study treatment. In the PEG+RBV group, the genotype 2 subjects had higher response rates throughout the treatment phase. The maximum

response rate reached 12 weeks after the start of the treatment for both genotypes, and the response rates decreased slightly towards the end of the treatment due to discontinuations.

Figure 1: Reviewer's Results for On-Treatment Response Rates by Treatment and Genotype in Study 1231 (All Treated, NC=F)

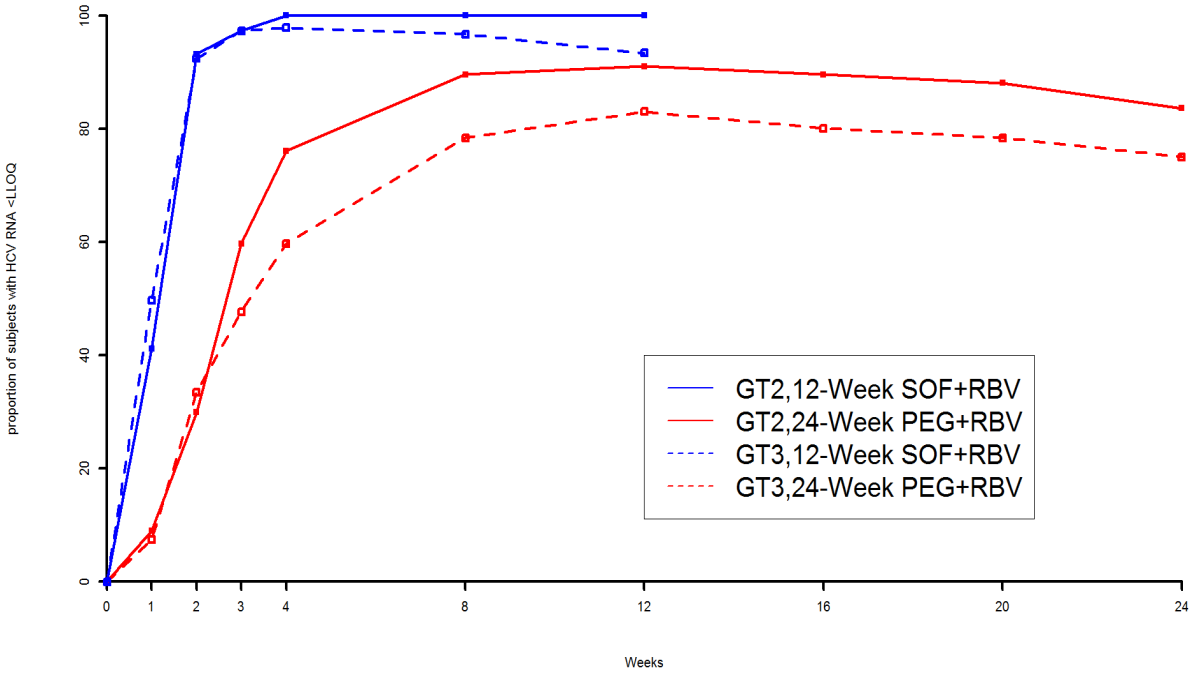


Table 7: Reviewer's Results for On-Treatment Virologic Response at Each Visit in Study 1231 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	**12-Week SOF+RBV (N=256)**	**24-Week PEG+RBV (N=243)**	**12-Week SOF+RBV (N=73)**	**24-Week PEG+RBV (N=67)**	**12-Week SOF+RBV (N=183)**	**24-Week PEG+RBV (N=176)**
Week 1	47% (121)	8% (19)	41% (30)	9% (6)	50% (91)	7% (13)
Week 2	93% (237)	33% (79)	93% (68)	30% (20)	92% (169)	34% (59)
Week 3	97% (249)	51% (124)	97% (71)	60% (40)	97% (178)	48% (84)
Week 4	98% (252)	64% (156)	100% (73)	76% (51)	98% (179)	60% (105)
Week 8	98% (250)	81% (198)	100% (73)	90% (60)	97% (177)	78% (138)
Week 12	95% (244)	85% (207)	100% (73)	91% (61)	93% (171)	83% (146)
Week 16	n/a	83% (201)	n/a	90% (60)	n/a	80% (141)
Week 20	n/a	81% (197)	n/a	88% (59)	n/a	78% (138)
Week 24	n/a	77% (188)	n/a	84% (56)	n/a	75% (132)

In addition, a smaller percentage of subjects in the SOF+RBV group experienced on-treatment virologic failure compared to those in the PEG+RBV group. Specifically, only 0.4% of the subjects

(1/256) receiving the SOF+RBV treatment had on-treatment virologic failure versus 7% (18/243) for the PEG+RBV treatment.

B2. Post-Treatment Relapses

According to the protocol, relapse was defined as subjects with HCV ≥ LLOQ during the post-treatment period after achieving HCV RNA < LLOQ at the end of treatment, confirmed with two consecutive values or the last available post-treatment measurement. As shown in Table 8, the relapses usually occurred at 4 or 8 weeks after the termination of treatment. Overall, higher relapse rates in the 12-week SOF+RBV group were observed compared with the 24-week PEG+RBV group. When the relapse rates were broken down by the different genotypes, it was noticed that the subjects with genotype 2 HCV had lower relapse rates than the subjects with genotype 3 HCV in both treatment groups. As a result, the SVR12 rates were high among genotype 2 subjects in both groups. In addition, compared with the 24-week PEG+RBV, the 12-week SOF+RBV treatment had much lower relapse rates among the subjects with genotype 2 infection but higher relapse rates in the subjects with genotype 3 infection, which caused the significant treatment-by-genotype interaction in SVR12 rate as described above.

Table 8: Reviewer's Results for Post-Treatment Relapse in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV
Overall		
by 4 weeks post-treatment	23% (57/252)	12% (25/217)
by 8 weeks post-treatment	28% (70/252)	20% (44/217)
by 12 weeks post-treatment	30% (76/252)	21% (46/217)
Genotype 2		
by 4 weeks post-treatment	3% (2/73)	6% (4/62)
by 8 weeks post-treatment	3% (2/73)	15% (9/62)
by 12 weeks post-treatment	5% (4/73)	15% (9/62)
Genotype 3		
by 4 weeks post-treatment	31% (55/179)	14% (21/155)
by 8 weeks post-treatment	38% (68/179)	23% (35/155)
by 12 weeks post-treatment	40% (72/179)	24% (37/155)

B3. Virologic Responses at End of Treatment (EOT) and Sustained Virologic Response (SVR) after Treatment

Table 9 displays the virologic responses at the EOT and SVR at 4 and 8 weeks after the EOT (i.e., SVR4 and SVR8). Figure 2 also presents the virologic response rate at the EOT and SVR rates up to post-treatment Week 12 visit. Overall, the 12-week SOF+RBV group had a higher percent of the subjects with virologic response at the EOT than the 24-week PEG+RBV group, but the SVR rates were comparable between the two treatment groups. Moreover, the SVR rates were different between the two genotypes. The SVR rates for the 12-week SOF+RBV treatment were numerically higher in the genotype 2 subjects but lower in the genotype 3 subjects as compared to the rates in the

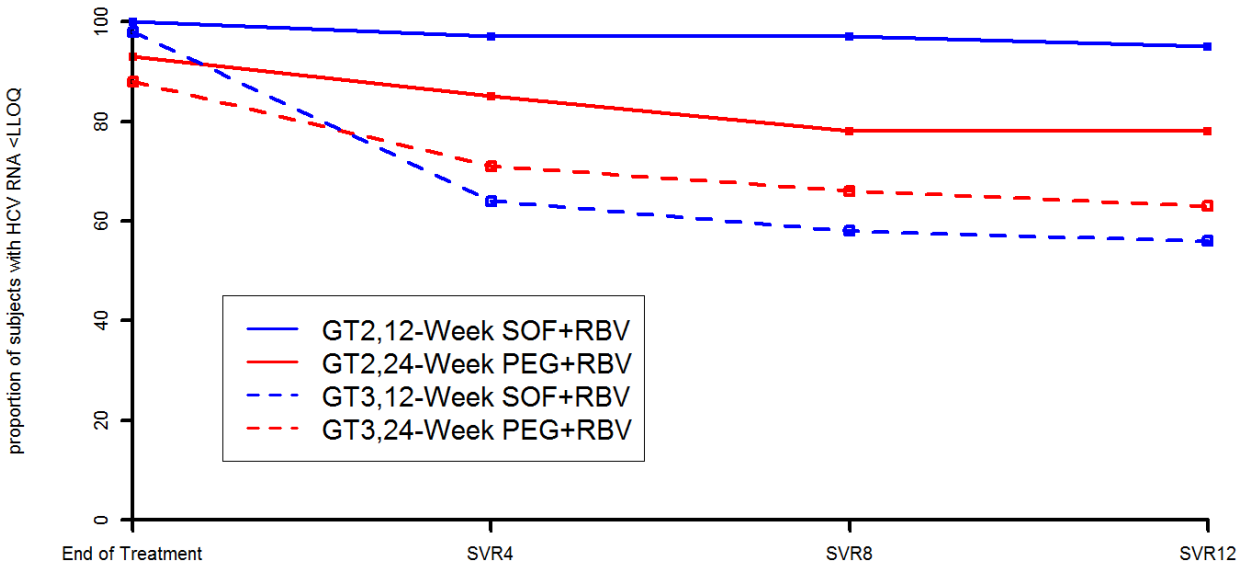
24-week PEG+RBV arm. This was because the SOF+RBV treatment arm had lower relapse rates in the genotype 2 subjects but higher relapse rates in the genotype 3 subjects as mentioned above.

Table 9: Reviewer's Results for EOT Response Rate, SVR4 and SVR8 Rates in Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
EOT response rate	98% (252/256)	89% (217/243)	9% (5%, 13%)
SVR4 rate	73% (188/256)	75% (181/243)	-1% (-9%, 7%)
SVR8 rate	69% (177/256)	68% (165/243)	1% (-7%, 9%)
Genotype 2			
EOT response rate	100% (73/73)	93% (62/67)	7% (1%, 14%)
SVR4 rate	97% (71/73)	85% (57/67)	12% (3%, 22%)
SVR8 rate	97% (71/73)	78% (52/67)	20% (9%, 30%)
Genotype 3			
EOT response rate	98% (179/183)	88% (155/176)	10% (5%, 15%)
SVR4 rate	64% (117/183)	71% (124/176)	-7% (-16%, 3%)
SVR8 rate	58% (106/183)	66% (113/176)	-6% (-16%, 4%)

[1]based on the Wald asymptotic confidence limits

Figure 2: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visits by Treatment and Genotype in Study 1231 (All Treated)



Partial SVR24 data was submitted in this NDA (Table 10). Only one quarter of the subjects in the 24-week PEG+RBV group had the SVR24 data, whereas 95% of the subjects in the 12-week

SOF+RBV group had their SVR24 data available. Specifically, all SVR24 data was available for the HCV genotype 2 subjects and for 93% of the HCV genotype 3 subjects in the 12-week SOF+RBV group. For the HCV genotype 2 subjects receiving the SOF+RBV treatment, the SVR24 rate remained the same as the SVR12 rate. The SVR24 rate was also quite consistent with the SVR12 rate among the HCV genotype 3 subjects.

Table 10: Reviewer's Results for SVR24 Rate by HCV Genotype in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV
Genotype 2		
SVR24 rate	95% (69/73)	21% (14/67)
Not achieving SVR24	5% (4/73)	10% (7/67)
Missing due to discontinuation	0	3% (2/67)
No SVR24 data yet	0	66% (44/67)
Genotype 3		
SVR24 rate	54% (99/183)	7% (13/176)
Not achieving SVR24	35% (64/183)	11% (19/176)
Missing due to discontinuation	4% (7/183)	3% (5/176)
No SVR24 data yet	7% (13/183)	79% (139/176)

3.2.2 Study 107

3.2.2.1 Study Design and Endpoints

This was an ongoing phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of the 12 weeks of SOF+RBV treatment versus placebo in subjects with chronic genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible or unwilling to take IFN. The primary efficacy hypothesis of the study was that 12-week SOF+RBV was superior to placebo as measured by the SVR12 rate.

The eligible subjects were randomized in a 3:1 ratio to either of the following two treatment groups:

1) 12-Week SOF+RBV: SOF 400 mg plus RBV 1000 to 1200 mg (based on baseline body weight) daily for 12 weeks;

2) placebo: SOF placebo administered once daily plus RBV placebo administered in a divided daily dose for 12 weeks.

The randomization was stratified by the presence or absence of cirrhosis at screening. The treatment duration was 12 weeks. Subjects who had HCV RNA < LLOQ at the post-treatment Week 4 visit were to complete the post-treatment Week 12 and 24 visits unless a confirmed viral relapse had occurred. The detailed study procedures and schedule of assessments are displayed in Table 44 and Table 45 in Appendix 6.2.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- proportion of subjects with HCV RNA < LLOQ by each study visit
- absolute values and HCV RNA and change from baseline in HCV RNA through Week 8
- proportion of subjects with on-treatment virologic failure and relapse.

Of note, the definitions of on-treatment failure and relapse were the same as those for Study 1231 in Section 3.2.1.1.

3.2.2.2 Statistical Methodologies

A. Efficacy Analysis

The efficacy analysis set included all chronic genotype 2 or 3 HCV-infected subjects who were randomized into the study and received at least one dose of study medicine, which was the same as Study 1231. In the primary efficacy analysis, the CMH test stratified by absence or presence of cirrhosis at baseline was applied to compare the SVR12 rates between the two arms (SOF+RBV – placebo). For the secondary efficacy endpoints, the proportion of subjects with HCV RNA < LLOQ and the corresponding 95% CI using the Clopper-Pearson method were calculated for each visit within each treatment group. The CMH test was used for the between treatment comparisons.

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that for Study 1231 described in Section 3.2.1.2, i.e., the half of the duration of time between two consecutive study visits. The visit window for each scheduled visit is provided in Table 46 in Section 6.2.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that in Study 1231 specified in Section 3.2.1.2.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 11 displays patient disposition in Study 107. A total of 280 subjects in 54 study sites in the United States (including Puerto Rico), Canada, Australia and New Zealand were randomized into the study with 209 in the SOF+RBV group and 71 in the placebo arm. There were 2 subjects who were erroneously randomized to the SOF+RBV group but did not receive study drug, and therefore these 2 subjects were excluded from the efficacy analysis.

Among the All Treated subjects, approximately 3% in the 12-week SOF+RBV group and 4% in the placebo group discontinued the study drug. The main reason for discontinuation was AE (2% in the 12-week SOF+RBV group and 4% in the placebo group). However, all of the placebo subjects prematurely terminated the study due to efficacy failure after 12 weeks of the assigned treatment, compared with 21% of the subjects in the SOF+RBV arm.

Table 11: Patient Disposition in Study 107

	12-week SOF+RBV	Placebo
Number of screened	410	
Number of randomized	209	71
Number of randomized and treated	207 (100%)	71 (100%)
Discontinued study drug	6 (3%)	3 (4%)
Adverse event	4 (2%)	3 (4%)
Lost to follow-up	2 (1%)	0
Discontinued study	43 (21%)	71 (100%)
Efficacy failure	38 (18%)	71 (100%)
Death	2 (1%)	0
Lost to follow-up	2 (1%)	0
Withdrew consent	1 (0.5%)	0

Source: Table 8-2 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Overall, the demographics were well balanced between the two treatment groups for most of the baseline measures with the exception of region (Table 48 in Appendix 6.2). Compared with the placebo group, the SOF+RBV group had a lower percent of subjects from North America (88% in the SOF+RBV group vs. 96% in the placebo group), and higher proportion of subjects from Australia/New Zealand (12% in the SOF+RBV group and 4% in the placebo group).

There were no notable imbalances between the two treatment groups for the baseline disease characteristics (Table 49 in Appendix 6.2). Of All Treated subjects in the SOF+RBV arm, slightly more than half of them had genotype 2 HCV infection (51%). They were classified as IFN ineligible (44%), intolerant (9%) or unwilling to take IFN (47%). The majority (81%) had never received HCV treatment previously and did not have cirrhosis at baseline (84%). Also, 45%, 43% and 12% of them had IL28B CC, CT or TT alleles, respectively. Most of them had baseline HCV RNA ≥ 6 $\log_{10}$IU/mL (70%) and ALT > 1xULN (76%).

3.2.2.4 Results and Conclusions

A. Primary Efficacy Endpoint

Since there were no patients with misclassified genotypes, the applicant's FAS was the same as the reviewer's All Treated set. Overall, around 78% of the subjects in the SOF+RBV arm achieved SVR12 while no placebo subjects achieved SVR12 (Table 12). The superiority of 12-week SOF+RBV to placebo was established.

Table 12: Results for Primary Efficacy Endpoint of SVR12 Rate in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs. Placebo Proportion Diff (95% CI)
SVR12 rate (number of subjects with SVR12)	78% (161)	0% (0)	77%[1] (71%, 84%)[1] 78%[2] (72%, 83%)[2]

[1]These were the applicant's results presented in Table 9-1 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA. Difference in proportions between treatment groups and associated 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
[2]These were reviewer's results. The difference in proportions between treatment groups were not adjusted by any baseline covariate. The 95% CI was based on the Wald asymptotic confidence limits.

Furthermore, the SVR12 rates for the SOF+RBV treatment differed between genotype 2 and 3 subjects and showed similar pattern as what was observed in Study 1231. Specifically, the SVR12 rates for the SOF+RBV group among the genotype 2 and 3 subjects were around 93% and 61%, respectively (p-value for difference based on Chi-Square test < 0.0001) (Table 13).

Table 13: Reviewer's Results for SVR12 Rate by HCV Genotype in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs. Placebo Proportion Diff (95% CI)[1]
Genotype 2			
SVR12 rate (number of SVR12 / number of treated)	93% (101/109)	0% (0/34)	93% (88%, 98%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	61% (60/98)	0% (0/37)	61% (52%, 71%)

[1]based on the Wald asymptotic confidence limits

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The reviewer performed the same NC=F analysis as that in Study 1231 to evaluate the virologic response at each scheduled visit during the treatment period. As there were few subjects discontinuing the study medicine in the study, the reviewer's results were close to the applicant's observed analyses. The reviewer's results are displayed in Figure 3 and Table 14 below. Similar to Study 1231, almost all subjects in the SOF+RBV arm achieved their viral load below LLOQ four weeks after receiving the treatment and maintained the high response rates thereafter up to the end of

treatment. On the other hand, no placebo subjects had their viral load suppressed during the 12-week treatment period.

Figure 3: Reviewer's Results for On-Treatment Response Rates by Treatment in Study 107 (All Treated, NC=F)

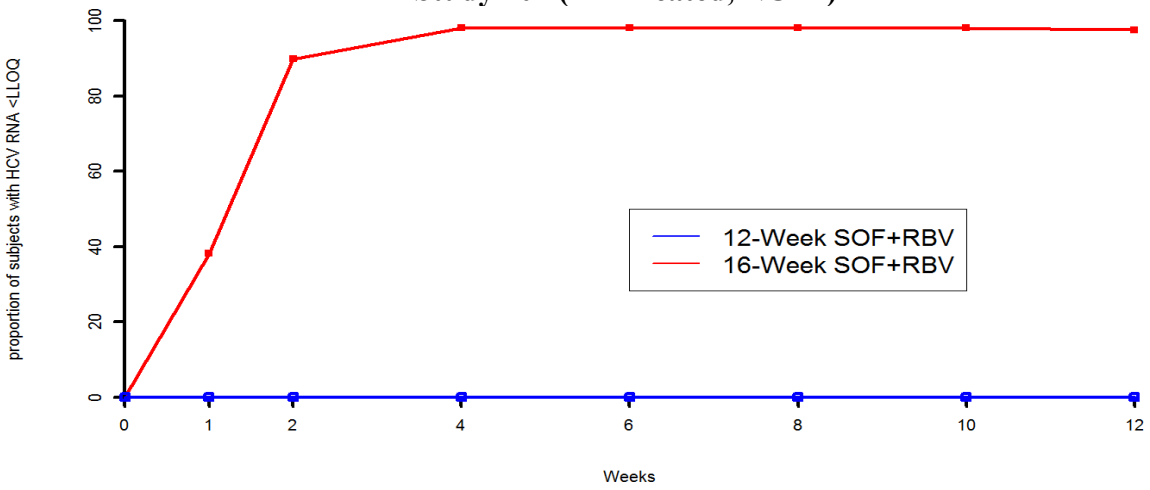


Table 14: Reviewer's Results for On-Treatment Virologic Response at Each Visit in Study 107 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV (N=109)	Placebo (N=34)	12-Week SOF+RBV (N=98)	Placebo (N=37)
Week 1	38% (79)	0%	38% (41)	0%	39% (38)	0%
Week 2	90% (186)	0%	90% (98)	0%	90% (88)	0%
Week 4	98% (203)	0%	98% (107)	0%	98% (96)	0%
Week 6	98% (203)	0%	97% (106)	0%	98% (97)	0%
Week 8	98% (203)	0%	98% (107)	0%	98% (97)	0%
Week 10	98% (203)	0%	98% (107)	0%	98% (97)	0%
Week 12	98% (202)	0%	98% (107)	0%	97% (95)	0%

In addition, no subjects in the SOF+RBV arm had on-treatment virologic failure, but almost all placebo subjects (97%) experienced on-treatment virologic failure.

B2. Post-Treatment Relapses

The visit at 4 weeks after the EOT was the only scheduled post-treatment visit before the Week 12 post-treatment visit. Table 15 below depicts relapses at 4 and 12 weeks post-treatment. Overall, 21% of the subjects receiving 12 weeks of SOF+RBV experienced relapse at 12 weeks after the EOT. Furthermore, a lower proportion of HCV genotype 2 subjects had relapses compared with the HCV genotype 3 subjects, which contributed to a higher SVR12 rate for the genotype 2 subjects in

comparison to the genotype 3 subjects. Also, the relapse rate within each genotype was similar to that in the 12-week SOF+RBV group in Study 1231 as shown in Table 8.

Table 15: Reviewer's Results for Post-Treatment Relapses in Study 107 (All Treated)

	12-week SOF+RBV (N=207)	Placebo[1] (N=71)
Overall		
by 4 weeks post-treatment	15% (31/205)	n/a
by 12 weeks post-treatment	20% (42/205)	n/a
Genotype 2		
by 4 weeks post-treatment	2% (2/107)	n/a
by 12 weeks post-treatment	5% (5/107)	n/a
Genotype 3		
by 4 weeks post-treatment	30% (29/98)	n/a
by 12 weeks post-treatment	38% (37/98)	n/a

[1]No subjects in the placebo group achieved HCV RNA < LLOQ at the end of treatment period.

B3. Virologic Responses at EOT and SVR

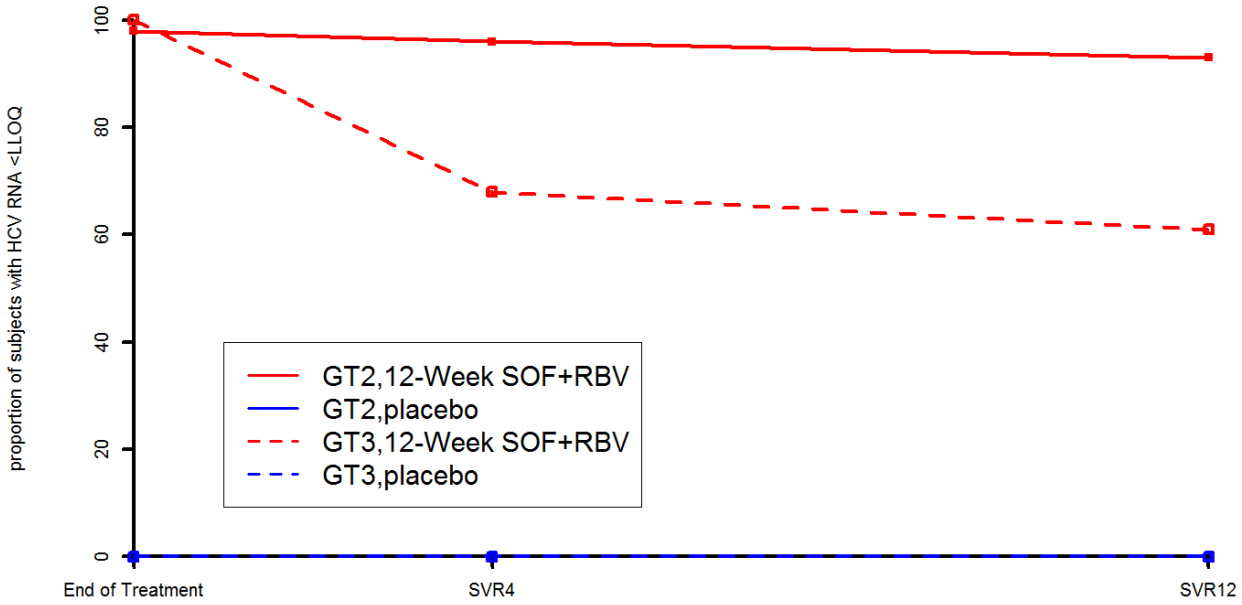
As shown in Table 16, almost all subjects (99%) in the SOF+RBV group achieved HCV RNA < LLOQ at the EOT, but no subjects in the placebo group did. Overall, the SVR4 was observed in 83% of the subjects in the SOF+RBV group. Further analysis demonstrated that 96% of the HCV genotype 2 subjects achieved SVR4 compared to the 68% SVR4 rate in the HCV genotype 3 subjects in the SOF+RBV group. The different relapse rates between genotypes 2 and 3 subjects described earlier contributed to the difference in SVR4 rates in the two genotypes.

Table 16: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs Placebo Proportion Diff (95% CI)[1]
Overall			
EOT response rate	99% (205/207)	0% (0/71)	99% (98%, 100%)
SVR4 rate	83% (172/207)	0% (0/71)	83% (78%, 88%)
Genotype 2			
EOT response rate	98% (107/109)	0% (0/34)	98% (96%, 100%)
SVR4 rate	96% (105/109)	0% (0/34)	96% (93%, 100%)
Genotype 3			
EOT response rate	100% (98/98)	0% (0/37)	n/a
SVR4 rate	68% (67/98)	0% (0/37)	68% (59%, 78%)

[1]based on the Wald asymptotic confidence limits

Figure 4: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visit by Treatment and Genotype in Study 107 (All Treated)



Finally, the SVR24 data for majority (95%) of subjects was available. Table 17 summarizes the SVR24 rate in the 12-week SOF+RBV treatment group. The SVR24 rates appeared fairly consistent with the SVR12 rates for both genotypes.

Table 17: Reviewer's Results for SVR24 Rate in 12-Week SOF+RBV Group in Study 107 (All Treated)

	12-Week SOF+RBV
Genotype 2	
Achieving SVR24	86% (94/109)
Discontinuation	6% (7/109)
Not having SVR24 data	7% (8/109)
Genotype 3	
Achieving SVR24	60% (59/98)
Discontinuation	37% (36/98)
Not having SVR24 data	3% (3/98)

C. Comparison of SVR12 Rates for 12 weeks of SOF+RBV in Treatment-Naïve Subjects between Study 107 and Study 1231

The reviewer conducted an exploratory analysis to evaluate the consistency of the SVR12 rate for 12 weeks of SOF+RBV in treatment-naïve subjects between Studies 1231 and 107. The reviewer compared the patient demographics and baseline disease characteristics between the subjects who were treatment-naïve and received 12 weeks of SOF+RBV treatment in Study 107 and the subjects

in the 12-week SOF+RBV group in Study 1231 within each genotype (Table 50 in Appendix 6.2). For the HCV genotype 2 subjects, there were not any notable differences in the baseline characteristics between the subjects in the two studies. However, it was noticed that there was a higher proportion of subjects with cirrhosis at baseline in Study 1231 than in Study 107 (21% in Study 1231, and 5% in Study 107) among the HCV genotype 3 subjects.

In theory, the subjects in Study 107 were supposed to be more difficult to treat because they were IFN ineligible, IFN intolerant or unwilling to take IFN. However, it was found that the SVR rates for 12 weeks of SOF+RBV in the two studies were similar among the genotype 2 subjects (95% in Study 1231 vs. 92% in Study 107). Among the genotype 3 subjects, 12 weeks of SOF+RBV treatment in Study 107 even had higher SVR12 rate compared to Study 1231 (56% in Study 1231 vs. 70% in Study 107). The reviewer then compared the SVR12 rates for the genotype 3 subjects between Studies 1231 and 107 across the subsets defined by the baseline measures. Study 1231 had lower SVR12 rates in almost all subsets (Table 51 in Appendix 6.2). In the subgroup of the subjects with cirrhosis at baseline, a lower percent of subjects in Study 1231 achieved SVR12 compared to Study 107 (i.e., 34% [13/38] in Study 1231 vs. 50% [2/4] in Study 107). The findings that Study 1231 had a higher percentage of the HCV genotype 3 subjects with cirrhosis at baseline but had lower SVR12 rate in this subset likely contributed to the treatment difference in genotype 3 subjects between Studies 1231 and 107.

Table 18: Reviewer's Analysis to Compare SVR12 Rates for Treatment-Naïve Subjects Receiving 12 Weeks of SOF+RBV in Study 1231 and Study 107

	12-Week SOF+RBV		
	Study 1231	**Study 107**	**Difference in SVR12 rate (95% CI)**
Genotype 2	95% (69/73)	92% (86/93)	-2% (-10%, 5%)
Genotype 3	56% (102/183)	70% (54/77)	-14% (-27%, -2%)

[1]based on the Wald asymptotic confidence limits

3.2.3 Study 108

3.2.3.1 Study Design and Endpoints

The study was a phase 3, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment regimens among subjects with chronic genotype 2 or 3 HCV infection who failed prior treatment with an IFN-based regimen. The primary hypothesis was that the SVR12 rate of each treatment regimen was no worse than 25%. The treatment guidelines recommend that subjects who fail to achieve SVR after a prior full course of PEG+RBV do not receive retreatment with PEG+RBV. There was no other treatment regimen available for the HCV genotype 2 or 3 treatment-experienced subjects. Therefore, a historical control was used. Assuming the SVR rate would be low had the HCV genotype 3 treatment-experienced subjects been

retreated with PEG+RBV, the 25% historical rate was chosen. The historical rate was based on clinical judgment.

Eligible subjects were randomized in a 1:1 ratio to 1 of the following treatment arms:

1) 12-week SOF+RBV: SOF 400 mg administered once daily plus RBV total daily dose of 1000 to 1200 mg administered in a divided daily dose for 12 weeks; followed by SOF placebo administered once daily plus RBV placebo administered in a divided daily dose for 4 weeks;

2) 16-week SOF+RBV: SOF 400 mg administered once daily plus RBV total daily of 1000 to 1200 mg administered in a divided daily dose for 16 weeks.

The randomization was stratified by two factors at baseline: cirrhosis status (yes vs. no) and HCV genotype (2 vs. 3).

The treatment period duration was 16 weeks in both groups, with the SOF+RBV 12 Week group receiving matching placebo between Weeks 12 and 16. All study subjects were to complete a post-treatment Week 4 visit regardless of their treatment duration. Subjects who had HCV RNA < LLOQ at the post-treatment Week 4 visit were to complete post-treatment Week 8, 12, 20 and 24 visits unless a confirmed viral relapse had occurred. Table 54 and Table 55 in Appendix 6.3 show the details of study procedures and schedule of assessments.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- SVR4 and SVR24
- proportion of subjects with HCV RNA below LLOQ by study visit
- HCV RNA (log_{10}IU/mL) and change from baseline in HCV RNA (log_{10}IU/mL) through Week 8
- proportion of on-treatment failure
- proportion of relapse

3.2.3.2 Statistical Methodologies

A. Efficacy Analysis

Similar to Studies 1231 and 107, the efficacy analyses were performed on the FAS which included subjects with genotype 2 or 3 HCV infection who were randomized into the study and received at least one dose of study medication.

The two-sided exact one-sample binomial test was used to test the primary efficacy hypotheses of whether the SVR12 rates in both treatment groups were greater than 25%. The two-sided exact CI for the SVR12 rate in each group was calculated based on the Clopper-Pearson method. Both hypotheses were tested at a significance level of 0.025 using a Bonferroni method to adjust for multiple testing. If the tests in the primary analysis were statistically significant at the 0.025

significance level, then the secondary analysis of comparing the SVR12 rates between the two groups was performed using the CMH test adjusted by the stratification factors in randomization (i.e., absence or presence of cirrhosis at baseline, HCV genotype 2 or 3).

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that in Study 1231 in Section 3.2.1.2. The visit window for each scheduled visit is provided in Table 56 and Table 57 in Appendix 6.3.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that described in Section 3.2.1.2 for Study 1231.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition is shown in Table 19. A total of 202 subjects from in 57 sites in the United States (including Puerto Rico), Canada and New Zealand were randomized into the study with 103 in the 12-week SOF+RBV arm and 99 in the 16-week SOF+RBV group. One randomized subject in the 16-week SOF+RBV group did not take the study drug. Among the 201 randomized and treated subjects, only one subject in the 12-week SOF+RBV arm discontinued the study medication due to an adverse event. However, approximately half of the subjects in the 12-week treatment arm discontinued the study compared with one third of the subjects in the 16-week arm. The most common reason for premature discontinuation from the study was efficacy failure.

Table 19: Patient Disposition for Study 108

	12-week SOF+RBV	16-week SOF+RBV
Number of screened	277	
Number of randomized	103	99
Number of randomized and treated	103 (100%)	98 (100%)
Discontinued study drug	1 (1%)	0
Adverse event	1 (1%)	0
Discontinued study	52 (50%)	28 (29%)
Efficacy failure	49 (48%)	28 (29%)
Lost to follow-up	2 (2%)	0
Withdrew consent	1 (1%)	0

Source: Table 8-2 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

The patient demographics and baseline characteristics were comparable between the two treatment groups (Table 58 in Appendix 6.3). Among the All Treated subjects, the mean (SD) age for was 54 (8) years. The majority of the subjects were male (70%), white (87%), non-Hispanic (91%), and from US sites (76%). The mean BMI (SD) was around 29 (5) kg/m^2.

The baseline disease characteristics were quite similar between the two treatment arms (Table 59 in Appendix 6.3). In general, the majority of the subjects (63%) had genotype 3 HCV infection. The overall mean (SD) baseline HCV RNA level for the subjects was 6.5 (0.7) $\log_{10}$ IU/mL and most subjects (73%) had baseline HCV RNA $\geq$ 6 $\log_{10}$IU/mL. Approximately 75% of subjects had relapse/breakthrough when receiving the prior HCV treatment, and 25% did not respond to the previous HCV treatment. The majority of the subjects (70%) had non-CC IL28B alleles and did not have cirrhosis (66%) at baseline.

There were six subjects who were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis instead of genotype 2 HCV infection as determined by LiPA at screening. As in Study 1231, the applicant excluded these six subjects from their efficacy analyses, which the reviewer deemed inappropriate due to violation of the intent-to-treat principle.

3.2.3.4 Efficacy Results and Conclusion

A. Primary Efficacy Results

The applicant's results shown in Table 20 demonstrated that about 50% of the subjects in the 12-week group and 73% in the 16-week group achieved SVR12. Both rates were statistically significantly greater than the 25% historical rate. Also, the SVR12 rate for the shorter duration appeared significantly lower than that in the longer duration.

The applicant's analysis excluded the six subjects with misclassified genotype by LiPA assay as done in Study 1231. Again, even though inclusion or exclusion of these subjects only slightly affected the results in this study, the reviewer included these subjects to follow the intent-to-treat principle. The reviewer carried out the analyses on the All Treated population. Table 21 summarizes the reviewer's results.

Similar to Study 1231, it was noticed that the HCV genotype appeared to affect the SVR12 rate in the treatment groups. Based on the reviewer's analysis (Table 23), the SVR12 rate for the HCV genotype 2 subjects was 82% in the 12-week treatment group, which was significantly greater than 30% rate for the genotype 3 subjects in the same group (p-value based on Chi-Square test <0.0001). Similarly, 89% of the genotype 2 subjects in the 16-week treatment arm achieved SVR12, which was significantly higher than 62% of the genotype 3 subjects (p-value based on Chi-Square test = 0.0052). On the other hand, for the HCV genotype 2 subjects, the 12-week and 16-week SOF+RBV had comparable SVR12 rates (i.e., 82% for the 12-week group and 89% for the 16-week group). Both rates were significantly higher than the 25% historical rate (p-value < 0.0001). However, in the HCV genotype 3 subjects, the SVR12 rate for the 12 weeks of treatment was 30%, which was only half of rate for the 16 weeks of treatment. The rate for the 12-week treatment duration did not show superior to the historical rate (p-value=0.4635), while the rate for the 16-week duration did (p-value<0.001). These results suggested that using SOF+RBV for 12 weeks was sufficient for the genotype 2 treatment-experienced subjects but not for the genotype 3 treatment-experienced subjects.

Table 20: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 108 (FAS)

	12-Week SOF+RBV (N=100)	16-Week SOF+RBV (N=95)	12-Week SOF+RBV vs. 16-Week SOF+RBV	
			Proportion Diff (95% CI)[1]	p-value[2]
SVR12	50% (50/100)	73% (69/95)	-23% (-35%, -11%)	<0.001
95% CI[3]	(40%, 60%)	(63%, 81%)		
p-value compared to 25%[3]	<0.001	<0.001		

Source: Table 9-1 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
[2]Between treatment group p-value was from Cochran-Mantel-Haenszel test stratified by randomization stratification factors.
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

Table 21: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week SOF+RBV vs. 16-Week SOF+RBV	
			Proportion Diff (95% CI)[1]	p-value[2]
SVR12	50% (51/103)	71% (70/98)	-22% (-35%, -9%)	0.0015
95% CI[3]	(40%, 60%)	(61%, 80%)		
p-value compared to 25%[3]	<0.001	<0.001		

[1]based on the Wald asymptotic confidence limits
[2]p-value based on Chi-squared test
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

Table 22: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate by HCV Genotype in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week SOF+RBV vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Genotype 2			
SVR12	86% (31/36)	94% (30/32)	-8% (-24%, 8.5%)
95% CI[2]	(71%, 95%)	(79%, 99%)	
Genotype 3			
SVR12	30% (19/64)	62% (39/63)	-32% (-48%, -15%)
95% CI[2]	(19%, 42%)	(49%, 74%)	

Source: Table 9-4 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]The 95% CI on the difference was based on the exact method (standardized statistic and inverting two 1-sided test).
[2]The exact 95% CI for the proportion within subgroup was based on the Clopper-Pearson method.

Table 23: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate by HCV Genotype in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	Proportion Diff (95% CI)[1]
Genotype 2			
SVR12	82% (32/39)	89% (31/35)	-7% (-23%, 9%)
p-value compared to 25%[2]	< 0.001	< 0.001	
Genotype 3			
SVR12	30% (19/64)	62% (39/63)	-32% (-49%, -16%)
p-value compared to 25%[2]	0.4635	< 0.001	

[1]Wald asymptotic confidence intervals
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The reviewer applied the same NC=F approach as that in Study 1231 to assess the on-treatment responses. Similar to Study 107, there were few subjects who discontinued the study medication prematurely. Therefore, the results from NC=F analysis were close to those based on the applicant's observed analysis.

Like the previous two studies, the SOF+RBV treatment quickly suppressed HCV regardless of the HCV genotype. Almost all subjects achieved HCV viral load below LLOQ within four weeks after starting the treatment. The high response rates sustained through the end of the treatment period in both genotypes and both groups (Figure 5 and Table 24). Additionally, no subject in either group experienced on-treatment virologic failure.

Figure 5: Reviewer's Results for On-Treatment Virologic Response by Treatment in Study 108 (All Treated)

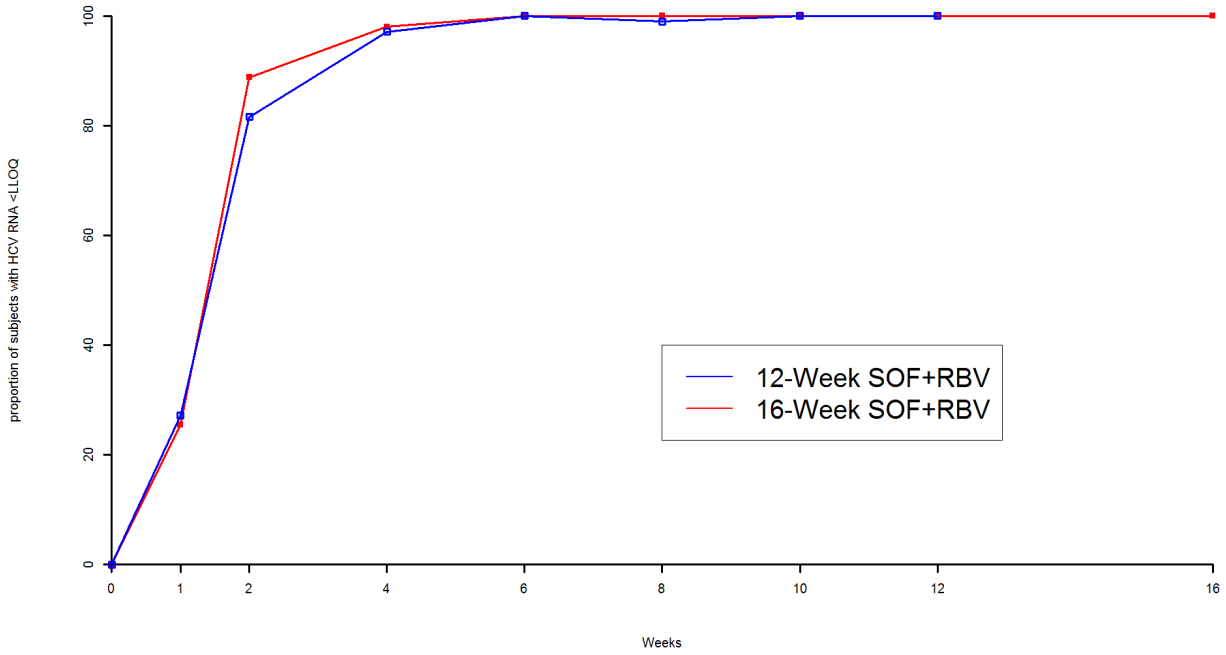


Table 24: Reviewer's Results for On-Treatment Virologic Responses in Study 108 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	**12-Week SOF+RBV (N=103)**	**16-Week SOF+RBV (N=98)**	**12-Week SOF+RBV (N=39)**	**16-Week SOF+RBV (N=35)**	**12-Week SOF+RBV (N=64)**	**16-Week PEG+RBV (N=63)**
Week 1	27% (28)	26% (25)	31% (12)	14% (5)	25% (16)	32% (20)
Week 2	82% (84)	89% (87)	85% (33)	86% (30)	80% (51)	90% (57)
Week 4	97% (100)	98% (96)	100% (39)	100% (35)	95% (61)	97% (61)
Week 6	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 8	99% (102)	100% (98)	100% (39)	100% (35)	98% (63)	100% (63)
Week 10	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 12	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 16	n/a	100% (98)	n/a	100% (35)	n/a	100% (63)

B2. Post-Treatment Relapses

The relapse pattern was similar to those observed in the SOF+RBV arms in Studies 1231 and 107. Table 25 shows that most relapses occurred 4 weeks following the EOT regardless of treatment duration and the HCV genotype. The HCV genotype 2 subjects had much lower relapse rates than the HCV genotype 3 subjects in both treatment groups. The relapse rates were comparable between

the two durations among the HCV genotype 2 subjects. However, the relapse rates varied between the two groups in the HCV genotype 3 subjects. Around 66% of the genotype 3 subjects in the 12-week group relapsed by 12 weeks after the EOT compared to 38% in the 16-week group. The observed differences in relapse rates between genotypes and between treatment groups within the HCV genotype 3 subjects attributed to the differences in SVR12 rates as discussed in the previous section. Finally, it was important to note that the 38% relapse rate in the 16-week arm was high and therefore the 16 weeks duration may not be long enough for the HCV genotype 3 treatment-experienced subjects.

Table 25: Reviewer's Results for Post-Treatment Relapse in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)
Overall		
by 4 weeks post-treatment	44% (45/103)	24% (24/98)
by 8 weeks post-treatment	46% (47/103)	29% (28/98)
by 12 weeks post-treatment	48% (49/103)	29% (28/98)
Genotype 2		
by 4 weeks post-treatment	15% (6/39)	9% (3/35)
by 8 weeks post-treatment	15% (6/39)	11% (4/35)
by 12 weeks post-treatment	18% (7/39)	11% (4/35)
Genotype 3		
by 4 weeks post-treatment	61% (39/64)	33% (21/63)
by 8 weeks post-treatment	64% (41/64)	38% (24/63)
by 12 weeks post-treatment	66% (42/64)	38% (24/63)

B3. Virologic Responses at EOT and SVR

All subjects had HCV RNA below LLOQ at the EOT but the SVR rates after the EOT were different between the two genotypes and between the two durations among the HCV genotype 3 subjects (Table 26 and Figure 6). The genotype 2 subjects had higher SVR rates than the genotype 3 subjects. The two durations had comparable SVR rates among the genotype 2 subjects, but the rates for the shorter duration appeared much lower than the longer duration in the genotype 3 subjects. The different relapse rates described in the previous section attributed to these different SVR rates.

Table 26: Reviewer's Results for Response Rate at EOT, SVR4 and SVR8 Rates in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)
Overall			
EOT response rate	100% (103/103)	100% (98/98)	n/a
SVR4 rate	55% (57/103)	76% (74/98)	-20% (-33%, -7%)
SVR8 rate	53% (55/103)	71% (70/98)	-18% (-31%, -5%)

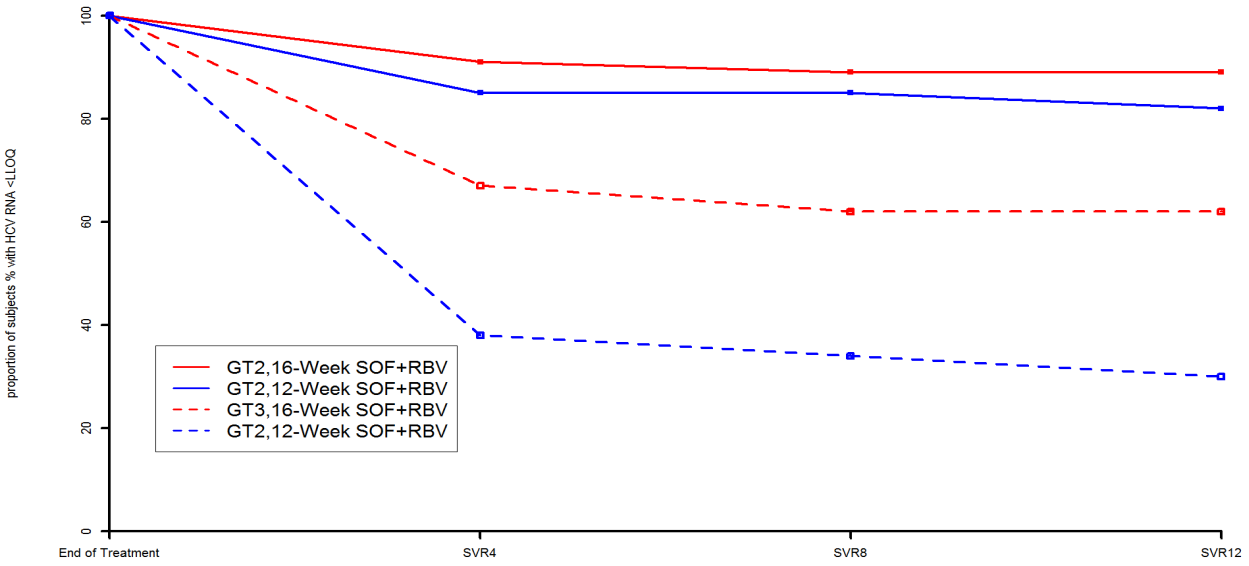
to be continued

Table 32: Reviewer's Results for Response Rate at EOT, SVR4 and SVR8 Rates in Study 108 (All Treated) (Continued)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Genotype 2			
EOT response rate	100% (39/39)	100% (35/35)	n/a
SVR4 rate	85% (33/39)	91% (32/35)	-7% (-21%, 8%)
SVR8 rate	85% (33/39)	89% (31/35)	-4% (-19%, 12%)
Genotype 3			
EOT response rate	100% (64/64)	100% (63/63)	n/a
SVR4 rate	38% (24/64)	67% (42/63)	-29% (-46%, -13%)
SVR8 rate	34% (22/64)	62% (39/63)	-28% (-44%, -11%)

[1]Wald asymptotic confidence intervals

Figure 6: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visits by Treatment and HCV Genotype in Study 108 (All Treated)



3.2.4 Study 110

3.2.4.1 Study Design and Endpoints

This was a Phase 3, open-label, single arm trial to evaluate the efficacy and safety of SOF in combination of with PEG and RBV in the treatment of treatment-naïve subjects with chronic genotype 1, 4, 5 or 6 HCV infection. The subjects enrolled in the study were treated for 12 weeks with SOF (400 mg once daily) in combination with PEG (180 µg/week) and RBV (1000 or 1200 mg based on baseline body weight). The treatment regimen will be referred as 12-Week

SOF+PEG+RBV hereafter. The primary hypothesis was that the SVR12 rate was greater than the 60% historical rate. The historical rate was based on clinical judgment.

All subjects were to complete a post-treatment Week 4 visit. Subjects with HCV RNA < LLOQ at the post-treatment Week 4 visit completed the post-treatment Week 12 and Week 24 visits unless the confirmed viral relapse occurred. Table 63 and Table 64 in Appendix 6.4 detail the study procedures and schedule of assessments.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- SVR4 and SVR24
- proportion of subjects with HCV RNA < LLOQ by study visit
- HCV RNA (log10 IU/mL) and change from baseline in HCV RNA (log10 IU/mL) through Week 8
- proportion of subjects with on-treatment virologic failure and relapse

Of note, the on-treatment virologic failure and relapse were defined the same as in Study 1231.

3.2.4.2 Statistical Methodologies

A. Efficacy Analysis

Two-sided one-sample exact test was performed to determine whether the SVR12 rate was higher than 60%. Also, the Clopper Pearson exact approach was used to construct the 95% CI on the SVR12 rate.

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that in Study 1231 in Section 3.2.1.2. The visit window for each scheduled visit is provided in Table 65 and Table 66 in Appendix 6.4.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that described in Section 3.2.1.2 for Study 1231.

3.2.4.3 Patient Disposition, Demographic and Baseline Characteristics

Table 27 presents the patient disposition. A total of 328 subjects from 55 US sites enrolled in the study, and 327 of them received 12-week SOF 400 mg once daily plus PEG 180 ug/week plus RBV 1000 or 1200 mg /day. Among the 327 enrolled and treated subjects, 2% of them (7 subjects) discontinued study treatment. The most common reason for discontinuation was AE (2%, 5

subjects), following by protocol violation (< 1%, 1 subject) and consent withdrawn (< 1%, 1 subject). After the 12 weeks of treatment, 9% of the treated subjects withdrew from the study mainly due to efficacy failure (8%, 26 subjects).

Table 27: Patient Disposition in Study 110

	12-Week SOF+PEG+RBV
Number of screened	456
Number of enrolled	328
Number of treated	327 (100%)
Discontinued study treatment	7 (2%)
Adverse event	5 (2%)
Protocol violation	1 (0.3%)
Withdrew consent	1 (0.3%)
Discontinued study	29 (9%)
Efficacy failure	26 (8%)
Lost to follow-up	2 (1%)
Withdrew consent	1 (0.3%)

Source: Table 8-2 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Overall the mean age (SD) was 52 years (10). The majority of subjects were male (64%), white (79%), non-Hispanic (86%). The mean (SD) baseline BMI was 29 (7) kg/m^2 (Table 67 in Section 6.4).

The baseline disease characteristics for all enrolled and treated subjects are displayed in Table 68 in Appendix 6.4. The majority of subjects (89%) had genotype 1 HCV infection. There was only one subject infected with genotype 5 HCV and six subjects with genotype 6 HCV infection. Most subjects (83%) did not have cirrhosis at baseline. More than two-third of the subjects had non-CC IL28B allele. The average baseline HCV RNA (SD) was 6.4 $\log_{10}$ (0.67) IU/mL, with majority of the subjects having a baseline HCV RNA $\geq$ 6 $\log_{10}$ IU/mL (78%).

3.2.4.4 Efficacy Results and Conclusion

A. Primary Efficacy Endpoint

Approximately 90% of the treated subjects achieved SVR12, and the rate was significantly greater than the 60% historical rate (Table 28).

Table 28: Applicant's Results for Primary Efficacy of SVR12 Rate in Study 110 (All Treated)

	12-Week SOF+PEG+RBV
SVR12	90% (295/327)
95% CI[1]	(86%, 93%)
p-value compared to 60%[1]	< 0.001

Source: Table 9-1 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA
[1]The exact 95% CI was based on the Clopper-Pearson method and the p-value was from the exact 1-sample binomial test.

Further analysis revealed the SVR12 rates were different between the HCV genotypes 1a and 1b subjects. Historically, the subjects infected with genotype 1a HCV are more difficult to treat than those infected with genotype 1b HCV infection. For the approved Telaprevir regimen, the SVR24 rates were 74% and 86% for the genotype 1a and 1b treatment-naïve subjects, respectively. Of note, the genotype was determined by the LiPA method. Please refer to the statistical review for Telaprevir (NDA 201917) by Dr. Thomas Hammerstrom for the details. For the approved Boceprevir treatment regimen, the SVR24 rate was 59% for the genotype 1a treatment-naïve subjects and 66% for the genotype 1b treatment-naïve subjects. Of note, the genotype was based on the (b) (4) method. Please refer to the statistical review for Boceprevir (NDA 202258) by Dr. Wen Zeng for the details.

The HCV genotype 1a subjects had 10% higher SVR12 rate than the HCV genotype 1b subjects in Study 110 (92% for the subjects with genotype 1a, 82% for the subjects with genotype 1b), and the difference was significant at the significance level of 0.05. The applicant attributed the difference to the higher proportion of IL28B CC subjects, black subjects, subjects with cirrhosis at baseline and mean age among subjects with genotype 1b compared to the subjects with genotype 1a (Table 69 in Section 6.4). The reviewer compared the SVR12 rates between the subjects with genotype 1a and 1b across the subgroups defined by the demographic and baseline characteristics (Table 71 in Section 6.4). The HCV genotype 1a subjects had numerically higher SVR12 rates than the HCV genotype 1b subjects in almost all subgroups. Therefore, the reviewer did not agree with the applicant's interpretation. In the reviewer's opinion, the lack of a control group in the study made it difficult to definitively conclude whether the observed difference in the SVR12 rates between subjects with genotype 1a and 1b was due to chance or not.

Finally, the sample sizes for the HCV genotype 5 and 6 subjects were too small to be conclusive although the 7 genotype 5 and 6 subjects achieved SVR12 in the study.

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The HCV viral load was rapidly suppressed after the subjects were treated with SOF+PEG+RBV. Almost all subjects had HCV RNA < LLOQ 4 weeks after the treatment. The high response rate was maintained throughout the rest of the treatment period (Figure 7 and Table 29). Also, no subject experienced the on-treatment virologic failure in the study.

Figure 7: On-Treatment Virologic Responses for Study 110 (All Treated)

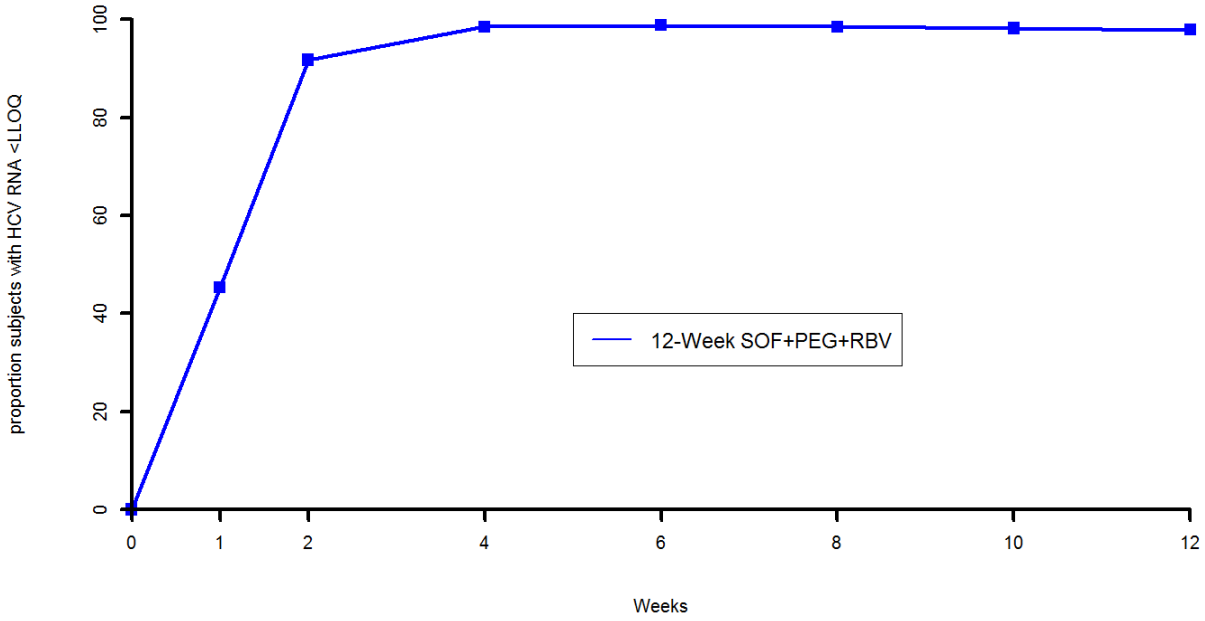


Table 29: Reviewer's Results for On-Treatment Virologic Responses in Study 110 (All Treated, NC=F)

	12-Week SOF+PEG+RBV (N=327)
Week 1	45% (148)
Week 2	92% (300)
Week 4	98% (322)
Week 6	99% (323)
Week 8	98% (322)
Week 10	98% (321)
Week 12	98% (320)

B2. Post-Treatment Relapses

Overall less than 10% of the subjects relapsed 12 weeks after the EOT (Table 30). Also, a higher proportion of the subjects with genotype 1b relapsed compared with the subjects with genotype 1a, which resulted in the lower SVR12 rate for the HCV genotype 1b subjects as described in Section 3.2.4.4 A.

Table 30: Reviewer's Results for Post-Treatment Relapse in Study 110 (All Treated)

	12-Week SOF+PEG+RBV
Overall	
by 4 weeks post-treatment	7% (22/326)
by 12 weeks post-treatment	9% (28/326)
Genotype 1a	
by 4 weeks post-treatment	6% (14/225)
by 12 weeks post-treatment	8% (18/225)
Genotype 1b	
by 4 weeks post-treatment	11% (7/65)
by 12 weeks after EOT	14% (9/65)
Genotype 4	
by 4 weeks post-treatment	4% (1/28)
by 12 weeks post-treatment	4% (1/28)
Genotype 5	
by 4 weeks post-treatment	0% (0/1)
by 12 weeks post-treatment	0% (0/1)
Genotype 6	
by 4 weeks post-treatment	0% (0/6)
by 12 weeks post-treatment	0% (0/6)

B3. Virologic Responses at EOT and Post-Treatment

Almost all subjects in the study achieved virologic suppression at the EOT regardless of the HCV genotype. The response rates remained high for all genotypes after the EOT (Table 31). Figure 9 displays the response rates at the EOT and SVR for the subjects with genotype 1a and 1b HCV.

Table 31: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 110 (All Treated)

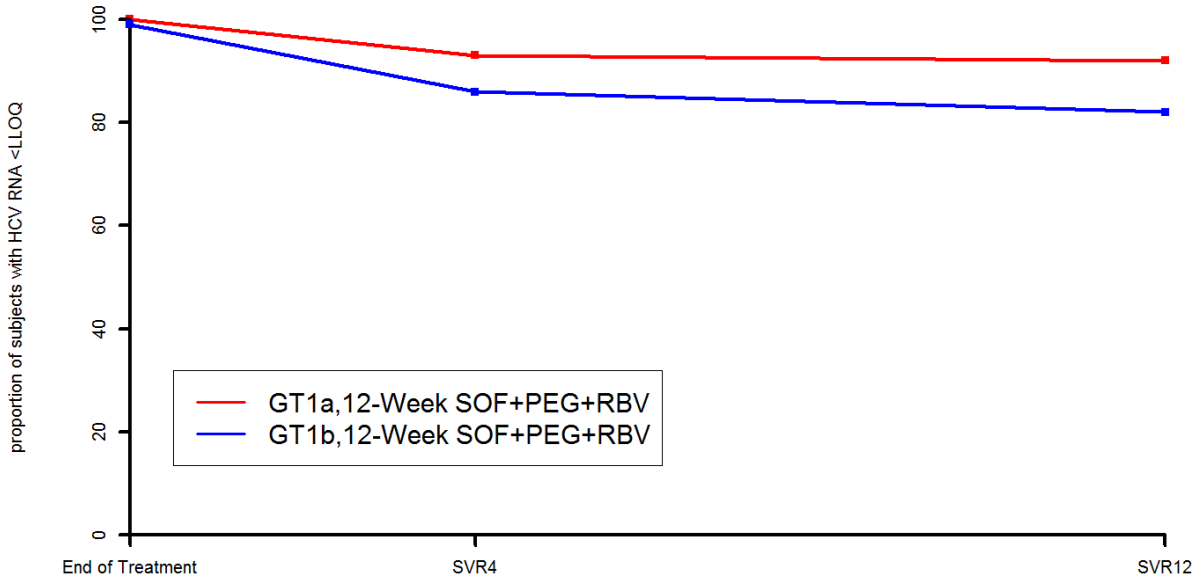
	12-Week SOF+PEG+RBV
Overall	
EOT response rate	99.7% (326/327)
SVR4 rate	92% (302/327)
Genotype 1a	
EOT response rate	100% (225/225)
SVR4 rate	93% (210/225)
Genotype 1b	
EOT response rate	99% (65/66)
SVR4 rate	86% (57/66)

to be continued

Table 40: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 110 (All Treated) (Continued)

	12-Week SOF+PEG+RBV
Genotype 4	
EOT response rate	100% (28/28)
SVR4 rate	96% (27/28)
Genotype 5	
EOT response rate	100% (1/1)
SVR4 rate	100% (1/1)
Genotype 6	
EOT response rate	100% (6/6)
SVR4 rate	100% (6/6)

Figure 8: Reviewer's Results for Virologic Response Rates at EOT and Post-Treatment by Subgenotype in Subjects with HCV Genotype 1 Infection in Study 110 (All Treated)



3.2.5 Bridging Analysis to Estimate SVR12 Rate for 16-Week SOF+RBV for Genotype 3 Treatment-Naïve Subjects

3.2.5.1 Background and Objective for Bridging Analysis

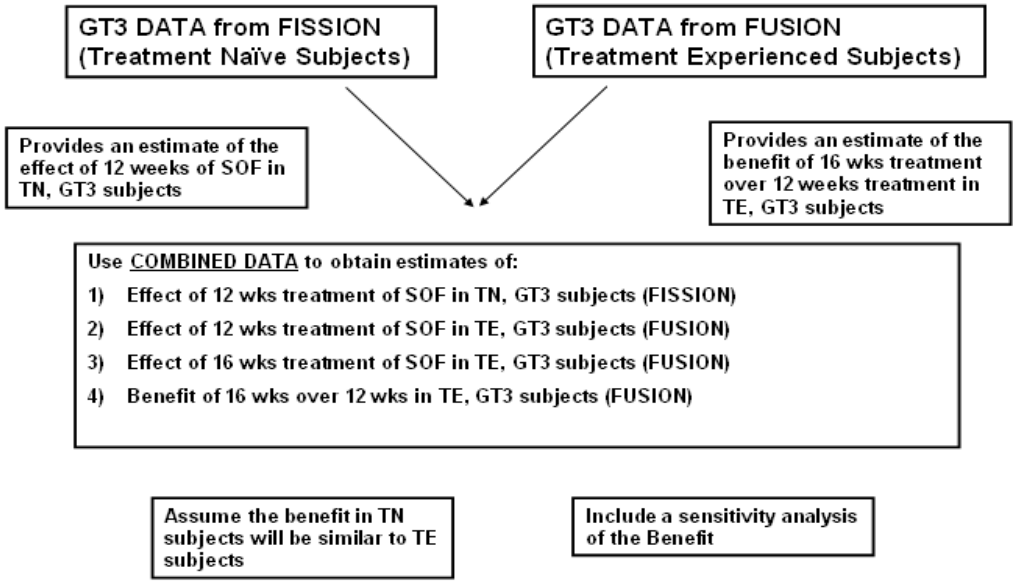
The results in Study 1231 demonstrated that the 12 weeks of SOF+RBV treatment had a lower SVR12 rate than the 24 weeks of PEG+RBV in treatment-naïve subjects with genotype 3 HCV infection (56% in the 12-week SOF+RBV group vs. 62% in the 24-week PEG+RBV group). This suggested that using SOF+RBV for 12 weeks could be insufficient to treat HCV genotype 3 treatment-naïve subjects. Study 108 showed that the 16 weeks of SOF+RBV had a SVR12 rate

twice as high as the 12 weeks of SOF+RBV among HCV genotype 3 treatment-experienced subjects. It implied that genotype 3 treatment-naïve subjects may require 16 weeks of treatment. However, there was no study evaluating the treatment effect of the 16 weeks of SOF+RBV in HCV genotype 3 treatment-naïve subjects. Therefore, the applicant proposed a post-hoc bridging analysis in order to estimate the SVR12 rate for the 16 weeks of treatment in the HCV genotype 3 treatment-naïve subjects based on the SVR12 rates seen in Studies 1231 and 108.

3.2.5.2 Applicant's Bridging Analysis

Figure 9 below displays the applicant's modeling framework for bridging analysis.

Figure 9: Modeling Framework for Bridging Analysis

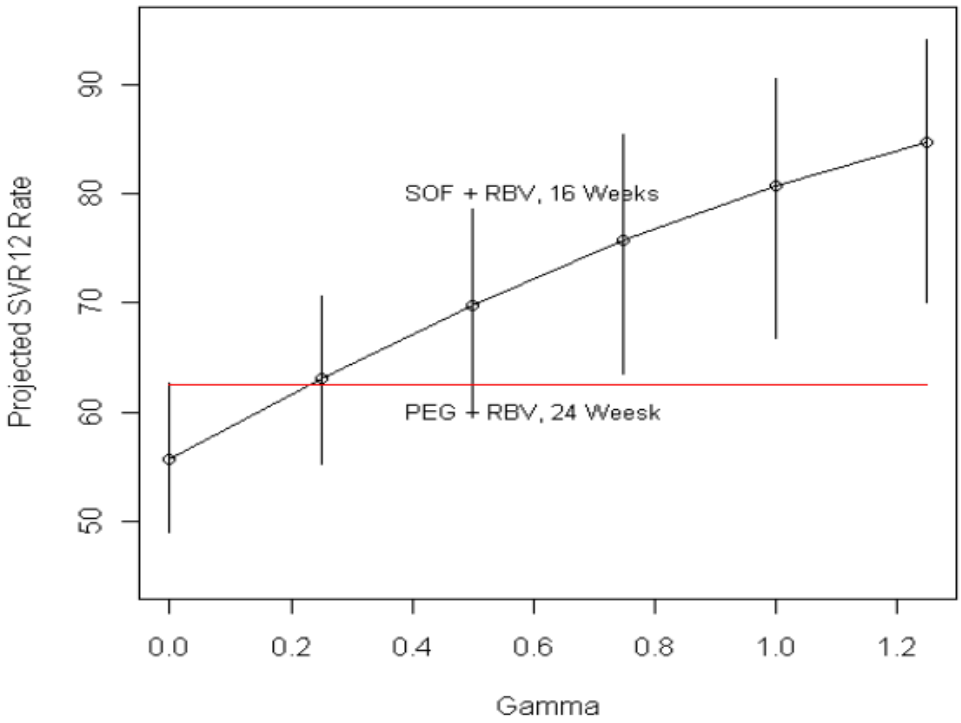


GT= genotype; TE = treatment-experienced; TN = treatment-naive

Source: Figure 1 in Section 2.7 3 Summary of Clinical Efficacy submitted in this NDA.
Note: Fission Study referred to Study 1231 and Fusion Study referred to Study 108.

(b) (4)

Figure 10: Applicant's Sensitivity Analysis for Impact of 16-Week Treatment Duration of SOF+RBV Using Model 1



Source: Figure 2 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.

3.2.5.3 Reviewer's Sensitivity Analyses

A. Maximum Likelihood Estimation (MLE)

The reviewer assessed whether the MLE approach would produce similar results to those from the Bayesian analysis. Therefore, the reviewer applied the MLE approach to estimate the parameters in the applicant's two logistic models. The reviewer found that the MLE approach led to almost identical SVR12 rates estimated by the Bayesian approach. Specifically, the SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects estimated by MLE was 80.9% based on the first model and was 78.5% based on the second model.

B. Models with Different Covariates

The applicant did not specify how they chose the three baseline covariates of gender, baseline cirrhotic and baseline HCV RNA level in their models. The reviewer used the stepwise procedure to select the important baseline covariates to predict the SVR12 rate. The reviewer found that IL28B status (CC vs. non-CC) was another significant prognostic factor in prediction of the SVR12 rate in addition to gender, baseline cirrhosis and HCV RNA level. Therefore, the reviewer developed a new model with treatment indicators, gender, baseline cirrhosis status, IL28B status and baseline HCV RNA level. Note that the only difference between this model and the applicant's first model was

that this model included IL28 B status. The reviewer used MLE to estimate the model parameters. The estimated SVR12 rate for the 16 weeks of SOF+RBV in treatment-naïve subjects was 80.3%, which was similar to the applicant's result based on their first model without interaction term. Additionally, the reviewer generated another new model which only contained the treatment indicators, gender and baseline cirrhosis status. The estimated SVR12 rate was 80.9%, which again was close to the applicant's result. In summary, models with different covariates resulted in similar estimated SVR12 rates for the 16 weeks of SOF+RBV in the HCV genotype 3 treatment-naïve subjects.

C. Extrapolation

Instead of applying the model to estimate the SVR12 rate for the 16 weeks of SOF+RBV, the reviewer extrapolated the rate using the observed SVR12 rates in Studies 1231 and 108 directly based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. A merit of the extrapolation is that it is easy to understand. The detailed calculation is summarized in the following paragraphs.

Let $P_{TN,\ 16w}$ = the estimated SVR12 rate for HCV genotype 3 treatment-naïve subjects receiving 16 weeks of SOF+RBV treatment;

$P_{TN,\ 12w}$ = the observed SVR12 rate for HCV genotype 3 treatment-naïve subjects who received 12 weeks of SOF+RBV treatment in Study 1231;

$P_{TE,\ 16w}$ = the observed SVR12 rate for HCV genotype 3 treatment-experienced subjects who received 16 weeks of SOF+RBV treatment in Study 108;

$P_{TE,\ 12w}$ = the observed SVR12 rate for HCV genotype 3 treatment-experienced subjects who received 12 weeks of SOF+RBV treatment in Study 108.

The extrapolation used the observed SVR12 rates for the HCV genotype 3 subjects in Studies 108 and 1231 to derive the SVR12 rate for the 16-week SOF+RBV treatment in genotype 3 treatment-naïve subjects (Figure 11).

Figure 11: Bridging Analysis based on Extrapolation

genotype 3 treatment-experienced (Study 108)

Treatment	SVR12 rate
12-week SOF+RBV	$P_{TE,\ 12w}$
16-week SOF+RBV	$P_{TE,\ 16w}$

genotype 3 treatment-naïve (Study 1231)

Treatment	SVR12 rate
12-week SOF+RBV	$P_{TN,\ 12w}$
16-week SOF+RBV	**? $P_{TN,\ 16w}$**

Specifically, the extrapolation of the SVR12 rate for the 16 weeks of SOF+RBV treatment was performed by solving the following equation which assumed the same OR of the 16 weeks of treatment over the 12 weeks of treatment in HCV genotype 3 treatment-naïve and treatment-experienced subjects:

$$\frac{P_{TN,16w}/(1-P_{TN,16w})}{P_{TN,12w}/(1-P_{TN,12w})} = \frac{P_{TE,16w}/(1-P_{TE,16w})}{P_{TE,12w}/(1-P_{TE,12w})}$$

The reviewer also used the relative risk (RR) and proportion difference (PD) to extrapolate the rate. Specifically, the extrapolation was done using the following two equations. The first equation assumed the RR of not achieving SVR12 for the 16 weeks of SOF+RBV treatment over the 12 weeks of SOF+RBV in the HCV genotype 3 treatment-naïve subjects was the same as the RR in the HCV genotype 3 treatment-experienced subjects observed in Study 108. The second equation assumed the treatment difference in the SVR12 rate between the 16 weeks and the 12 weeks of SOF+RBV in HCV genotype 3 treatment-naïve was the same as that in the treatment-experienced subjects seen in Study 108.

$$\frac{1-P_{TN,16w}}{1-P_{TN,12w}} = \frac{1-P_{TE,16w}}{1-P_{TE,12w}}$$

$$P_{TN,16w} - P_{TN,12w} = P_{TE,16w} - P_{TE,12w}$$

Table 32 below summarizes the analysis results. Note that the extrapolation based on OR had similar results to those obtained from the logistic regression.

Table 32: Reviewer's Bridging Analysis Results for Estimated SVR12 Rate for 16 Weeks of SOF+RBV in HCV Genotype 3 Treatment-Naïve Subjects based on Extrapolation Approach

Measures	Estimated SVR12 rate for 16-week SOF+RBV in HCV Genotype 3 treatment-naive subjects (95% CI)
Odds ratio	83% (69%, 92%)
Relative risk	76% (65%, 84%)
Proportion difference	88% (70%, 100%)

Similar to the applicant's sensitivity analysis, the reviewer calculated the SVR12 rates for 16 weeks of SOF+RBV in the genotype 3 treatment-naïve subjects based on the different percent of benefit or risk retained (Table 33). The lowest estimated rate was 64% when it was assumed that the RR of 16-week treatment over the 12-week treatment in genotype 3 treatment-naïve subjects was 50% higher than what was observed in genotype 3 treatment-experienced subjects in Study 108. This low rate was about the same as the 63% SVR12 rate for the HCV genotype 3 treatment-naïve subjects receiving the 24 weeks of PEG+RBV treatment in Study 1231.

Table 33: Reviewer's Sensitivity Analysis

Measures	% benefit/risk retained	Estimated SVR12 rate for 16-week SOF+RBV in GT3 TN subjects
Odds ratio	50%	71%
	75%	78%
	100%	83%
Relative risk	150%	64%
	125%	70%
	100%	76%
Proportion difference	50%	72%
	75%	80%
	100%	88%

3.3 Evaluation of Safety

The medical officer, Dr. Poonam Mishra, had reviewed the safety data. Based on her review, there were no major safety issues related to the use of SOF. She pooled the safety data from the 12-week SOF+RBV arms in Studies 1231, 107 and 108 in her integrated safety evaluation. In the reviewer's opinion, it was reasonable to combine the data since the proportions of some adverse events were consistent across the three studies even though the randomization ratio in Study 107 was different in Studies 1231 and 108 (Table 77 in Section 6.7). For a detailed safety evaluation, please refer to Dr. Poonam Mishra's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses will be reported by each study individually because the four studies had different patient populations. In all studies, the subgroup analyses were planned in the subsets defined by the following baseline measures: age (< 50 years, ≥ 50 years), gender, race (black, non-black), geographic region (US, non-US), ethnicity (Hispanic, non-Hispanic), baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2), HCV genotype, cirrhosis status at baseline (absence, presence), IL28B (CC, non-CC), baseline HCV RNA (< 6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL), and baseline ALT level (≤ 1.5xULN, > 1.5xULN). In Study 107, subgroup analyses by IFN (IFN intolerant, IFN eligible, unwilling to take IFN), and duration of previous HCV treatment (no, ≤ 12 weeks, > 12 weeks) were also planned. In Study 108, an additional pre-specified subgroup analysis included the response to prior HCV treatment (nonresponse, relapse/breakthrough). The Breslow Day test was applied to evaluate whether the odds ratios of achieving SVR12 between the treatment arms were homogeneous

between the subgroups defined by a baseline measure. In other words, the test assessed the consistency of the treatment effect between the subgroups.

4.1 Study 1231

The applicant conducted the subgroup analyses based on the FAS which excluded the three subjects with misclassified genotype, while the reviewer's subgroup analyses were based on the All Treated population. The results from the reviewer's analyses will be presented in this section (also see Table 41, Table 42 and Table 43 in Section 6.1).

4.1.1 Age, Gender, Race, and Geographic Region

The treatment difference (i.e., 12-Week SOF+RBV – 24-week PEG+RBV) was approximately -10% in the subgroup <50 years of age and 10% in the subgroup of ≥ 50 years of age (p-value = 0.0200 based on the Breslow-Day test for the homogeneity of the odds ratios between the 2 age groups).

The interaction between treatment and gender was not obvious. For the subgroup analysis by race, the SOF+RBV arm had a better SVR12 rate than the PEG+RBV arm in Black subjects, but the sample size was too small to be informative. Also, there was not an evident difference between the two treatment groups in the non-Black subjects.

The treatment difference varied between the US and non-US subjects. Specifically, the difference was 6% in the US subjects versus -10% among the non-US subjects (p-value = 0.0718 based on the Breslow-Day test for the homogeneity of the odds ratios between the two geographic regions). However, the fluctuation in treatment difference between the US and non-US subjects was confounded by genotype as the majority of the non-US subjects had a genotype 3 HCV infection.

4.1.2 Other Special/Subgroup Populations

Except for the two genotype groups mentioned earlier, there was not any significant treatment by subgroup interaction. However, the treatment differences in the subgroups defined by cirrhosis, IL28B and baseline HCV RNA level appeared large. The findings are highlighted as follows:

- As compared to the PEG+RBV treatment, the SOF+RBV treatment resulted in 2% lower SVR12 rate in non-cirrhotic subjects but 8% higher among cirrhotic subjects (p-value = 0.3402 based on the Breslow-Day test for the homogeneity of the odds ratios between the two cirrhotic subgroups).

- The SOF+RBV treatment had a 8% higher rate in the subjects with baseline HCV RNA <6 log10 IU/mL and a 6% lower rate in the subjects with baseline HCV RNA ≥ 6 log10 IU/mL (p-value = 0.1045 based on the Breslow-Day test for the homogeneity of the odds ratios between the two subgroups for the baseline HCV RNA level).

- Compared with the subjects in the PEG+RBV group, 8% more subjects in the SOF+RBV group achieved SVR12 among the IL28B CC subjects and 6% less achieved SVR12 among IL28B

non-CC subjects (p-value = 0.0848 based on the Breslow-Day test for the homogeneity of the odds ratios between the two IL28B subgroups).

4.1.3 Subgroup Analysis for Each Genotype

As discussed in Section 3.2.1.4, the HCV genotype appeared to affect the SVR12 rate. The SOF+RBV treatment group had significantly higher SVR12 rates than the PEG+RBV treatment among the genotype 2 subjects, whereas the SOF+RBV treatment resulted in lower SVR12 rates than the PEG+RBV treatment in the genotype 3 subjects. The post-hoc subgroup analyses for each genotype were conducted to examine the consistency of the results for the groups defined by patient demographics and baseline disease characteristics (Table 42 and Table 43). The SOF+RBV treatment group had consistently greater SVR12 rates than the PEG+RBV treatment group across all subgroups in the genotype 2 subjects. Meanwhile, the SOF+RBV regimen led to lower SVR12 rates in most of the subgroups among the genotype 3 subjects.

4.2 Study 107

Because no subject in the placebo group in the study achieved SVR12, the purpose of the subgroup analyses was to check the consistency of the SVR12 rates for 12 weeks of SOF+RBV in the subgroups. Table 52 in Appendix 6.2 summarizes the reviewer's subgroup analyses results for the study.

4.2.1 Age, Gender, Race, Geographic Region

Similar SVR12 rates for the SOF+RBV treatment were observed in the two age subsets. Also, females had a higher SVR12 rate than males (84% for females and 73% for males). In the subgroup analysis for race, a higher proportion of black subjects (89%) achieved SVR12 than the non-black subjects (77%). However, there were only nine black subjects, and the sample size was too small to make a conclusion. Finally, the SVR12 rates were comparable between the US and non-US subjects (77% for the US subjects, and 79% for the non-US subjects).

4.2.2 Other Special/Subgroup Populations

Analyses resulted in similar SVR12 rates for the subgroups defined by most of the baseline measures. However, the SVR12 rates for the 12-week SOF+RBV treatment arm differed for the HCV genotype, duration of prior HCV treatment and cirrhosis subgroups, which are highlighted as follows:

- A higher proportion of genotype 2 subjects receiving 12-week SOF+RBV achieved SVR12 compared to the genotype 3 subjects (93% for the genotype 2 subjects, 61% for the genotype 3 subjects). A detailed discussion regarding different performance between the genotypes 2 and 3 subjects was presented in Section 3.2.2.4.

- The duration of prior HCV treatment appeared to have an impact on the SVR12 rate for 12-week SOF+RBV. The rate was highest in the treatment-naïve subjects (82%), followed by the subjects who had previously received HCV treatment for no longer than 12 weeks (71%). The rate was lowest among subjects who had prior HCV treatment for more than 12 weeks (38%).

- The SVR12 rate in the cirrhotic subjects was approximately 20% lower than the non-cirrhotic subjects (61% for cirrhotic subjects, 81% for non-cirrhotic subjects).

4.2.3 Subgroup Comparisons for 12 Weeks of SOF+RBV between Genotype 2 and 3

The significant difference in the SVR12 rate between the subjects with genotype 2 HCV infection and those with genotype 3 infection as described in Section 3.2.2.4. Of note, the patient demographics and baseline disease characteristics were well balanced between the subjects infected with genotype 2 HCV and those infected genotype 3 HCV (Table 53 in Appendix 6.2). The reviewer compared the SVR12 rates for the 12-week SOF+RBV between the two genotypes in the subgroups defined by the patient demographics and baseline disease characteristics. The results indicated that genotype 2 HCV infected-subjects had consistently higher SVR12 rates than the genotype 3 HCV infected-subjects across all subgroups (Table 53 in Appendix 6.2). Some observations are summarized as follows:

- Females and males had similar SVR12 rates among the subjects with genotype 2 HCV infection (93% for females, 92% for males), but females had a much greater SVR12 rate than males in subjects with genotype 3 HCV infection (76% for females, 49% for males).

- The SVR12 rates were relatively high for the subjects infected with genotype 2 HCV infection regardless of duration of prior HCV treatment (92% for the treatment-naïve subjects, 100% for the subjects who had ≤ 12 weeks of prior treatment, 80% for the subjects who received > 12 weeks of prior treatment). In contrast, the prior treatment duration appeared to affect the SVR12 rates in the subjects infected with genotype 3 HCV. Specifically the SVR12 rates were 70% for treatment-naïve subjects, 40% for the subjects who had ≤ 12 weeks of prior treatment, and 18% for the subjects who had > 12 weeks of prior treatment. However, the sample sizes in the subgroups of the subjects having ≤ 12 weeks of prior treatment and the subjects having > 12 weeks of prior treatment were too small to be conclusive.

- In the genotype 2 HCV infected-subject, the SVR12 rates were unaffected by the cirrhosis status. However, the cirrhotic subjects had notably lower SVR12 rate than the non-cirrhotic subjects among the subjects infected with genotype 3 HCV.

4.3 Study 108

4.3.1 Age, Gender, Race, Geographic Region

As shown in Table 60 in Appendix 6.3, the SVR rates in the SOF+RBV 16-week group were greater than those in the SOF+RBV 12-week group in both age subsets.

For gender, a higher proportion of females than males achieved SVR12 in the 12-week treatment group (70% for females vs. 41% for males) and in the 16-week group (87% for females vs. 64% for males). However, the result from Breslow-Day test for the homogeneity of the odds ratios between gender did not show significant treatment by gender interaction (p=0.8743).

There were only 6 black subjects, and all of them achieved SVR12 in the study. For non-Black subjects, the longer treatment duration again had a better SVR12 rate than the shorter duration.

In both geographic subgroups, the SVR12 rates for the 16-week SOF+RBV were greater than those in the 12-week SOF+RBV. Also, higher SVR12 rates were observed among US subjects compared with non-US subjects in both treatment groups. This was confounded by genotype because US sites enrolled more genotype 2 subjects than non-US sites.

4.3.2 Other Special/Subgroup Populations

The SVR12 rate appeared to be affected by the genotype. The differences in genotype 2 and genotype 3 subjects had been discussed in Section 3.2.3.4. The subgroup analyses the SOF+RBV 16 Week group had consistently higher SVR12 rates than the SOF+RBV 12 Week group for all other subgroups.

4.3.3 Subgroup Analysis for Each Genotype

Because of the apparent treatment by genotype interaction, subgroup analyses for each genotype were performed to evaluate whether the treatment difference between the two treatment durations were consistent across the subgroups stratified by the patient demographics and baseline disease characteristics and to identify whether there was a subgroup of subjects who would benefit from a longer duration of treatment in particular among the genotype 2 subjects. Table 61 summarizes the result for the genotype 2 subjects and Table 62 for the genotype 3 subjects.

It was of clinical interest to investigate whether genotype 2 subjects with poor prognostic factors such as cirrhosis, CC IL28B genotype, or prior lack of response to previous HCV treatment would benefit from longer treatment. Although the 16-week treatment produced numerically higher SVR12 rates compared to the 12-week treatment, the sample sizes in these subsets were approximately 10 subjects, which was too small to be conclusive.

Among genotype 3 subjects, 16 weeks of SOF+RBV showed consistently greater SVR12 rates than the 12 weeks of treatment in almost all subgroups except for black subjects because there were only two black subjects with genotype 3 HCV infection in the study. Also, it was noticed that females had much higher SVR12 rates than males in both durations (i.e., 44% and 25% for females and males in the 12-Week SOF+RBV group, respectively; 81% and 52% for females and males in the 16-Week SOF+RBV group, respectively). A further investigation of the gender difference in genotype 3 subjects in terms of response to the SOF+RBV treatment based on the data from both Studies 1231 and 108 was done, and the results are presented in Section 4.5.

4.4 Study 110

Study 110 was a single arm trial. Therefore, the purpose of the subgroup analyses was to evaluate the consistency of the SVR12 rate for 12-weeks of SOF+PEG+RBV across different subgroups. The results are shown in Table 70 in Section 6.4.

4.4.1 Age, Gender, Race, Geographic Region

The SVR12 rates in the subgroups determined by age, gender, geographic region and ethnicity were at least 87%. There was no any notable difference between the subgroups defined by a covariate.

4.4.2 Other Special/Subgroup Populations

All subgroups defined by baseline characteristics had SVR12 rates greater than 80%. Subgroup analyses demonstrated that the subjects infected with genotype 1a HCV had a higher SVR12 rate than the subjects infected with genotype 1b HCV, (see Section 3.2.4.4). In addition, a higher SVR12 rate was observed in the noncirrhotic subjects than the cirrhotic subjects (92% for noncirrhotic subjects, 80% for cirrhotic subjects). Moreover, subjects with IL28B CC allele had a higher SVR12 rate compared with the subjects with non-CC IL28B CC allele (98% for the CC subjects, 87% for the non-CC subjects).

4.5 Gender Difference in HCV Genotype 3 Subjects

There was a clinical concern regarding the gender difference in response to SOF+RBV in genotype 3 subjects. Therefore, the reviewer compared the SVR12 rates between female and male subjects among the HCV genotype 3 subjects in Studies 1231, 107 and 108. The post-hoc analyses showed that females with genotype 3 infection tended to have better SVR12 rates than males in all of the SOF+RBV groups in the three studies (Table 34). In addition, compared with the 24-week PEG+RBV group, the gender difference was more notable for the 12-week SOF+RBV in Study 1231. The reviewer also found that the females had better SVR12 rates across almost all subsets determined by the baseline measures as shown in the tables in Appendix 6.6. In summary, the post-hoc exploratory analyses showed that gender appeared to affect the SVR rate for SOF+RBV among the HCV genotype 3 subjects.

Table 34: SVR12 Rates by Gender in HCV Genotype 3 Subjects in Study 1231, 107 and 108

	Females	Males	Females vs. Males Proportion Diff (95% CI)
Study 1231			
12-week SOF+RBV	71% (41/58)	49% (61/125)	22% (7%, 37%)
24-week PEG+RBV	69% (41/59)	59% (69/117)	10.5% (-4%, 25%)
Study 107			
12-week SOF+RBV	76% (34/45)	49% (26/53)	27% (8%, 45%)
Placebo	0%	0%	n/a

to be continued

Table 34: SVR12 Rates by Gender in HCV Genotype 3 Subjects in Study 1231, 107 and 108 (Continued)

	Females	Males	Females vs. Males Proportion Diff (95% CI)
Study 108			
12-week SOF+RBV	44% (7/16)	25% (12/48)	19% (-8%, 46%)
16-week SOF+RBV	81% (17/21)	52% (22/42)	29% (6%, 51%)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

One statistical issue was the apparent treatment differences between the HCV genotypes 2 and 3 subjects. In the reviewer's opinion, the observed differences in the SVR12 rates between genotypes 2 and 3 subjects, in particular for the difference in the SOF+RBV treatment regimens in Studies 1231, 107 and 108, were not due to the chance. It was expected the HCV genotype would have an impact on the SVR12 rate beforehand. Therefore, HCV genotype was one of the stratification factors in the randomization for Studies 1231 and 108, and the subgroup analysis by HCV genotype was one of the pre-defined subgroup analyses in the statistical analysis plan (SAP) in each study. In Study 1231, the 12-week SOF+RBV regime was compared to the 24 weeks PEG+RBV regime and the treatment-by-genotype interaction was significant (p-value = 0.0002). The difference in the SVR12 rate between genotypes 2 and 3 was greater in the 12-week SOF+RBV treatment arm than in the 24-week PEG+RBV treatment arm. In the 12-week SOF+RBV group, 97% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001). On the other hand, 78% and 63% of genotypes 2 and 3 subjects, respectively, achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326). Study 107 compared 12-weeks of SOF+RBV against placebo where no placebo subjects achieved SVR12. In the 12-week SOF+RBV group, the HCV genotype 2 subjects had significantly higher SVR12 rate than the HCV genotype 3 subjects (i.e., 93% vs. 61%, p-value < 0.0001). In Study 108 where two durations of SOF+RBV were evaluated, the difference in SVR12 rates between the genotypes 2 and 3 subjects were significant within each duration group. In the 12-week SOF+RBV group, 83% of the HCV genotype 2 subjects achieved SVR12 compared with 30% of the HCV genotype 3 subjects (p-value < 0.0001). In the 16-week SOF+RBV group, the SVR12 rates were 82% and 62% for the genotypes 2 and 3 subjects, respectively (p-value = 0.0052). The collective evidence from the three studies strongly suggested that the HCV genotype 2 subjects did have a higher SVR rate than the HCV genotype 3 subjects. The small and consistent p values could overcome the concern of the lack of a pre-specified plan to control Type 1 error.

Another major statistical issue was the appropriateness of the statistical methods in the applicant's bridging analyses to derive the SVR12 rate for the 16-week SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection based on the observed rates in Studies 1231 and 108. The applicant used the data from all HCV genotype 3 subjects in Studies 1231 and 108 to generate the logistic regression models. They estimated the model parameters using a Bayesian approach and derived the SVR12 rate for the 16 week SOF+RBV regimen in the genotype 3 treatment-naïve subjects based on the assumption that the OR of the 16-week SOF+RBV over the 12-week SOF+RBV in the genotype

3 treatment-naïve subjects was the same as the OR in the genotype 3 treatment-experienced subjects. The reviewer conducted several analyses to test the sensitivity of the results to various methodologies. First, the reviewer used the maximum likelihood estimation (MLE) approach to estimate the model parameters. The reviewer obtained almost identical results to the applicant's results. Also, the reviewer estimated the SVR12 rate by extrapolating from the observed rates in Studies 1231 and 108 based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. The merit of the extrapolation was that it was relatively easy to follow. The reviewer obtained an 83% SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects based on the extrapolation, which was similar to the applicant's result. The reviewer also used relative risk (RR) and proportion difference (PD) to extrapolate the SVR rate. The estimated SVR12 rate was 76% based on RR and 88% based on PD. All of these post-hoc analyses suggested that 16 weeks of SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects would lead to a higher SVR12 rate than the observed 56% rate for the 12 weeks of SOF+RBV treatment seen in Study 1231. Again, the strong assumptions in the bridging analysis and the lack of Week 16 data made it difficult to determine the optimal treatment duration from the statistical point of view.

Another issue worth noting applicant's exclusion of subjects from the efficacy analysis sets in Studies 1231 and 108. There were nine subjects who were misclassified as having genotype 2 HCV infection by the LiPA method at screening but were subsequently found to have genotype 1 infection by population sequencing in the two studies. The LiPA method is currently used to determine the genotype in the clinical practice, whereas population sequencing is not. The applicant excluded these subjects from the efficacy analysis. The inclusion or exclusion of these subjects slightly affected the study results, and the reviewer included the subjects in the analysis in order to follow the intent-to-treat principle.

The final issue was the interpretation of the finding that the HCV genotype 1a treatment-naïve subjects had higher SVR12 rate than the genotype 1b subjects in Study 110 (i.e., 92% vs. 82%). Historically, the subjects infected with genotype 1a HCV are more difficult to treat compared to the subjects with genotype 1b HCV infection. The applicant attributed the observed treatment difference to the findings that the subjects with genotype 1a had a lower percentage of IL28B CC subjects, black subjects, non-cirrhotic subjects and had a lower mean age as compared to the subjects infected with genotype 1b HCV in the study. However, the reviewer compared the SVR12 rates between the two subgenotypes across the subgroups defined by the demographics and baseline characteristics, and found that the genotype 1a subjects had numerically higher SVR12 rate than the genotype 1b subjects in all subgroups. Therefore, the reviewer disagreed with the applicant's interpretation. However, the lack of a control group in the study made it difficult to definitively conclude whether the observed differences between the two subgenotypes were due to chance.

5.2 Collective Evidence

The four Phase 3 studies had different patient populations, study designs and SOF-containing regimens. In all studies, the SOF-involved treatments rapidly suppressed the HCV virus regardless of the HCV genotype. Almost all subjects receiving the SOF-containing regimens achieved HCV RNA < LLOQ approximately four weeks after receiving treatment, and the high response rates were maintained through the end of treatment period. Very few subjects had a protocol-defined on-

treatment virologic failure. Also, the relapses usually occurred four or eight weeks after the end of treatment. The relapse rates varied among the treatment regimens and HCV genotypes, and the variation was attributed to the different SVR rates.

In Study 110, the SVR12 rate for the 12 weeks of SOF+PEG+RBV treatment was 90% for the overall population including the treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection. The rate was statistically significantly better than the pre-specified 60% historical rate. However, the study only recruited one HCV genotype 5 subject and six HCV genotype 6 subjects. The sample size was too small to make conclusions for these two genotypes.

Study 1231 demonstrated that the SVR12 rate for the 12-week SOF+RBV regimen was non-inferior to the 24-week PEG and RBV active control in HCV genotype 2 or 3 treatment-naïve subjects (i.e., 67% vs. 67%). However, the pre-specified subgroup analyses showed a significant interaction between treatment and HCV genotype. Use of SOF+RBV for 12 weeks was sufficient for the HCV genotype 2 treatment-naïve subjects since the 12-week treatment regimen had significantly higher SVR12 rate compared to the 24 weeks of PEG and RBV in the subset (i.e., 97% vs. 78%). However, the 12-week duration was insufficient for the genotype 3 treatment-naïve subjects since it had lower SVR12 rate than the 24-week PEG+RBV in this subpopulation (i.e., 56% vs. 63%).

Study 107 showed the 12 weeks of SOF+RBV had superior efficacy to the placebo with respect to the SVR12 rate (93% vs. 0%) in the genotype 2 or 3 subjects who were IFN intolerant, IFN ineligible or unwilling to take IFN. In addition, the HCV genotype 2 subjects had better SVR12 rate than genotype 3 subjects in the 12-week SOF+RBV group (i.e., 93% vs. 61%).

Study 108 revealed that both 12 and 16 weeks of SOF+RBV regimens had significantly better SVR12 rates than the pre-specified 25% historical rate for the treatment of treatment-experienced subjects infected with genotype 2 or 3 HCV (i.e., 50% for the 12-week SOF+RBV, 73% for the 16-week SOF+RBV). However, the pre-defined subgroup analyses showed an apparent treatment by genotype interaction. The 12-week SOF+RBV regimen was sufficient to treat the HCV genotype 2 treatment-experienced subjects because it had significantly better SVR12 rate than the historical rate, and the SVR12 rate was also comparable to that for the 16-week SOF+RBV in the subpopulation (i.e., 82% for 12-week SOF+RBV, 89% for 16-week SOF+RBV). However, the 12-week duration was not long enough for the genotype 3 treatment-experienced subjects since it only produced 30% SVR12 rate in the subset. Also, although the 16-week SOF+RBV led to a 62% SVR12 rate in the subpopulation, 16 weeks might not be the optimal duration because it still resulted in 38% relapse rate.

Finally, the bridging analyses using the observed rates from Studies 1231 and 108 resulted in an estimated SVR12 rate of approximately 80% for the 16-week SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects.

5.3 Conclusions and Recommendations

After reviewing the submitted data, the reviewer concludes the following:

1) The 12-week SOF+PEG+RBV treatment regimen demonstrated efficacy in treatment-naïve subjects with genotype 1 or 4 HCV infection.

2) The 12-week SOF+RBV treatment regimen demonstrated efficacy in subjects with genotype 2 HCV infection.

3) The 16-week SOF+RBV treatment regimen has efficacy in treatment-experienced subjects infected with genotype 3 HCV. However, use of SOF+RBV for a duration longer than 16 weeks could potentially improve the efficacy since the 16-week regimen still resulted in approximately 38% relapse rate.

4) The results from the bridging analyses suggested that 16 weeks of SOF+RBV would yield a better SVR12 rate compared with 12 weeks of SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection. However, it is difficult to recommend the 16-week duration from the statistical prospective due to the lack of the data.

5) The sample sizes were too small to support the 12 weeks of SOF+PEG+RBV for the treatment of the subjects with genotype 5 or 6 infection.

5.4 Labeling Recommendations

The Dosage and Administration Section and Section 14 in the label are provided in the following sections and are relevant to the efficacy results in the four pivotal phase 3 studies reviewed in this report.

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

One 400 mg tablet taken once daily with or without food. (2)
Should be used in combination with (b) (4). Recommended combination therapy: (2)
(b) (4)

14 CLINICAL STUDIES

(b) (4)

[redacted]

[redacted]

[redacted] **Clinical Trials in Subjects with Genotype 1, 4, [redacted] CHC**

Treatment-Naïve Adults – NEUTRINO (Study 110)

NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with [TRADENAME] in combination with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection.

Treated subjects (N=327) had a median age of 54 years (range: 19 to 70); 64% of the subjects were male; 79% were White, 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 18 to 56 kg/m^2); 78% had baseline HCV RNA greater than 6 log_{10}IU per mL; 17% had cirrhosis; 89% had HCV genotype 1 [redacted] Table 9 presents the response rates for the treatment group of [TRADENAME] + peginterferon alfa + ribavirin.

Table 9 Response Rates in Study NEUTRINO

	[TRADENAME] + Peg-IFN alfa + RBV 12 weeks N=327
Overall SVR	90% (295/327)
[redacted]	
On-treatment virologic failure	0/327
Relapse[a]	9% (28/326)
Other[b]	1% (4/327)

a. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 10.

Table 10 SVR Rates for Selected Subgroups in NEUTRINO

	[TRADENAME] + Peg-IFN alfa + RBV 12 weeks
[redacted]	
Cirrhosis	
No	92% (252/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-black	91% (248/273)

[redacted]

14.2 Clinical Trials in Subjects with Genotype 2 or 3 CHC

Treatment-Naïve Adults – FISSION (Study 1231)

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with [TRADENAME] and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin doses used in the [TRADENAME] + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV genotype (2 vs. 3) and baseline HCV RNA level (< 6 $\log_{10}$IU/mL vs. ≥ 6 $\log_{10}$IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. Treated subjects (N=499) had a median age of 50 years (range: 19 to 77); 66% of the subjects were male; 87% were White, 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 17 to 52 kg/m^2); 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 11 presents the response rates for the treatment groups of [TRADENAME] + ribavirin and peginterferon alfa + ribavirin.

Table 11 Response Rates in Study FISSION

	[TRADENAME] + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N= (b) (4)	N=243[a]
Overall SVR	67% (b) (4)	67% (162/243)
Genotype 2	(b) (4)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for subjects without SVR		
On-treatment virologic failure	<1% (b) (4)	7% (18/243)
Relapse[b]	30% (b) (4)	21% (46/217)
Other[c]	3% (b) (4)	7% (17/243)

(b) (4)

b. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

(b) (4)

Response rates for subjects with cirrhosis at baseline are presented in Table 12 by genotype.

Table 12 SVR Rates by Cirrhosis and Genotype in Study FISSION

	Genotype 2		Genotype 3	
	[TRADENAME] + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks	[TRADENAME] + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N= (b) (4)	N=67	N=183	N=176
Cirrhosis				
No	(b) (4)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	(b) (4)	62% (8/13)	34% (13/38)	30% (11/37)

Interferon Intolerant, Ineligible or Unwilling Adults – POSITRON (Study 107)

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with [TRADENAME] and ribavirin (N=207) compared to placebo (N=71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence).

Treated subjects (N=278) had a median age of 54 years (range: 21 to 75); 54% of the subjects were male; 91% were White, 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 53 kg/m^2); 70% had baseline HCV RNA levels greater than 6 log_{10} IU per mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of subjects who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most subjects had no prior HCV treatment (81.3%). Table 13 presents the response rates for the treatment groups of [TRADENAME] + ribavirin and placebo.

Table 13 Response Rates in Study POSITRON

	[TRADENAME] + RBV 12 weeks	Placebo 12 weeks
	N=207	N=71
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
Outcome for subjects without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse[a]	20% (42/205)	0/0
Other[b]	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

(b) (4)

Table 14 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 14 SVR Rates for Selected Subgroups by Genotype in POSITRON

	[TRADENAME] + RBV 12 weeks	
	Genotype 2	Genotype 3
	N=109	N=98
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon Classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously Treated Adults – FUSION (Study 108)

FUSION was a randomized, double-blinded trial that evaluated 12 or 16 weeks of treatment with [TRADENAME] and ribavirin in subjects who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence) and HCV genotype (2 vs. 3).

Treated subjects (N=201) had a median age of 56 years (range: 24 to 70); 70% of the subjects were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 19 to 44 kg/m^2); 73% had baseline HCV RNA levels greater than $6log_{10}$ IU per mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 15 presents the response rates for the treatment groups of [TRADENAME] + ribavirin for 12 weeks and 16 weeks.

Table 15 Response Rates in Study FUSION

	[TRADENAME] + RBV 12 weeks	[TRADENAME] + RBV 16 weeks
	N= (b) (4)	N= (b) (4)
Overall SVR	50% (b) (4)	(b) (4)
Genotype 2	(b) (4)	(b) (4)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for subjects without SVR		
On-treatment virologic failure	(b) (4)	(b) (4)
Relapse[b]	(b) (4)	(b) (4)
Other[c]	(b) (4)	(b) (4)
(b) (4)		

b. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

The reviewer has the following comments regarding the label.

1) The efficacy results for Studies 1231 (Fission) and 108 (Fusion) presented in the label were based on the applicant's FAS where the subjects whose HCV genotype was misclassified by LiPA were excluded. The reviewer suggested using the results based on the intent-to-treat population, i.e., All Treated set.

2) (b) (4)

3) (b) (4)

4) The relapse rates at post-treatment Week 12 by the HCV genotypes 2 and 3 in Studies 1231, 107 and 108 should be presented in the label because the rates differed greatly between the two genotypes.

6 APPENDICES

6.1 Study 1231

Table 35: Study Procedures for Study 1231

Assessment	Screening Day –42 to –1	Baseline Day 1	Weeks 1, 2, 3[e]	Weeks 4, 8[e] (SOF+RBV)	Weeks 4, 8, 12, 16, 20[e] (PEG+RBV)	EOT[e]	Posttreatment Week 4[e]	Posttreatment Weeks 8, 12, 16, 20, 24[e]
Informed Consent [a]	X							
Medical History	X							
Physical Examination	X					X		
FibroSure/APRI/liver biopsy/transient elastograph[b]	X							
Blood sample for optional genetic testing[g]		X						
Quality of life questionnaire[h]		X			X[h]	X[h]		X[h]
Height/weight/BMI[c]	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
ECG	X	X				X		
Clinical laboratory assessments	X	X	X	X	X	X	X	X
Pregnancy test (females only)		X		X	X	X	X	X
Pharmacodynamic testing (HCV RNA)	X	X	X	X	X	X	X	X
HCV phenotyping and HCV RNA sequencing		X	X	X	X	X	X	X
Blood sampling for PK analysis[d]			X	X	X	X		

to be continued

Table 35: Study Procedures for Study 1231 (Continued)

Assessment	Screening Day –42 to –1	Baseline Day 1	Weeks 1, 2, 3[e]	Weeks 4, 8[e] (SOF+RBV)	Weeks 4, 8, 12, 16, 20[e] (PEG+RBV)	EOT[e]	Posttreatment Week 4[e]	Posttreatment Weeks 8, 12, 16, 20, 24[e]
Concomitant medication monitoring	X	X	X	X	X	X	X	
Review of inclusion/exclusion criteria	X	X						
Adverse events monitoring	X[f]	X	X	X	X	X	X	X[f]
Study drug(s) dispensation		X	X[i]	X	X			
Study drug(s)			X	X	X	X		

a Informed consent was obtained prior to performance of any study procedures.

b Results from 1 or more of these tests may have been used to establish the presence or absence of cirrhosis.

c Height was measured at screening only.

d Blood samples for PK analysis were collected at Weeks 1, 4, 8, and 12/EOT.

e A 2-day window applied to visits at Weeks 1, 2, and 3. A 5-day window applied to visits after Week 3.

f Only SAEs were collected prior to Day 1. For subjects in the SOF+RBV group, AEs were captured at the posttreatment Week 8, posttreatment Week 12, and posttreatment Week 16 visits so that the duration of AE monitoring was the same for each treatment group. Serious adverse events that occurred after posttreatment Week 16 were captured only if they were assessed as possibly or probably related to study drug(s).

g If separate, specific consent was obtained for optional genetic testing, a blood sample should have been drawn at the Day 1 visit. Samples not obtained at Day 1 may have been obtained at any time during the study once consent was provided.

h All subjects who attended the Day 1 visit subsequent to IRB/IEC approval of protocol Amendment 3 completed the SF-36 Health Survey at the following time points: Day 1, Week 12/EOT, posttreatment Week 12, and posttreatment Week 24 (SOF+RBV group) and Day 1, Weeks 12 and 24/EOT, and posttreatment Week 12 (PEG+RBV group).

i Study drugs were not dispensed at these visits; rather, they were 'redispensed.'

Source: Table 7-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 36: On-Treatment Visit Windows for Study 1231

Visit ID	On-Treatment Visit Windows for HCV RNA (GS-7977+RBV)	On-Treatment Visit Windows for HCV RNA (PEG+RBV)	Visit Windows for Vital Signs and Safety Labs
Baseline	Study Day ≤ 1	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 17	12 ≤ Study Day ≤ 17	12 ≤ Study Day ≤ 17
Week 3	18 ≤ Study Day ≤ 24	18 ≤ Study Day ≤ 24	18 ≤ Study Day ≤ 24
Week 4	25 ≤ Study Day ≤ 42	25 ≤ Study Day ≤ 42	25 ≤ Study Day ≤ 42
Week 8	43 ≤ Study Day ≤ 70	43 ≤ Study Day ≤ 70	43 ≤ Study Day ≤ 70
Week 12	71 ≤ Study Day ≤ 98	71 ≤ Study Day ≤ 98	71 ≤ Study Day ≤ 98
Week 16	N/A	99 ≤ Study Day ≤ 126	99 ≤ Study Day ≤ 126
Week 20	N/A	127 ≤ Study Day ≤ 154	127 ≤ Study Day ≤ 154
Week 24	N/A	155 ≤ Study Day ≤ 182	155 ≤ Study Day ≤ 182

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 37: Post-Treatment Visit Windows for Selected Tests for Study 1231

Post-Trt FU Visit ID	Post-Treatment Visit Windows for HCV RNA [a] (Days from Last Study Drug Dose)	Vital Signs and Other Safety Labs[b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 41	3 ≤ FU Day ≤ 30
FU-8	42 ≤ FU Day ≤ 69	N/A
FU-12	70 ≤ FU Day ≤ 97	N/A
FU-16	98 ≤ FU Day ≤ 125	N/A
FU-20	126 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7 (SVR4), 14 (SVR8, SVR12, SVR16, and SVR20), and 21 days (SVR24) of target, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow up visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 38: Patient Demographics and Baseline Characteristics for Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	Total (N=499)
Age (years)			
Mean (SD)	48 (11)	48 (11)	48 (11)
Median (Q1, Q3)	50 (41, 56)	50 (40, 56)	50 (40, 56)
Sex			
Male	171 (67%)	156 (64%)	327 (66%)
Female	85 (33%)	87 (36%)	172 (35%)
Race			
Black	12 (5%)	5 (2%)	17 (3%)
White	223 (87%)	212 (87%)	435 (87%)
Asian	14 (6%)	15 (6%)	29 (6%)
Others	7 (3%)	11 (5%)	18 (4%)
Ethnicity			
Hispanic	41 (16%)	31 (13%)	72 (14%)
Non-Hispanic	215 (84%)	212 (87%)	427 (86%)
Region[2]			
North America	180 (70%)	175 (72%)	355 (71%)
Canada	15 (6%)	24 (10%)	39 (8%)
USA	165 (65%)	151 (62%)	316 (63%)
Australia/New Zealand	61 (24%)	59 (24%)	120 (24%)
Australia	32 (13%)	29 (12%)	61 (12%)
New Zealand	29 (11%)	30 (12%)	59 (12%)
Europe	15 (6%)	9 (4%)	24 (5%)
Italy	8 (3%)	4 (2%)	12 (2%)
Netherland	3 (1%)	1 (<1%)	4 (1%)
Sweden	4 (2%)	4 (2%)	8 (2%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (5)	28 (6)	28 (6)
Median (Q1, Q3)	27 (24, 31)	27 (24, 31)	27 (24, 31)
< 30 kg/m^2	179 (70%)	172 (71%)	351 (70%)
≥ 30 kg/m^2	77 (30%)	71 (29%)	148 (30%)

Source: Table 8-4 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA
[1]All Treated population included all randomized subjects who had received at least one dose of study medication
[2]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 39: Baseline Disease Characteristics for Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	Total (N=499)
HCV genotype			
Genotype 1[1]	3 (1%)	0	0
Genotype 2	70 (27%)	67 (28%)	137 (28%)
Genotype 3	183 (72%)	176 (72%)	359 (72%)
Cirrhosis[2]			
No	205 (80%)	189 (78%)	394 (80%)
Yes	50 (20%)	50 (21%)	100 (20%)
Missing	1 (<1%)	4 (2%)	5 (2%)
IL28 B[2]			
CC	108 (42%)	106 (44%)	214 (43%)
CT	121 (47%)	98 (40%)	219 (44%)
TT	25 (10%)	38 (16%)	63 (13%)
Missing	2 (1%)	1 (<1%)	3 (%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6 (0.8)	6 (0.8)	6 (0.8)
Median (Q1, Q3)	6 (5.5, 6.7)	6 (5.5, 6.7)	6 (5.5, 6.7)
< 6 log_{10} IU/mL	108 (42%)	106 (44%)	214 (43%)
≥ 6 log_{10} IU/mL	148 (58%)	137 (56%)	285 (57%)
Baseline ALT[3]			
< 1 x ULN	54 (21%)	47 (19%)	101 (20%)
≥ 1 x ULN	202 (79%)	196 (81%)	398 (80%)
≤ 1.5 x ULN	118 (46%)	97 (40%)	215 (43%)
> 1.5 x ULN	138 (54%)	146 (60%)	284 (57%)

Source: Table 8-5 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

[1]There were three subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by population sequencing.

[2]The applicant did not count the subjects with missing data when calculating the percentage of subjects in each category. The statistical reviewer re-calculated the percentage of subjects in each category including all subjects, i.e., the denominator was the randomized and treated subjects in each treatment group.

[3]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 40: Patient Demographics and Baseline Disease Characteristics by Genotype in Study 1231 (All Treated)

	Genotype 2		Genotype 3	
	12-Week SOF+RBV (N=73)	24-Week PEG+RBV (N=67)	12-Week SOF+RBV (N=183)	24-Week PEG+RBV (N=176)
Age (years)				
< 50 years old	23 (32%)	18 (27%)	104 (57%)	100 (57%)
≥ 50 years old	50 (68%)	49 (73%)	79 (43%)	76 (43%)
Sex				
Male	46 (63%)	39 (58%)	125 (68%)	117 (66%)
Female	27 (37%)	28 (42%)	58 (32%)	59 (34%)
Race				
Black	4 (5%)	2 (3%)	8 (4%)	3 (2%)
White	65 (89%)	62 (93%)	158 (86%)	150 (85%)
Asian	1 (1%)	1 (1%)	13 (7%)	14 (8%)
Others	3 (4%)	2 (3%)	4 (2%)	9 (5%)
Region				
North America	71 (97%)	66 (99%)	109 (60%)	109 (62%)
Canada	0	0	15 (8%)	24 (14%)
USA	71 (97%)	66 (99%)	94 (51%)	85 (48%)
Australia/New Zealand	2 (3%)	1 (1%)	59 (32%)	58 (33%)
Australia	0	0	32 (17%)	29 (16%)
New Zealand	2 (3%)	1 (1%)	27 (15%)	29 (16%)
Europe	0	0	15 (8%)	9 (5%)
Italy	0	0	8 (4%)	4 (2%)
Netherland	0	0	3 (2%)	1 (1%)
Sweden	0	0	4 (2%)	4 (2%)
Ethnicity				
Hispanic	17 (23%)	9 (13%)	24 (13%)	22 (13%)
Non-Hispanic	56 (77%)	58 (87%)	159 (87%)	154 (88%)
Baseline body mass index				
< 30 kg/m^2	53 (73%)	45 (67%)	126 (69%)	127 (72%)
≥ 30 kg/m^2	20 (27%)	22 (33%)	57 (31%)	49 (28%)
Cirrhosis				
No	61 (84%)	54 (81%)	145 (79%)	139 (79%)
Yes	12 (16%)	13 (19%)	38 (21%)	37 (21%)
IL28 B				
CC	33 (45%)	34 (51%)	75 (41%)	72 (41%)
CT or TT	40 (55%)	33 (49%)	108 (59%)	104 (59%)
Baseline HCV RNA				
< 6 log_{10} IU/mL	25 (34%)	23 (34%)	83 (45%)	83 (47%)
≥ 6 log_{10} IU/mL	48 (66%)	44 (66%)	100 (55%)	93 (53%)
Baseline ALT				
≤ 1.5 x ULN	37 (51%)	35 (52%)	81 (44%)	62 (35%)
> 1.5 x ULN	36 (49%)	32 (48%)	102 (56%)	114 (65%)

Table 41: Reviewer's Results for Subgroup Analysis in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	63% (80/127)	73% (86/118)	-10% (-22%, 2%)
≥ 50 years old	71% (91/129)	61% (76/125)	10% (-2%, 21%)
Sex			
Male	61% (104/171)	62% (96/156)	-0.1% (-11%, 10%)
Female	79% (67/85)	76% (66/87)	3% (-10%, 15%)
Race			
Black	75% (9/12)	40% (2/5)	35% (-14%, 84%)
Other	66% (162/244)	67% (160/238)	-0.1% (-9%, 8%)
Region			
US	75% (123/165)	69% (104/151)	6% (-4%, 16%)
Non-US	53% (48/91)	63% (58/92)	-10% (-25%, 4%)
Ethnicity			
Hispanic	71% (29/41)	65% (20/31)	6% (-16%, 28%)
Non-Hispanic	66% (142/215)	67% (142/212)	-1% (-10%, 8%)
Baseline body mass index			
< 30 kg/m^2	68% (121/179)	68% (117/172)	-0.4% (-10%, 9%)
≥ 30 kg/m^2	65% (50/77)	63% (45/71)	2% (-14%, 17%)
Cirrhosis			
No	72% (148/206)	74% (143/193)	-2% (-11%, 6%)
Yes	46% (23/50)	38% (19/50)	8% (-11%, 27%)
IL28 B			
CC	69% (75/108)	77% (82/106)	-8% (-20%, 4%)
CT or TT	65% (96/148)	58% (80/137)	6% (-5%, 18%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	75% (81/108)	67% (71/106)	8% (-4%, 20%)
≥ 6 $\log_{10}$ IU/mL	61% (90/148)	66% (91/137)	-6% (-17%, 6%)
Baseline ALT			
≤ 1.5 x ULN	70% (83/118)	72% (70/97)	-1% (-14%, 10%)
> 1.5 x ULN	63% (92/146)	64% (88/138)	-1% (-12%, 10%)

[1]based on the Wald asymptotic confidence limits

Table 42: Reviewer's Results for Subgroup Analysis among Genotype 2 Subjects in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	96% (22/23)	78% (14/18)	18% (-3%, 39%)
≥ 50 years old	94% (47/50)	78% (38/49)	16% (3%, 30%)
Sex			
Male	93% (43/46)	69% (27/39)	24% (8%, 40%)
Female	96% (26/27)	89% (25/28)	7% (-6%, 21%)
Race			
Black	75% (3/4)	50% (1/2)	25% (-56%, 100%)
Non Black	96% (66/69)	78% (51/65)	17% (6%, 28%)
Region			
US	94% (67/71)	77% (51/66)	17% (6%, 29%)
Non-US	100% (2/2)	100% (1/1)	n/a
Ethnicity			
Hispanic	88% (15/17)	67% (6/9)	22% (-13%, 56%)
Non-Hispanic	96% (54/56)	79% (46/58)	17% (6%, 29%)
Baseline body mass index			
< 30 kg/m^2	96% (51/53)	78% (35/45)	18.5% (5%, 32%)
≥ 30 kg/m^2	90% (18/20)	77% (17/22)	13% (-9%, 35%)
Cirrhosis			
No	97% (59/61)	81% (44/54)	15% (4%, 27%)
Yes	83% (10/12)	62% (8/13)	22% (-12%, 56%)
IL28 B			
CC	97% (32/33)	82% (28/34)	15% (0.5%, 29%)
CT or TT	93% (37/40)	73% (24/33)	20% (2.5%, 37%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	100% (25/25)	74% (17/23)	26% (8%, 44%)
≥ 6 $\log_{10}$ IU/mL	92% (44/48)	80% (35/44)	12% (-2%, 26%)
Baseline ALT			
≤ 1.5 x ULN	95% (35/37)	80% (28/35)	15% (-0.5%, 30%)
> 1.5 x ULN	94% (34/36)	75% (24/32)	19% (3%, 36%)

[1]based on the Wald asymptotic confidence limits

Table 43: Reviewer's Results for Subgroup Analysis among Genotype 3 Subjects in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	56% (58/104)	72% (72/100)	-16% (-29%, -3%)
≥ 50 years old	56% (44/79)	50% (38/76)	6% (-10%, 21%)
Sex			
Male	49% (61/125)	59% (69/117)	-10% (-23%, 2 %)
Female	71% (41/58)	69% (41/59)	1% (-15%, 18%)
Race			
Black	75% (6/8)	33% (1/3)	42% (-20%, 100%)
Non Black	55% (96/175)	63% (109/173)	-8% (-18%, 2%)
Region			
US	60% (56/94)	62% (53/85)	-3% (-17%, 12%)
Non-US	52% (46/89)	63% (57/91)	-11% (-25%, 3%)
Ethnicity			
Hispanic	58% (14/24)	64% (14/22)	-5% (-33%, 23%)
Non-Hispanic	55% (88/159)	62% (96/154)	-7% (-18%, 4%)
Baseline body mass index			
< 30 kg/m^2	56% (70/126)	65% (82/127)	-9% (-21%, 3%)
≥ 30 kg/m^2	56% (32/57)	57% (28/49)	-1% (-20%, 18%)
Cirrhosis			
No	61% (89/145)	71% (99/139)	-10% (-21%, 1%)
Yes	34% (13/38)	30% (11/37)	4% (-17%, 26%)
IL28 B			
CC	57% (43/75)	75% (54/72)	-18% (-33%, -3%)
CT or TT	55% (59/108)	54% (56/104)	1% (-13%, 14%)
Baseline HCV RNA			
< 6 log_{10} IU/mL	67% (56/83)	65% (54/83)	2% (-12%, 17%)
≥ 6 log_{10} IU/mL	46% (46/100)	60% (56/93)	-14% (-28%, -0.3%)
Baseline ALT			
≤ 1.5 x ULN	59% (48/81)	68% (42/62)	-8% (-24%, 7%)
> 1.5 x ULN	53% (54/102)	60% (68/114)	-7% (-20%, 7%)

[1]based on the Wald asymptotic confidence limits

6.2 Study 107

Table 44: On-Treatment Study Procedures in Study 107

			Visit Identified by On-Treatment Study Week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X									
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Health-Related Quality of Life Survey (SF-36)[f]		X							X	
Review of Study Drugs Compliance			X	X	X	X	X	X	X	
Study Drug Dispensing[b]		X			X		X			
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X

to be continued

Table 44: On-Treatment Study Procedures in Study 107 (Continued)

	Screening	Baseline/Day 1[c]	Visit Identified by On-Treatment Study Week							Early Termination
			1	2	4	6	8	10	12	
Coagulation Tests	X	X							X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA_{1c}, FibroTest	X									
Thyroid-Stimulating Hormone	X									
Pharmacogenomics, GGT		X[e]								

EGC = electrocardiogram; GGT = gamma-glutamyl transpeptidase; HbA_{1c} = hemoglobin A_{1c}; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = interactive web response system; PK = pharmacokinetic(s); RNA = ribonucleic acid

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b The IWRS provided information regarding each subject's study drug dispensing.

c Day 1 (baseline) assessments were performed prior to dosing.

d Plasma samples were collected and stored for potential HCV sequencing and other virology studies

e Pharmacogenomic testing was only for subjects who consented to this testing. If consent was not obtained at baseline, the sample could be drawn at any time during the study.

f SF-36 Health Survey collected if a site was approved to use the survey.

Source: Table 7-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 45: Post-Treatment Study Procedures in Study 107

	4 Weeks Posttreatment	12 Weeks Posttreatment	24 Weeks Posttreatment
Clinical Assessments			
Vital Signs[a]	X	X	X
Weight		X	X
Adverse Events	X		
Concomitant Medications	X		
Health-Related Quality of Life Survey (SF-36)[b]	X		
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
Viral Sequencing (archive)[c]	X	X	X
Urine Pregnancy Test	X	X	X
Pregnancy Prevention Counseling	X	X	X

HCV = hepatitis C virus; RNA = ribonucleic acid

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b SF-36 Health Survey collected if a site was approved to use the survey.

c Plasma samples were collected and stored for potential HCV sequencing and other virology studies

Source: Table 7-3 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 46: On-Treatment Visit Windows in Study 107

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital Signs and Other Safety Labs
Baseline	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Table 47: Post-Treatment Visit Windows in Study 107

Off-Treatment FU Visit ID	Post-Treatment Visit Windows for HCV RNA [a] (Days from Last Study Drug Dose)	Vital Signs and Other Safety Labs [b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow up visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Table 48: Patient Demographics and Baseline Characteristics in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	Total (N=278)
Age (years)			
Mean (SD)	52 (10)	52 (8)	52
Median (Q1, Q3)	53 (47, 58)	54 (49, 57)	54 (47, 58)
Sex			
Male	117 (57%)	34 (48%)	151 (54%)
Female	90 (44%)	37 (52%)	127 (46%)
Race			
Black	9 (4%)	4 (6%)	13 (5%)
White	188 (91%)	66 (93%)	254 (91%)
Asian	7 (3%)	1 (1%)	8 (3%)
Others	3 (2%)	0	3 (2%)
Ethnicity			
Hispanic	19 (9%)	11 (16%)	30 (11%)
Non-Hispanic	188 (91%)	60 (85%)	248 (89%)
Region[1]			
North America	183 (88%)	68 (96%)	251 (90%)
Canada	15 (7%)	8 (11%)	23 (8%)
USA	168 (81%)	60 (85%)	228 (82%)
Australia/New Zealand	24 (12%)	3 (4%)	27 (10%)
Australia	18 (9%)	3 (4%)	21 (8%)
New Zealand	6 (3%)	0	6 (3%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (6)	28 (6)	28 (6)
Median (Q1, Q3)	28 (24, 31)	27 (23, 32)	28 (24, 31)

Source: Table 8-4 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA
[1]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 49: Baseline Disease Characteristics for Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	Total (N=278)
HCV genotype			
Genotype 2	109 (53%)	34 (48%)	143 (51%)
Genotype 3	98 (47%)	37 (52%)	135 (49%)
Interferon classification			
Ineligible	88 (43%)	33 (47%)	121 (44%)
Intolerant	17 (8%)	8 (11%)	25 (9%)
Unwilling	102 (49%)	30 (42%)	132 (47%)
Duration on prior HCV treatment			
No	170 (82%)	56 (79%)	226 (81%)
≤ 12 weeks	21 (10%)	8 (11%)	29 (10%)
> 12 weeks	16 (8%)	7 (10%)	23 (8%)
Cirrhosis			
No	176 (85%)	58 (82%)	234 (84%)
Yes	31 (15%)	13 (18%)	44 (16%)
IL28 B			
CC	97 (47%)	29 (41%)	126 (45%)
CT	84 (41%)	36 (51%)	120 (43%)
TT	26 (13%)	6 (9%)	32 (12%)
Baseline HCV RNA (log_{10} IU/mL)	6.3 (0.8)	6.3 (0.8)	6.3 (0.8)
Mean (SD)	6.4 (5.8, 6.8)	6.5 (6.1, 6.8)	6.4 (5.9, 6.8)
Median (Q1, Q3)			
	67 (32%)	17 (24%)	84 (30%)
< 6 log_{10} IU/mL	140 (68%)	54 (76%)	194 (70%)
≥ 6 log_{10} IU/mL			
Baseline ALT[1]			
≤ 1 x ULN	52 (25%)	15 (21%)	67 (24%)
> 1 x ULN	155 (75%)	56 (79%)	211 (76%)
≤ 1.5 x ULN	90 (44%)	29 (41%)	119 (43%)
> 1.5 x ULN	117 (57%)	42 (59%)	159 (57%)

Source: Table 8-5 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA
[1]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 50: Reviewer's Results for Patient Demographics and Baseline Disease Characteristics for Subjects Receiving 12 Weeks of SOF+RBV by HCV Genotype in Study 1231 and Study 107

	Genotype 2		Genotype 3	
	Study 1231 (N=73)	**Study 107 (N=93)**	**Study 1231 (N=183)**	**Study 107 (N=77)**
Age (years)				
Mean (SD)	52 (10)	54 (10)	46 (11)	48 (10)
Median (Q1, Q3)	54 (46, 58)	56 (49, 60)	48 (39, 54)	50 (41, 55)
< 50 years old	23 (32%)	25 (27%)	104 (57%)	38 (49%)
≥ 50 years old	50 (68%)	68 (73%)	79 (43%)	39 (51%)
Sex				
Male	46 (63%)	54 (58%)	58 (32%)	37 (48%)
Female	27 (37%)	39 (42%)	125 (68%)	40 (52%)
Race				
Black	4 (5%)	9 (10%)	8 (4%)	0
White	65(89%)	81 (87%)	158 (86%)	70 (91%)
Others	4 (5%)	3 (3%)	17 (9%)	7 (9%)
Region				
North America	71 (97%)	89 (96%)	109 (59%)	59 (78%)
USA	71 (97%)	81 (87%)	94 (51%)	53 (69%)
Canada	0	8 (9%)	15 (8%)	6 (8%)
Australia/New Zealand	2 (3%)	4 (4%)	59 (32%)	18 (23%)
Australia	0	3 (3%)	32 (17%)	14 (18%)
New Zealand	2 (3%)	1 (1%)	27 (15%)	4 (5%)
Europe	0	0	15 (8%)	0
Italy	0	0	8 (4%)	0
Netherland	0	0	3 (2%)	0
Sweden	0	0	4 (2%)	0
Ethnicity				
Hispanic	17 (23%)	9 (10%)	24 (13%)	7 (9%)
Non-Hispanic	56 (77%)	84 (90%)	159 (87%)	70 (91%)
Baseline body mass index				
< 30 kg/m^2	53 (73%)	56 (60%)	126 (69%)	55 (71%)
≥ 30 kg/m^2	20 (27%)	37 (40%)	57 (31%)	22 (29%)
Cirrhosis				
No	61 (84%)	79 (85%)	144 (79%)	73 (95%)
Yes	12 (16%)	14 (15%)	38 (21%)	4 (5%)
Missing	0	0	1(1%)	0
IL28 B				
CC	33 (45%)	38 (41%)	75 (41%)	40 (52%)
CT or TT	40 (55%)	55 (59%)	108 (59%)	37 (48%)
Baseline HCV RNA (log_{10} IU/mL)				
Mean (SD)	6.2 (0.9)	6.3 (0.8)	6.0 (0.8)	6.1 (0.8)
Median (Q1, Q3)	6.4 (5.6, 6.7)	6.5 (5.9, 6.9)	6.1 (5.4, 6.3)	6.3 (5.8, 6.7)
< 6 log_{10} IU/mL	25 (34%)	27 (29%)	83 (45%)	31 (40%)
≥ 6 log_{10} IU/mL	48 (66%)	66 (71%)	100 (55%)	46 (60%)
Baseline ALT				
≤ 1.5 x ULN	37 (51%)	49 (53%)	81 (44%)	29 (38%)
> 1.5 x ULN	36 (49%)	44 (47%)	102 (56%)	48 (62%)

Table 51: Reviewer's Results for Subgroup Comparison between Study 1231 and Study 107 in HCV Genotype 3 Treat-Naïve Subjects

	12-Week SOF+RBV		
	Study 1231	**Study 107**	**Study 1231 vs. Study 107 Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	56% (58/104)	66% (25/38)	-10% (-28%, 8%)
≥ 50 years old	56% (44/79)	74% (28/28)	-19% (-36%, -1%)
Sex			
Male	49% (61/125)	58% (23/40)	-9% (-26%, 9%)
Female	71% (41/58)	84% (31/37)	-13% (-30%, 4%)
Race			
White	54% (85/158)	67% (47/70)	-13% (-27%, 0.1%)
Other	68% (17/25)	100% (7/7)	-32% (-50%, -14%)
Region			
US	60% (56/94)	66% (35/53)	-6% (-23%, 10%)
Non-US	52% (46/89)	79% (19/24)	-27% (-47%, -8%)
Ethnicity			
Hispanic	58% (14/24)	71% (5/7)	-13% (-52%, 26%)
Non-Hispanic	55% (88/159)	70% (49/70)	-15% (-28%, -1%)
Baseline body mass index			
< 30 kg/m^2	56% (70/126)	69% (38/55)	-14% (-29%, 1%)
≥ 30 kg/m^2	56% (32/57)	73% (16/22)	-17% (-39%, 6%)
Cirrhosis			
No	61% (89/145)	71% (52/73)	-10% (-23%, 3%)
Yes	34% (13/38)	50% (2/4)	-16% (-67%, 35.5%)
IL28 B			
CC	57% (43/75)	78% (31/40)	-20% (-37%, -3%)
CT or TT	55% (59/108)	62% (23/37)	-8% (-26%, 11%)
Baseline HCV RNA			
<6 log_{10} IU/mL	67% (56/83)	68% (21/31)	-0.3% (-20%, 19%)
≥ 6 log_{10} IU/mL	46% (46/100)	72% (33/46)	-26% (-42%, -10%)
Baseline ALT			
≤ 1.5 x ULN	59% (48/81)	55% (16/29)	4% (-17%, 25%)
> 1.5 x ULN	53% (54/102)	79% (38/48)	-26% (-41%, -11%)

[1]based on the Wald asymptotic confidence limits

Table 52: Reviewer's Results for Subgroup Analysis in Study 107 (All Treated)

	12-Week SOF+RBV	Placebo	12-Week SOF+RBV vs. Placebo Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	74% (53/72)	0% (0/20)	74% (63%, 84%)
≥ 50 years old	80% (108/135)	0% (0/51)	80% (73%, 87%)
Sex			
Male	73% (85/117)	0% (0/34)	73% (65%, 81%)
Female	84% (76/90)	0% (0/37)	84% (77%, 92%)
Race			
Black	89% (8/9)	0% (0/4)	89% (68%, 100%)
Other	77% (153/198)	0% (0/67)	77% (71%, 83%)
Region			
US	77% (130/168)	0% (0/60)	77% (71%, 84%)
Non-US	79% (31/39)	0% (0/11)	79.5% (67%, 92%)
Ethnicity			
Hispanic	74% (14/19)	0% (0/11)	74% (54%, 93%)
Non-Hispanic	78% (147/188)	0% (0/60)	78% (72%, 84%)
Baseline body mass index			
< 30 kg/m^2	76% (103/136)	0% (0/49)	76% (69%, 83%)
≥ 30 kg/m^2	82% (58/71)	0% (0/22)	82% (73%, 91%)
HCV Genotype			
Genotype 2	93% (101/109)	0% (0/34)	93% (88%, 98%)
Genotype 3	61% (60/98)	0% (0/37)	61% (52%, 71%)
Interferon Classification			
Ineligible	78% (69/88)	0% (0/33)	78% (70%, 87%)
Intolerant	76% (13/17)	0% (0/8)	77% (56%, 97%)
Unwilling	77% (79/102)	0% (0/30)	78% (69%, 86%)
Duration of prior HCV treatment			
No	82% (140/170)	0% (0/56)	82% (77%, 88%)
≤ 12 weeks	71% (15/21)	0% (0/8)	71% (52%, 91%)
> 12 weeks	38% (6/16)	0% (0/7)	37.5% (14%, 61%)
Cirrhosis			
No	81% (142/176)	0% (0/58)	81% (75%, 87%)
Yes	61% (19/31)	0% (0/13)	61% (44%, 78%)
IL28B			
CC	76% (74/97)	0% (0/29)	76% (68%, 85%)
CT or TT	79% (87/110)	0% (0/42)	79% (71%, 87%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	76% (51/67)	0% (0/17)	76% (66%, 86%)
≥ 6 $\log_{10}$ IU/mL	79% (110/140)	0% (0/54)	79% (72%, 85%)
Baseline ALT			
≤ 1.5 x ULN	79% (71/90)	0% (0/29)	79% (71%, 87%)
> 1.5 x ULN	77% (90/117)	0% (0/42)	77% (69%, 85%)

[1]based on the Wald asymptotic confidence limits

Table 53: Reviewer's Results for SVR12 Rates by Genotype and Subgroup in 12-Week SOF+RBV Group in Study 107 (All Treated)

	12-Week SOF+RBV		
	Genotype 2	**Genotype 3**	**Genotype 2 vs. Genotype 3 Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	93% (27/29)	60% (26/43)	33% (15%, 50%)
≥ 50 years old	93% (74/80)	62% (34/55)	31% (17%, 45%)
Sex			
Male	92% (59/64)	49% (26/53)	43% (28%, 58%)
Female	93% (42/45)	76% (34/45)	18% (3%, 32%)
Race			
Black	89% (8/9)	0/0	n/a
Other	93% (93/100)	61% (60/98)	32% (21%, 43%)
Region			
US	94% (89/95)	56% (41/73)	38% (25%, 50%)
Non-US	86% (12/14)	76% (19/25)	10% (-15%, 35%)
Ethnicity			
Hispanic	82% (9/11)	63% (5/8)	19% (-21%, 60%)
Non-Hispanic	94% (92/98)	61% (55/90)	33% (22%, 44%)
Baseline body mass index			
< 30 kg/m^2	92% (61/66)	60% (42/70)	32% (19%, 45%)
≥ 30 kg/m^2	93% (40/43)	64% (18/28)	29% (9%, 48%)
Interferon Classification			
Ineligible	88% (36/41)	70% (33/47)	18% (1%, 34%)
Intolerant	100% (9/9)	50% (4/8)	50% (15%, 85%)
Unwilling	95% (56/59)	53% (23/43)	41% (26%, 57%)
Duration of prior HCV treatment			
No	92% (86/93)	70% (54/77)	22% (11%, 34%)
≤ 12 weeks	100% (11/11)	40% (4/10)	60% (30%, 90%)
> 12 weeks	80% (4/5)	18% (2/11)	62% (20%, 100%)
Cirrhosis			
No	92% (85/92)	68% (57/84)	25% (13%, 36%)
Yes	94% (16/17)	21% (3/14)	73% (48%, 97%)
IL28B			
CC	89% (40/45)	65% (34/52)	24% (8%, 39%)
CT or TT	95% (61/64)	57% (26/46)	39% (24%, 54%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	88% (29/33)	65% (22/34)	23% (4%, 43%)
≥ 6 $\log_{10}$ IU/mL	95% (72/76)	59% (38/64)	35% (22%, 48%)
Baseline ALT			
≤ 1.5 x ULN	91% (53/58)	56% (18/32)	35% (16%, 54%)
> 1.5 x ULN	94% (48/51)	64% (42/66)	30% (17%, 44%)

[1]based on the Wald asymptotic confidence limits

6.3 Study 108

Table 54: On-Treatment Study Procedures in Study 108

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week								Early Termination
			1	2	4	6	8	10	12	16	
Clinical Assessments											
Informed Consent	X										
Determine Eligibility	X	X									
Medical History	X										
Physical Examination	X	X							X	X	X
Height	X										
Weight	X	X							X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X										
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X		X
Quality of Life Surveys[c]		X			X				X	X	X
Review of Study Drug Compliance			X	X	X	X	X	X	X	X	
Study Drug Dispensing[d]		X			X		X		X		

to be continued

Table 54: On-Treatment Study Procedures in Study 108 (Continued)

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week								Early Termination
			1	2	4	6	8	10	12	16	
Laboratory Tests											
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[e]		X	X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X	X
Urinalysis	X										
Urine Drug Screen	X										
HCV Genotyping, IL28B	X										
HCV, HIV, HBV Serology	X										
HbA_{1c}	X										
Thyroid-Stimulating Hormone	X										
Pharmacogenomics		X[f]									

a Day 1 (baseline) assessments were performed prior to dosing.

b Vital signs included blood pressure, pulse, respiratory rate, and temperature.

c Quality of life surveys were completed by subjects at Day 1, and at the Week 4, 12, and 16 visits if a site was approved to use the survey.

d The IWRS provided information regarding each subject's study drug dispensing.

e Plasma samples were collected and stored for potential HCV sequencing and other virology studies.

f Pharmacogenomic testing was only for subjects who consented to this testing. If the blood sample was not obtained at baseline, the sample could have been drawn at any time during the study.

Source: Table 7-2 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 55: Post-Treatment Study Procedures in Study 108

	4 Weeks Posttreatment	8 Weeks Posttreatment	12 Weeks Posttreatment	20 Weeks Posttreatment	24 Weeks Posttreatment
Clinical Assessments					
Vital Signs[a]	X	X	X	X	X
Weight			X		X
Adverse Events	X				
Concomitant Medications	X				
Quality of Life Surveys[b]	X	X	X		X
Pregnancy Prevention Counseling	X	X	X	X	X
Laboratory Assessments					
Hematology, Chemistry	X	X	X		
HCV RNA	X	X	X	X	X
Viral Sequencing[c]	X	X	X	X	X
Urine Pregnancy Test	X	X	X	X	X

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b Quality of life surveys were completed by all subjects at posttreatment Week 4, 8, 12, and 24 visits if a site was approved to use the survey.

c Plasma samples were collected and stored for potential HCV sequencing and other virology studies.

Source: Table 7-3 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 56: On-Treatment Visit Windows in Study 108

Visit ID	On-Treatment Visit Windows for Group 1	On-Treatment Visit Windows for Group 2
Baseline	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98	78 ≤ Study Day ≤ 98
Week 16	99 ≤ Study Day ≤ 126 [a]	99 ≤ Study Day ≤ 126

a Visit Week-16 of Group 1 will be summarized for vital signs and safety labs, but not for HCV RNA.
Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 57: Post-Treatment Visit Windows in Study 108

Off-Treatment FU Visit ID	Posttreatment Visit Windows for HCV RNA [a] (Days from Last Dose of Active Treatment)	Vital Signs and Other Safety Labs[c] (Days from Last Dose Date)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow-up visit (up to 30 days post last dose of study drugs).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 58: Patient Demographics and Baseline Characteristics for Study 108 (All Treated)

	12-week SOF+RBV (N=103)	16-week SOF+RBV (N=98)	Total (N=201)
Age (years)			
Mean (SD)	54 (7.7)	54 (7.8)	54 (7.8)
Median (Q1, Q3)	56 (51, 59)	55 (50, 58)	56 (51, 59)
Sex			
Male	73 (71%)	67 (68%)	140 (70%)
Female	30 (29%)	31 (32%)	61 (30%)
Race			
Black	5 (5%)	1 (1%)	6 (3%)
White	88 (85%)	86 (88%)	174 (87%)
Asian	7 (8%)	5 (5%)	12 (6%)
Others	3 (3%)	6 (6%)	9 (3%)
Ethnicity			
Hispanic	10 (10%)	8 (8%)	18 (9%)
Non-Hispanic	93 (90%)	89 (91%)	182 (91%)
Declined to disclose	0	1 (1%)	1 (1%)
Country[1]			
Canada	26 (25%)	17 (17%)	43 (21%)
USA	74 (72%)	76 (78%)	150 (76%)
New Zealand	3 (3%)	5 (5%)	8 (4%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (5)	29 (5)	29 (5)
Median (Q1, Q3)	27 (25, 31)	29 (26, 32)	28 (25, 31)
< 30 kg/m^2	74 (72%)	62 (63%)	136 (68%)
≥ 30 kg/m^2	29 (28%)	36 (37%)	65 (32%)

Source: Table 8-4 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 59: Baseline Disease Characteristics for Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	Total (N=201)
HCV genotype			
Genotype 1[1]	3 (3%)	3 (3%)	6 (3%)
Genotype 2	36 (35%)	32 (33%)	68 (34%)
Genotype 3	64 (62%)	63 (64%)	127 (63%)
Cirrhosis			
No	66 (65%)	66 (67%)	132 (66%)
Yes	36 (35%)	32 (33%)	68 (34%)
IL28 B			
CC	31 (30%)	30 (31%)	61 (30%)
CT	53 (52%)	56 (57%)	109 (54%)
TT	19 (18%)	12 (12%)	31 (15%)
Response to prior HCV trt			
Nonresponse	25 (24%)	25 (26%)	50 (25%)
Relapse/Breakthrough	78 (76%)	73 (75%)	151 (75%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.5 (0.7)	6.5 (0.6)	6.5 (0.7)
Median (Q1, Q3)	6.6 (6.0, 7.0)	6.6 (5.9, 7.1)	6.6 (6.0, 7.0)
< 6 log_{10} IU/mL	26 (25%)	29 (30%)	55 (27%)
≥ 6 log_{10} IU/mL	77 (75%)	69 (70%)	146 (73%)
Baseline ALT[2]			
≤ 1 x ULN	23 (22%)	20 (20%)	43 (21%)
> 1 x ULN	80 (78%)	78 (80%)	158 (79%)
≤ 1.5 x ULN	40 (39%)	42 (43%)	82 (41%)
> 1.5 x ULN	63 (61%)	56 (57%)	119 (59%)

Source: Table 8-5 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

[1]There were six subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis.

[2]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 60: Reviewer's Results for Subgroup Analysis in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Age (years)			
< 50 years old	43% (9/21)	70% (16/23)	-27% (-55%, 2%)
≥ 50 years old	51% (42/82)	72% (54/75)	-21% (-36%, -6%)
Sex			
Male	41% (30/73)	64% (43/67)	-23% (-39%, -7%)
Female	70% (21/30)	87% (27/31)	-17% (-37%, 3%)
Race			
Black	100% (1/1)	100% (5/5)	n/a
Other	71% (69/97)	47% (46/98)	-24% (-38%, -11%)
Region			
US	53% (39/74)	75% (57/76)	-22% (-37%, -7%)
Non-US	41% (12/29)	59% (13/22)	-18% (-45%, 10%)
Ethnicity			
Hispanic	40% (4/10)	63% (5/8)	-23% (-68%, 23%)
Non-Hispanic	51% (47/93)	72% (64/89)	-21% (-35%, -8%)
Baseline body mass index			
< 30 kg/m^2	54% (40/74)	71% (45/63)	-17% (-33%, -1%)
≥ 30 kg/m^2	38% (11/29)	71% (25/35)	-34% (-57%, -10%)
Cirrhosis			
No	60% (40/67)	74% (49/66)	-5% (-30%, 1%)
Yes	31% (11/36)	66% (21/32)	-35% (-6%, -13%)
IL28B			
CC	52% (16/31)	67% (20/30)	-15% (-39%, 9%)
CT or TT	49% (35/72)	74% (50/68)	-25% (-1%, -9%)
Response to prior HCV trt			
Nonresponse	44% (11/25)	64% (16/25)	-20% (-47%, 7%)
Relapse/Breakthrough	51% (40/78)	74% (54/73)	-23% (-38%, -8%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	50% (13/26)	62% (18/29)	-12% (-38%, 14%)
≥ 6 $\log_{10}$ IU/mL	49% (38/77)	75% (52/69)	-26% (-41%, -11%)
Baseline ALT			
≤ 1.5 x ULN	65% (26/40)	76% (32/42)	-11% (-31%, 8%)
> 1.5 x ULN	40% (25/63)	68% (38/56)	-28% (-45%, -11%)

[1]based on the Wald asymptotic confidence limits

Table 61: Reviewer's Results for Subgroup Analysis among Genotype 2 Subjects in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	83% (5/6)	75% (3/4)	8% (-44%, 60%)
≥ 50 years old	82% (27/33)	90% (28/31)	-9% (-25%, 8%)
Sex			
Male	72% (18/25)	84% (21/25)	-12% (-35%, 11%)
Female	100% (14/14)	100% (10/10)	n/a
Race			
Black	0	100% (4/4)	n/a
Other	80% (28/35)	86% (31/35)	-9% (-26%, 8%)
Region			
US	82% (27/33)	91% (29/32)	-9% (-25%, 8%)
Non-US	83% (5/6)	67% (2/3)	17% (-44%, 78%)
Ethnicity			
Hispanic	80% (4/5)	100% (1/1)	-20% (-55%, 15%)
Non-Hispanic	82% (28/34)	88% (30/34)	-6% (-23%, 11%)
Baseline body mass index			
< 30 kg/m^2	86% (24/28)	94% (16/17)	8% (-9%, 26%)
≥ 30 kg/m^2	73% (8/11)	83% (15/18)	-11% (-42%, 21%)
Cirrhosis			
No	90% (26/29)	92% (24/26)	-3% (-18%, 12%)
Yes	60% (6/10)	78% (7/9)	-18% (-59%, 23%)
IL28 B			
CC	88% (7/8)	71% (10/14)	16% (-17%, 49%)
CT or TT	81% (25/31)	100% (21/21)	-19% (-33%, -5%)
Response to prior HCV trt			
Nonresponse	70% (7/10)	88% (7/8)	-18% (-54%, 19%)
Relapse/Breakthrough	86% (25/29)	89% (24/27)	-3% (-20%, 15%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	89% (8/9)	100% (3/3)	-11% (-32%, 9%)
≥ 6 $\log_{10}$ IU/mL	80% (24/30)	88% (28/32)	-8% (-26%, 11%)
Baseline ALT			
≤ 1.5 x ULN	83% (20/24)	91% (20/22)	-8% (-27%, 12%)
> 1.5 x ULN	80% (28/35)	86% (31/35)	-5% (-33%, 24%)

[1]based on the Wald asymptotic confidence limits

Table 62: Reviewer's Results for Subgroup Analysis among Genotype 3 Subjects in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	27% (4/15)	68% (13/19)	-42% (-72%, -11%)
≥ 50 years old	31% (15/49)	59% (26/44)	-28% (-48%, -9%)
Sex			
Male	25% (12/48)	52% (22/42)	-27% (-47%, -8%)
Female	44% (7/16)	81% (17/21)	-37% (-67%, -8%)
Race			
Black	100% (1/1)	100% (1/1)	n/a
Other	29% (18/63)	61% (38/62)	-33% (-49%, -16%)
Region			
US	29% (12/41)	64% (28/44)	-34% (-54%, -14%)
Non-US	30% (7/23)	58% (11/19)	-27% (-57%, 2%)
Ethnicity			
Hispanic	0% (0/5)	57% (4/7)	-57% (-94%, -20%)
Non-Hispanic	32% (19/59)	62% (34/55)	-30% (-47%, -12%)
Baseline body mass index			
< 30 kg/m^2	35% (16/46)	63% (29/46)	-28% (-48%, -9%)
≥ 30 kg/m^2	17% (3/18)	59% (10/17)	-42% (-71%, -13%)
Cirrhosis			
No	37% (14/38)	63% (25/40)	-26% (-47%, -4%)
Yes	19% (5/26)	61% (14/23)	-42% (-67%, -17%)
IL28 B			
CC	39% (9/23)	63% (10/16)	-23% (-54%, 8%)
CT or TT	24% (10/41)	62% (29/47)	-37% (-56%, -18%)
Response to prior HCV trt			
Nonresponse	27% (4/15)	53% (9/17)	-26% (-59%, 6%)
Relapse/Breakthrough	31% (15/49)	65% (30/46)	-35% (-53%, -16%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	29% (5/17)	58% (15/26)	-28% (-57%, 0.5%)
≥ 6 $\log_{10}$ IU/mL	30% (14/47)	65% (24/37)	-35% (-55%, -15%)
Baseline ALT			
≤ 1.5 x ULN	38% (6/16)	60% (12/20)	-23% (-55%, 10%)
> 1.5 x ULN	27% (13/48)	63% (27/43)	-36% (-55%, -17%)

[1]based on the Wald asymptotic confidence limits

6.4 Study 110

Table 63: On-Treatment Study Procedures in Study 110

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week							
			1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination[b]	X[b]	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X							X	X
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Quality of Life Surveys		X							X	X
Review of Study Drug Compliance			X	X	X	X	X	X	X	
Study Drug Dispensing[d]		X			X		X			

to be continued

Table 63: On-Treatment Study Procedures for Study 110 (Continued)

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week							
			1	2	4	6	8	10	12	Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[e]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA_{1c}	X									
TSH	X								X	X
Pharmacogenomic		X[f]								

a Day 1 assessments were performed prior to dosing

b Retinal examination was performed at screening only

c Vital signs included blood pressure, pulse, respiratory rate, and temperature

d The interactive web response system (IWRS) provided direction on the specifics of each subject's study drug dispensing.

e Plasma samples were collected and stored for potential HCV sequencing and other virology studies

f Only for subjects who consented to this testing. If not obtained at Day 1, the sample was drawn at any time during the study.

Source: Table 7-2 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 64: Post-Treatment Study Procedures for Study 110

	Posttreatment Week 4	Posttreatment Week 12	Posttreatment Week 24
Clinical Assessments			
Vital Signs	X		
Weight	X		
AEs	X		
Concomitant Medications	X		
Laboratory Assessments			
Hematology, Chemistry	X	X	
HCV RNA	X	X	X
Viral Sequencing	X	X	X
Urine Pregnancy Test	X	X	X
Quality of Life Surveys	X	X	X
Pregnancy Prevention Counseling	X	X	X

Source: Table 7-3 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 65: On-Treatment Visit Windows for Study 110

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital signs, Safety Labs	Coagulation Tests
Baseline	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	N/A
Week 2	12 ≤ Study Day ≤ 21	N/A
Week 4	22 ≤ Study Day ≤ 35	N/A
Week 6	36 ≤ Study Day ≤ 49	N/A
Week 8	50 ≤ Study Day ≤ 63	N/A
Week 10	64 ≤ Study Day ≤ 77	N/A
Week 12	78 ≤ Study Day ≤ 98	2 ≤ Study Day ≤ 98

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 66: Post-Treatment Visit Windows for Selected Tests for Study 110

Post - Treatment FU Visit ID	Post-Treatment Visit Windows for HCV RNA[a] (Days from Last Study Drug Dose)	Vital Signs[b] (Days from Last Study Drug Dose)	Safety Labs[b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A	NA
FU-24	147 ≤ FU Day ≤ 190	N/A	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the FU-4 visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 67: Patient Demographics and Baseline Characteristics for Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)
Age (years)	
Mean (SD)	52 (10)
Median (Q1, Q3)	54 (46, 59)
Sex	
Male	209 (64%)
Female	118 (36%)
Race	
Black	54 (17%)
White	257 (79%)
Asian	7 (2%)
Others	9 (3%)
Ethnicity	
Hispanic	46 (14%)
Non-Hispanic	281 (86%)
Baseline body mass index (kg/m^2)	
Mean (SD)	29 (7)
Median (Q1, Q3)	28 (25, 32)

Source: Table 8-4 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 68: Baseline Disease Characteristics for Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)
HCV genotype	
Genotype 1a/1b	1 (<1%)
Genotype 1a	225 (69%)
Genotype 1b	66 (20%)
Genotype 4	28 (9%)
Genotype 5	1 (<1%)
Genotype 6	6 (2%)
Cirrhosis	
No	270 (83%)
Yes	54 (17%)
Missing	3 (1%)
IL28 B	
CC	95 (29%)
CT	181 (55%)
TT	51 (16%)
Baseline HCV RNA (log_{10} IU/mL)	
Mean (SD)	6.4 (0.67)
Median (Q1, Q3)	6.6 (6.1, 6.9)
< 6 log_{10} IU/mL	71 (22%)
≥ 6 log_{10} IU/mL	256 (78%)
Baseline ALT[2]	
≤ 1 x ULN	68 (21%)
> 1 x ULN	259 (79%)
≤ 1.5 x ULN	161 (49%)
> 1.5 x ULN	51% (166)

Source: Table 8-5 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

[1]There were six subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis.

[2] The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 69: Patient Demographics and Baseline Characteristics by HCV Genotype in Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)	
	Genotype 1a (n=225)	**Genotype 1b (n=66)**
Age (years)		
Mean (SD)	51 (11)	56 (8)
Median (Q1, Q3)	53 (46, 58)	58 (53, 62)
< 50 years old	81 (36%)	12 (18%)
≥ 50 years old	144 (64%)	54 (82%)
Sex		
Male	143 (64%)	45 (68%)
Female	82 (36%)	21 (32%)
Race		
Black	33 (15%)	17 (26%)
White	185 (82%)	48 (73%)
Others	7 (3%)	1 (2%)
Ethnicity		
Hispanic	36 (16%)	6 (9%)
Non-Hispanic	189 (84%)	60 (91%)
Baseline body mass index		
< 30 kg/m^2	134 (60%)	91 (59%)
≥ 30 kg/m^2	91 (40%)	27 (41%)
Cirrhosis		
No	180 (80%)	56 (85%)
Yes	43 (19%)	9 (14%)
Missing	2 (1%)	1 (2%)
IL28 B		
CC	72 (32%)	13 (20%)
CT or TT	153 (68%)	53 (80%)
Baseline HCV RNA (log_{10} IU/mL)		
Mean (SD)	6.5 (0.7)	6.5 (0.6)
Median (Q1, Q3)	6.6 (6.2, 7.0)	6.7 (6.2, 6.9)
< 6 log_{10} IU/mL	46 (20%)	9 (14%)
≥ 6 log_{10} IU/mL	179 (80%)	57 (86%)
Baseline ALT[2]		
≤ 1.5 x ULN	98 (44%)	38 (58%)
> 1.5 x ULN	127 (56%)	28 (42%)

Source: Table 3.2 in Section 15.1 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 70: Applicant's Results for Subgroup Analysis in Study 110 (All Treated)

	SVR12 Rate	95% CI[1]
Age (years)		
< 50 years old	95% (104/110)	(89%, 98%)
≥ 50 years old	88% (191/217)	(83%, 92%)
Sex		
Male	88% (184/209)	(83%, 92%)
Female	94% (111/118)	(88%, 98%)
Race		
Black	87% (47/54)	(75%, 95%)
Non-black	91% (248/273)	(87%, 94%)
Ethnicity		
Hispanic	91% (42/46)	(79%, 98%)
Non-Hispanic	90% (253/281)	(86%, 93%)
Baseline body mass index		
< 30 kg/m^2	93% (184/198)	(88%, 96%)
≥ 30 kg/m^2	86% (111/129)	(79%, 91.5%)
HCV Genotype		
Genotype 1a	92% (206/225)	(87%, 95%)
Genotype 1b	82% (54/66)	(70%, 90%)
Genotype 4	96% (27/28)	(82%, 100%)[3]
Genotype 5	100% (1/1)	n/a
Genotype 6	100% (6/6)	n/a
Cirrhosis		
No[2]	92% (252/273)	(87%, 95%)
Yes	80% (43/54)	(66%, 89%)
IL28 B		
CC	98% (93/95)	(93%, 100%)
CT or TT	87% (202/232)	(82%, 91%)
Baseline HCV RNA		
< 6 $\log_{10}$ IU/mL	96% (68/71)	(88%, 99%)
≥ 6 $\log_{10}$ IU/mL	89% (227/256)	(84%, 92%)
Baseline ALT		
≤ 1.5 x ULN	90% (145/161)	(84%, 94%)
> 1.5 x ULN	90% (150/166)	(85%, 94%)

Source: Table 9-4 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA
[1]Clopper-Pearson exact 95% CI
[2]CIRRHOSIS = NO for subjects with missing cirrhosis status
[3]calculated by reviewer using Clopper-Pearson exact 95% CI

Table 71: Reviewer's Results for Subgroup Comparisons between HCV Genotype 1a and Genotype 1b in Study 110 (All Treated)

	12-Week SOF+PEG+RBV		
	Genotype 1a (n=225)	**Genotype 1b (n=66)**	**Genotype 1a vs. Genotype 1b Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	94% (76/81)	92% (11/12)	2% (-14%, 19%)
≥ 50 years old	90% (130/144)	80% (43/54)	11% (-1%, 22%)
Sex			
Male	90% (128/143)	78% (35/45)	12% (-1%, 25%)
Female	95% (78/82)	91% (19/21)	5% (-9%, 18%)
Race			
Black	91% (30/33)	77% (13/17)	14% (-8%, 37%)
Non-black	92% (176/192)	84% (41/49)	8% (-3%, 19%)
Ethnicity			
Hispanic	92% (33/36)	83.3% (5/6)	8% (-23%, 39%)
Non-Hispanic	92% (173/189)	82% (49/60)	10% (-1%, 20%)
Baseline body mass index			
< 30 kg/m^2	95% (127/134)	85% (33/39)	10% (-2%, 22%)
≥ 30 kg/m^2	87% (79/91)	78% (21/27)	9% (-8%, 26%)
Cirrhosis			
No	93% (168/180)	84% (47/56)	9% (-1%, 20%)
Yes	84% (36/43)	67% (6/9)	17% (-16%, 50%)
IL28 B			
CC	99% (71/72)	92% (12/13)	6% (-8%, 21%)
CT or TT	88% (135/153)	79% (42/53)	9% (-3%, 21%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	96% (44/46)	100% (9/9)	-4% (-2%, 10%)
≥ 6 $\log_{10}$ IU/mL	91% (162/179)	79% (45/57)	12% (0.1%, 23%)
Baseline ALT[2]			
≤ 1.5 x ULN	91% (89/98)	82% (31/38)	9% (-4%, 23%)
> 1.5 x ULN	92% (117/127)	82% (23/28)	10% (-5%, 25%)

[1]based on the Wald asymptotic confidence limits

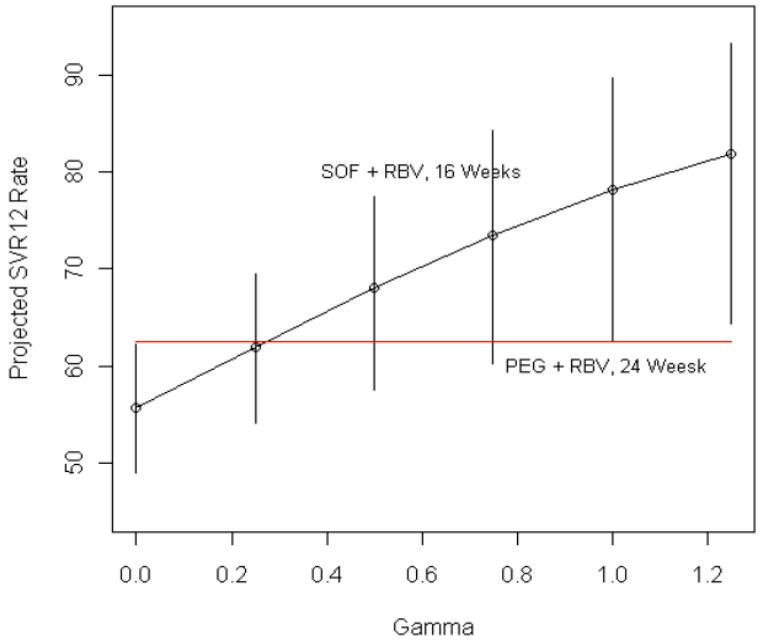
6.5 Bridging Analysis

Table 72: Applicant's Bridging Analyses Results

Study	Treatment	Estimated and Predicted SVR12 Rate (95% Credible Set) from Bayesian Model Based on Data from Studies P7977-1231 and GS-US-334-0108	Actual SVR12 Rate
Noninteraction Model			
P7977-1231	SOF+RBV for 12 weeks (Estimated)	55.7% (49%, 62.7%)	55.7%
GS-US-334-0108	SOF+RBV for 12 weeks (Estimated)	29.7% (19.8%, 40.5%)	29.7%
GS-US-334-0108	SOF+RBV for 16 weeks(Estimated)	61.9% (50.3%, 73.1%)	61.9%
P7977-1231	SOF+RBV for 16 weeks (Projected)	80.7% (66.8%, 90.5%)	NA
Interaction Model			
P7977-1231	SOF+RBV for 12 weeks (Estimated)	55.7% (49.1%, 62.3%)	55.7%
GS-US-334-0108	SOF+RBV for 12 weeks (Estimated)	29.7% (19.4%, 40.8%)	29.7%
GS-US-334-0108	SOF+RBV for 16 weeks(Estimated)	62.0% (50.1%, 73.1%)	61.9%
P7977-1231	SOF+RBV for 16 weeks (Projected)	78.2% (62.5%, 89.6%)	NA

Source: Table 1 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.

Figure 12: Applicant's Sensitivity Analysis for Impact of 16-Week Treatment Duration of SOF+RBV Using Model 2



Source: Figure 3 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.

6.6 Exploratory Analysis to Evaluate Gender Difference in SVR12 Rate for SOF+RBV among HCV Genotype 3 Subjects

Table 73: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 1231 (All Treated)

	Females (N=58)	Males (N=125)	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	71% (22/31)	49% (36/73)	22% (2%, 41%)
≥ 50 years old	70% (19/27)	48% (25/52)	22% (0.4%, 44%)
Race			
White	69% (33/48)	47% (52/110)	21% (5%, 386%)
Other	80% (8/10)	60% (9/15)	20% (-15%, 55%)
Region			
US	67% (20/30)	56% (36/64)	10% (-10%, 31%)
Non-US	75% (21/28)	41% (25/61)	34% (14%, 54%)
Ethnicity			
Hispanic	80% (4/5)	53% (10/19)	27% (-14%, 69%)
Non-Hispanic	70% (37/53)	48% (51/106)	22% (6%, 37%)
Baseline body mass index			
< 30 kg/m^2	69% (27/39)	49% (43/87)	20% (2%, 38%)
≥ 30 kg/m^2	74% (14/19)	47% (18/38)	26% (1%, 52%)
Cirrhosis			
No	43% (3/7)	32% (10/31)	11% (-30%, 51%)
Yes	75% (38/51)	54% (51/94)	20% (5%, 36%)
IL28 B			
CC	70% (14/20)	53% (29/55)	17% (-7%, 41%)
CT or TT	71% (27/38)	46% (32/70)	25% (7%, 44%)
Baseline HCV RNA			
< 6 log_{10} IU/mL	76% (26/34)	61% (30/49)	15% (-4%, 35%)
≥ 6 log_{10} IU/mL	63% (15/24)	41% (31/76)	22% (-1%, 44%)
Baseline ALT			
≤ 1 x ULN	79% (11/14)	47% (9/19)	31% (0.1%, 62%)
> 1 x ULN	68% (30/44)	49% (52/106)	19% (2%, 36%)

[1]based on the Wald asymptotic confidence limits

Table 74: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 107 (All Treated)

	Females (N=45)	Males (N=53)	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	65% (11/17)	58% (15/26)	7% (-23%, 37%)
≥ 50 years old	82% (23/28)	41% (11/27)	41% (18%, 65%)
Race			
Black	0	0	n/a
Other	76% (34/45)	49% (26/53)	27% (8%, 45%)
Region			
US	71% (25/35)	42% (16/38)	29% (8%, 51%)
Non-US	90% (9/10)	67% (10/15)	23% (-7%, 54%)
Ethnicity			
Hispanic	100% (1/1)	57% (4/7)	43% (6%, 80%)
Non-Hispanic	75% (33/44)	48% (22/46)	27% (8%, 46%)
Baseline body mass index			
< 30 kg/m^2	75% (24/32)	47% (18/38)	28% (6%, 49%)
≥ 30 kg/m^2	77% (10/13)	53% (8/15)	24% (-11%, 58%)
Cirrhosis			
No	77% (33/43)	59% (24/41)	18% (-1%, 38%)
Yes	50% (1/2)	17% (2/12)	33% (-39%, 100%)
IL28 B			
CC	72% (18/25)	59% (16/27)	13% (-13%, 38%)
CT or TT	80% (16/20)	38% (10/26)	42% (16%, 67%)
Duration of Prior HCV Trt			
No	84% (31/37)	58% (23/40)	26% (7%, 46%)
≤ 12 weeks	67% (2/3)	29% (2/7)	38% (-25%, 100%)
> 12 weeks	20% (1/5)	17% (1/6)	3% (-43%, 49%)
Interferon Class			
Ineligible	81% (17/21)	62% (16/26)	19% (-6%, 45%)
Intolerant	100% (2/2)	33% (2/6)	67% (29%, 100%)
Unwilling	68% (15/22)	38% (8/21)	30% (2%, 59%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	94% (15/16)	39% (7/18)	55% (29%, 80%)
≥ 6 $\log_{10}$ IU/mL	66% (19/29)	54% (19/35)	11% (-13%, 35%)
Baseline ALT			
≤ 1.5 x ULN	71% (12/17)	40% (6/15)	31% (-2%, 64%)
> 1.5 x ULN	79% (22/28)	53% (20/38)	26% (4%, 48%)

[1]based on the Wald asymptotic confidence limits

Table 75: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 108 (All Treated)

	Females	Males	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	100% (1/1)	21% (3/14)	79% (57%, 100%)
≥ 50 years old	40% (6/15)	26% (9/34)	15% (-15%, 42%)
Race			
White	50% (2/4)	40% (2/5)	10% (-55%, 75%)
Other	42% (5/12)	23% (10/43)	18% (-12%, 49%)
Region			
US	50% (5/10)	23% (7/31)	27% (-7%, 62%)
Non-US	33% (2/6)	29% (5/17)	4% (-40%, 47%)
Ethnicity			
Hispanic	0/0	0% (0/5)	n/a
Non-Hispanic	44% (7/16)	28% (12/43)	16% (-12%, 44%)
Baseline BMI			
< 30 kg/m^2	60% (6/10)	28% (10/36)	32% (-1%, 66%)
≥ 30 kg/m^2	17% (1/6)	17% (2/12)	0% (-37%, 37%)
Cirrhosis			
No	56% (5/9)	31% (9/29)	25% (-12%, 61%)
Yes	29% (2/7)	16% (3/19)	13% (-24%, 50%)
IL28 B			
CC	33% (2/6)	41% (7/17)	-8% (-52%, 37%)
CT or TT	50% (5/10)	16% (5/31)	34% (0.3%, 67%)
Response to prior HCV trt			
Nonresponse	33% (2/6)	22% (2/9)	11% (-35%, 58%)
Relapse/Breakthrough	50% (5/10)	26% (10/39)	24% (-10%, 58%)
Baseline HCV RNA			
< 6 log_{10} IU/mL	40% (2/5)	25% (3/12)	15% (-34%, 64%)
≥ 6 log_{10} IU/mL	45% (5/11)	25% (9/36)	20% (-12%, 53%)
Baseline ALT			
≤ 1 x ULN	100% (2/2)	40% (2/5)	60% (17%, 100%)
> 1 x ULN	36% (5/14)	23% (10/43)	12% (-16%, 41%)

[1]based on the Wald asymptotic confidence limits

Table 76: Subgroup Comparison between Females and Males in 16-Week SOF+RBV Group in Study 108 (All Treated)

	Females	Males	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	86% (6/7)	58% (7/12)	27% (-11%, 65%)
≥ 50 years old	79% (11/14)	50% (15/30)	29% (1%, 57%)
Race			
White	80% (12/15)	53% (20/38)	27% (2%, 53%)
Other	83% (5/6)	50% (2/4)	33% (-24%, 91%)
Region			
US	83% (10/12)	56% (18/32)	27% (-0.1%, 54%)
Non-US	78% (7/9)	40% (4/10)	38% (-3%, 79%)
Ethnicity			
Hispanic	0/0	57% (4/7)	n/a
Non-Hispanic	80% (16/20)	51% (18/35)	29% (4.5%, 53%)
Baseline BMI			
< 30 kg/m^2	86% (12/14)	53% (17/32)	33% (7%, 58%)
≥ 30 kg/m^2	71% (5/7)	50% (5/10)	21% (-24%, 67%)
Cirrhosis			
No	75% (12/16)	54% (13/24)	21% (-8%, 50%)
Yes	100% (5/5)	50% (9/18)	50% (27%, 73%)
IL28 B			
CC	100% (3/3)	54% (7/13)	46% (19%, 73%)
CT or TT	78% (14/18)	52% (15/29)	26% (-0.4%, 53%)
Response to prior HCV trt			
Nonresponse	63% (5/8)	44% (4/9)	18% (-29%, 65%)
Relapse/Breakthrough	92% (12/13)	55% (18/33)	38% (15%, 60%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	75% (6/8)	50% (9/18)	25% (-13%, 63%)
≥ 6 $\log_{10}$ IU/mL	85% (11/13)	54% (13/24)	30% (2%, 58%)
Baseline ALT			
≤ 1 x ULN	50% (1/2)	50% (3/6)	0% (-80%, 80%)
> 1 x ULN	84% (16/19)	53% (19/36)	31% (8%, 55%)

[1]based on the Wald asymptotic confidence limits

6.7 Adverse Events for 12-Week SOF+RBV in Studies 1231, 107 and 108

Table 77: Adverse Events for 12-Week SOF+RBV in Studies 1231, 107 and 108 (All Treated)

	Study 1231 (N=256)	Study 107 (N=207)	Study 108 (N=103)	Total (N=566)
Number (%) of Subjects Experiencing Any				
Adverse Event (AE)	220 (86)	185 (89)	92 (89)	496 (88)
Treatment-Related AE	183 (72)	150 (73)	75 (73)	408 (72)
Serious Adverse Event (SAE)	7 (3)	11 (5)	5 (5)	22 (4)
Treatment-Related SAE	1 (<1)	1 (<1)	0	2 (<1)
Grade 3 & 4 AE	18 (7)	17 (8)	8 (8)	41 (7)
Treatment-Related Grade 3 & 4 AE	8 (3)	3 (1)	4 (4)	15 (3)
AE Leading to Permanent Discontinuation from Study Drugs (Any Study Drug)	3 (1)	5 (2)	1 (1)	9 (2)
AE Leading to Permanent Discontinuation from All Study Drugs	3 (1)	4 (2)	1 (1)	8 (1)
AE Leading to Modification or Interruption of Study Drugs (Any Study Drug)	25 (10)	29 (14)	9 (9)	63 (11)
Death	1 (<1)	0	0	1 (<1)

Source: report from the medical officer, Dr. Poonam Mishra

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/s/

XIAOJING K QI
11/20/2013

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11/20/2013

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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

Addendum

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	204671
Supplement #:	0000
Drug Name:	Sofosbuvir
Indication(s):	Treatment of chronic hepatitis C for adults
Applicant:	Gilead Sciences, Inc.
Date(s):	Original NDA Submitted Date: April 8, 2013
	Additional Studies Submitted Date: October 9, 2013
	PDUFA date: December 6, 2013
Review Priority:	Priority
Biometrics Division:	DB4
Statistical Reviewer:	Karen Qi, Ph.D.
Concurring Reviewers:	Wen Zeng, Ph.D.
Medical Division:	Antiviral
Clinical Team:	Poonam Mishra, MD
Project Manager:	Linda Onaga, M.P.H.

Keywords:

Clopper-Person exact confidence interval, logistic regression, odds ratio, relative risk

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1 EXECUTIVE SUMMARY

Gilead submitted four Phase 3 trials in the original NDA to support the use of a sofosbuvir (SOF)-involved regimen for the treatment of subjects infected with genotype 1, 2, 3, 4, 5, or 6 hepatitis C virus (HCV). The four studies were Study US-334-0110 (Study 110), Study P7977-1231 (Study 1231), Study US-334-0107 (Study 107) and Study US-334-0108 (Study 108). I have completed the NDA review including an evaluation of these studies. Also, the results from the studies were presented at the Antiviral Drugs Advisory Committee (AC) Meeting held on October 25, 2013.

This is an addendum to the statistical review. The addendum includes the review of Study GS-US-334-0133 (Study 133) and Study GS-US-334-0123 (Study 123), both submitted late in the review cycle. The addendum also includes a summary of the analyses to explore the extension of 12 weeks of SOF in combination with a pegylated interferon and ribavirin (SOF+PEG+RBV) in the HCV genotype 1 treatment-naïve subjects to the HCV genotype 1 PEG+RBV treatment-experienced population. The exploratory analyses were discussed at the AC meeting.

Study 133 was a non-IND European study. The study originally was a Phase 3, randomized, double-blind and placebo-controlled trial to evaluate the efficacy and safety of 12 weeks of SOF+RBV in HCV genotype 2 or 3 subjects versus placebo. During the treatment phase, the emerging data from Study 108 implied that the longer treatment duration of SOF in combination with RBV (SOF+RBV) could benefit HCV genotype 3 subjects. Therefore, the study was amended to extend the treatment duration from 12 to 24 weeks for the HCV genotype 3 subjects who were initially randomized to receive 12 weeks of treatment with SOF+RBV. The study amendment also discontinued the subjects initially randomized to the placebo group and offered them the SOF+RBV treatment under a separate protocol. Hence, the study became an open-label study and was no longer placebo-controlled after the amendment. The study demonstrated that 12 weeks of SOF+RBV treatment resulted in a high sustained virologic response below lower limit of quantitation (LLOQ) 12 weeks after the end of treatment (SVR12) rate for the HCV genotype 2 subjects, which was consistent with that observed in Studies 1231 and 108. More importantly, 24 weeks of SOF+RBV treatment appeared to have a better SVR12 rate and a lower relapse rate in the HCV genotype 3 subjects than the rates observed with the 12- and 16-week treatment durations evaluated in Studies 1231 and 108. The study results were presented at the AC meeting, and the AC members unanimously voted to support the use of SOF+RBV treatment for 24 weeks in HCV genotype 3 population.

Study 123 investigated the SOF+RBV regimen in subjects with genotype 1, 2 or 3 HCV infection and HIV-1 co-infection. The study consisted of three treatment groups including 12 weeks of SOF+RBV in the HCV genotype 2 or 3 treatment-naïve subjects (i.e., Group 1), 24 weeks of SOF+RBV in HCV genotype 2 or 3 treatment-experienced subjects (i.e., Group 2), and 24 weeks of SOF+RBV in HCV genotype 1 treatment-naïve subjects (i.e., Group 3). At the time of the submission, all subjects in Groups 1 and 3 and approximately two-thirds of the subjects in Group 2 completed post-treatment follow-up through the timing of the primary efficacy endpoint of SVR12 or prematurely discontinued study. The study results were consistent with that

observed in other Phase 3 trials for the HCV mono-infection. The 12 weeks of SOF+RBV treatment led to an 88% SVR12 rate in the genotype 2 treatment-naïve subjects, but only a 67% SVR12 rate in the genotype 3 treatment-naïve subjects with a 29% relapse rate. The SVR12 rate for the 24 weeks SOF+RBV treatment in genotype 1a treatment-naïve subjects was 82%, whereas the SVR12 rate was only 54% in genotype 1b treatment-naïve subjects with a 42% relapse rate. For the partial data submitted for the 24-week SOF+RBV regimen in genotype 2 or 3 treatment-experienced subjects, the SVR12 rates were above 90% for both genotypes. In the study, the SOF+RBV regimen did not appear to have an impact on HIV viral load since the majority of the subjects who had baseline HIV viral load below 50 copies/mL maintained their HIV viral suppression at the end of treatment. Also, the SOF+RBV regimens resulted in decreased total CD4 counts, which could be caused by RBV. However, the CD4 counts bounced back after the treatment was terminated. Meanwhile, the percentage of CD4 cells remained relatively stable.

Finally, the addendum summarizes the exploratory analyses performed to bridge the use of 12 weeks of SOF+PEG+RBV in the HCV genotype 1 treatment-naïve subjects to the HCV genotype 1 PEG+RBV treatment-experienced population. Study 110 which was submitted in the original NDA submission resulted in an 89% SVR12 rate for the 12-week SOF+PEG+RBV treatment regimen in the HCV genotype 1 treatment-naïve subjects. Late in the review cycle, the review team discussed extensively whether the high SVR rate observed in Study 110 could be utilized as evidence to support use of the SOF regimen in the HCV genotype 1 PEG+RBV treatment-experienced population even though there were no data from SOF studies. This exploration was deemed important since the regimen may offer an important treatment option for HCV genotype 1 PEG+RBV treatment-experienced patients.

Several exploratory analyses were performed to predict the SVR rate for 12-week SOF+PEG+RBV in genotype 1 PEG+RBV treatment-experienced population. The pharmacometrics reviewer, Dr. Jeff Florian, conducted an exploratory analysis that predicted the SVR rate for the SOF regimen in the prior PEG+RBV partial and null responders using the SVR rate in the harder-to-treat subset among the genotype 1 treatment-naïve subjects in Study 110. The statistical team also conducted two exploratory analyses. The first analysis used the SVR rate for the PEG+RBV treatment regime observed in historical trials. The second analysis extrapolated the predicted SVR rate for the prior PEG+RBV null responders based on the assumption of equivalent odds ratios or relative risks between the treatment-naïve subjects and prior PEG+RBV null responders in the SOF regimen and previous HCV programs.

The exploratory analyses resulted in predicted SVR rates for the treatment-experienced population that ranged from 52% to 81%; however, all of the analyses were based on various assumptions. The collective review team will need to weigh the benefits and risks of the use of the regimen in genotype 1 treatment-experienced patients.

2 INTRODUCTION

2.1 Overview

Sofosbuvir is a novel nucleotide analogue inhibitor of the HCV NS5B protein to prevent viral replication. The SOF-containing treatment regimens were shown to be an effective and safe alternative to current standard of care regimens from the early phase studies, and therefore the regimens were considered to be breakthrough therapies. The Antiviral Division granted Fast Track designation in August of 2010.

The results of the four phase 3 studies in the original NDA submission as well as the results of Study 133 included submitted late in the review cycle were presented at the AC meeting. The AC members unanimously voted to support use of SOF+RBV treatment for 12 weeks in the HCV genotype 1 or 4 treatment-naïve subjects, use of SOF+RBV treatment for 12 weeks in the HCV genotype 2 subjects, and use of SOF+RBV treatment for 24 weeks in the HCV genotype 3 subjects.

This review focused on the efficacy of the two additional Phase 3 studies, Studies 133 and 123, submitted late in the review cycle. Table 1 summarizes the key elements of the study design for each study.

Table 1: List of All Phase 3 Studies Included in Review

Study Number	Phase and Design	Study Population	Treatment Arms and Number of Enrolled Subjects per Arm
GS-US-334-0133 (Study 133) (Valence)	The original design was a Phase 3, randomized, double-blind and placebo-controlled, European study. The study was later changed to be an open-label observational study without placebo-control.	treatment-naïve and treatment-experienced subjects with chronic genotype 2 or 3 HCV infection	The treatment arms listed below were after changes to the original study design. • 12-week SOF+RBV in the HCV genotype 2 subjects, N=73 • 24-week SOF+RBV in the HCV genotype 3 subjects, N=250 • 12-week SOF+RBV in the HCV genotype 3 subjects, N=11

(to be continued)

Table 1: List of All Phase 3 Studies Included in Review (continued)

Study Number	Phase and Design	Study Population	Treatment Arms and Number of Enrolled Subjects per Arm
GS-US-334-0123 (Study 123) (Photon)	Phase 3, observational study	Subjects with genotype 1, 2 or 3 HCV infection and HIV-1 co-infection	Group 1: 12-week SOF+RBV in treatment-naïve subjects co-infected with genotype 2 or 3 HCV and HIV, N=68 Group 2: 24-week SOF+RBV in treatment-experienced subjects co-infected with genotype 2 or 3 HCV and HIV, N=41 Group 3: 24-week SOF+RBV in treatment-naïve subjects co-infected with genotype 1 HCV and HIV, N=114

2.2 Data Sources

The data were submitted electronically and are located in \\CDSESUB1\evsprod\NDA204671\0035. The proposed label discussed in Section 5.4 is located in \\CDSESUB1\evsprod\NDA204671\0047.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Due to time constraints, the applicant only submitted partial raw and derived datasets which enabled the review of the efficacy and safety of the studies. Overall, the data quality was good.

3.2 Evaluation of Efficacy

Because the two studies had different patient populations, the statistical reviewer will present the review results for each study individually in the following sections.

3.2.1 Study 133

3.2.1.1 Study Design and Endpoints

Study 133 was a non-IND European study. The study originally was a phase 3 randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the treatment regimen of SOF+RBV for 12 weeks compared with placebo in treatment-naïve or treatment-experienced subjects with chronic genotype 2 or 3 HCV infection.

Initially, the subjects were randomized in a 4:1 ratio to the following two groups:

1) 12-week SOF+RBV: SOF 400 mg once daily (QD) plus RBV 1000 to 1200 mg (based on baseline body weight) twice daily (BID) for 12 weeks;

2) placebo: matching SOF placebo QD plus RBV placebo BID.

The randomization was stratified by prior treatment experience (naïve vs. experienced) and cirrhosis status at screening (presence vs. absence).

During the treatment phase of the study, the emerging data from Study 108 suggested that the HCV genotype 3 subjects could benefit from longer treatment duration. Therefore, the treatment duration was extended from 12 to 24 weeks for the genotype 3 subjects who were randomized to receive 12 weeks of SOF+RBV and had not completed the 12 weeks of treatment course. Also, all the placebo subjects were discontinued from the study and offered treatment with SOF+RBV under Study GS-US-334-0109. Specifically, the following changes were made to the study in Amendment 2 of the protocol.

- The 73 HCV genotype 2 subjects initially randomized to the 12-week SOF+RBV group completed 12 weeks of treatment and follow-up visits as originally planned.

- The treatment duration for SOF+RBV for the 250 HCV genotype 3 subjects initially randomized to the 12-week SOF+RBV group was extended to 24 weeks for those who had not completed 12 weeks of treatment.

- The 11 HCV genotype 3 subjects initially randomized to the 12-week SOF+RBV who had already completed 12 weeks of treatment with SOF+RBV or who had prematurely discontinued treatment continued to complete the follow-up visits as originally planned.

- The 85 subjects who were initially randomized into the placebo group were discontinued from the study and offered the SOF+RBV treatment under Study GS-US-334-0109.

The study became an observational trial and was no longer blinded after the changes. Also, all placebo subjects were discontinued from the study without having the follow-up HCV RNA measurements to calculate the primary efficacy endpoint of SVR12. Thus, the study was not placebo-controlled following the amendment. The primary objective was switched to estimate the efficacy for the two main groups in the study, i.e., the SOF+RBV treatment for 12 weeks in HCV genotype 2 subjects, and the SOF+RBV treatment for 24 weeks in HCV genotype 3 subjects. Table 27, Table 28 and Table 29 in Section 6.1 provide the study procedures and assessments.

The primary efficacy endpoint was the SVR12 rate defined as the proportion of subjects with HCV RNA < LLOQ 12 weeks after the last dose of the study drug.

The secondary efficacy endpoints included the following:

- proportion of subjects who attain SVR at 4 and 24 weeks after stopping therapy, defined as HCV RNA < LLOQ (i.e., < 25 IU/mL) 4 and 24 weeks after stopping treatment (SVR4 and SVR24)

- proportion of subjects with HCV RNA below LLOQ (i.e., < 25 IU/mL) by study visit HCV RNA (log_{10} IU/mL) and change from baseline in HCV RNA (log_{10} IU/mL) through Week 8

- proportion of subjects with virologic failure defined as follows:

  — on-treatment virologic failure

    - 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 (i.e., breakthrough)

    - > 1 log_{10}IU/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 on-treatment measurement with no subsequent follow up values (i.e., rebound)

    - HCV RNA persistently ≥ LLOQ through 8 weeks of treatment (i.e., nonresponse)

  — relapse

    - HCV RNA ≥ LLOQ during the post-treatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available post-treatment measurement

3.2.1.2 Statistical Methodologies

A. Efficacy Analysis

The proportion of subjects achieving SVR12 in each SOF+RBV treatment regimen along with the exact 95% confidence interval (CI) was constructed using the Clopper-Pearson method.

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 visit windows during the treatment period were calculated from the first dose of

study drug (i.e., study day = collection date – date of the first dose; +1 if result is ≥0), while the windows after treatment 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 data in the statistical analysis plan (SAP) as follows:

> When the calculated IU/mL is within the linear range of the assay, then the result will be reported as "<< numeric value>> IU/mL". This result will be referred to in this document as the numeric result or as "≥ LLOQ detected" for the categorical result.
>
> When HCV RNA is not detected, the result is reported as "HCV RNA not detected" or "target not detected". This result will be referred to in this document as "< LLOQ target not detected" or "< LLOQ TND".
>
> When the calculated HCV RNA IU/mL is below LLOQ of the assay, the result is reported as "< 25 IU/mL, HCV RNA detected". This result will be referred to in this document as "< LLOQ detected".
>
> For numerical HCV RNA data, values below LLOQ will be set to the LLOQ minus 1 (i.e., 24 HCV RNA IU/mL). HCV RNA values returned as "target not detected" will also be set to 24 IU/mL.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows the patient disposition for Study 133. A total of 419 subjects were originally randomized in the study and received at least one dose of study drug. All of the 73 HCV genotype 2 subjects in the 12-week SOF+RBV group completed the treatment and stayed in the study. Among the 250 HCV genotype 3 subjects who received SOF+RBV for 24 weeks, only 2% of them discontinued the study medication. Ninety-five percent of the 85 placebo subjects discontinued the placebo treatment early and switched to receive SOF+RBV in a separate study.

Table 2: Patient Disposition in Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)	Genotype 2/3 Placebo (N=85)
Number of enrolled and treated	73 (100%)	250 (100%)	11 (100%)	85 (100%)
Discontinued study treatment	0	99 (2%)	99 (27%)	81 (95%)
Adverse event	0	1 (<1%)	1 (9%)	1 (1%)
Terminated by sponsor	0	0	0	79 (93%)
Subject withdrew consent	0	2 (1%)	2 (18%)	0
Lost to follow-up	0	1 (<1%)	0	1 (1%)
Discontinued study[1]				
Adverse event	0	1 (<1%)	1 (9%)	1 (1%)
Efficacy failure	0	17 (7%)	99 (27%)	0
Terminated by sponsor	0	1 (<1%)	0	83 (98%)
Subject withdrew consent	0	0	2 (18%)	0
Lost to follow-up	0	1 (<1%)	0	1 (1%)

Source: Table 1 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]summarized by the statistical reviewer

Table 30 and Table 31 in Section 6.1 summarize patient demographics and baseline disease characteristics.

Among the 73 HCV genotype 2 subjects who received 12 weeks of SOF+RBV, the mean age (SD) was 58 (10) years old. Fifty-five percent of the subjects were male, 89% were white, and 89% were non-Hispanic. They were from nine European countries. The mean BMI (SD) at baseline was 26 (4) kg/m^2. Fifty-six percent of the subjects were treatment-experienced and 44% were treatment-naïve. The majority (86%) did not have cirrhosis at baseline. Approximately one-third of the subjects had CC IL28B alleles. The majority of the subjects (78%) had baseline viral load ≥ 6 log10 IU/mL. Approximately half of the subjects had ALT > 1.5 x ULN at baseline.

Among the 250 HCV genotype 3 subjects who received 24 weeks of SOF+RBV, the average age (SD) was 48 (10) years old. The majority of them were male (62%), white (94%) and non-Hispanic (81%). The subjects were from 10 European countries. The mean BMI (SD) was 25 (4) kg/m^2. Fifty-eight percent of them were treatment-experienced, and 42% were treatment-naïve. Approximately 77% of the subjects did not have cirrhosis at baseline, and 68% had non-CC IL28B. The majority had baseline viral load ≥ 6 log_{10} IU/mL (71%) and baseline ALT > 1.5 x ULN (74%).

3.2.1.4 Results and Conclusions

A. Primary Efficacy Endpoint

Table 3 and Table 4 display the applicant's results which the reviewer had verified. The SVR rate was 93% in HCV genotype 2 subjects receiving 12 weeks of SOF+RBV (Table 3), with 97% in the genotype 2 treatment-naïve subjects and 90% in the genotype treatment-experienced subjects (Table 4). These high SVR rates were consistent with that observed in the subjects infected with genotype 2 HCV who received 12 weeks of SOF+RBV treatment in Studies 1231, 107 and 108 reviewed previously. The detailed discussion of the SVR12 rates for the SOF+RBV treatment regimen in HCV genotype 2 subjects among the phase 3 studies are presented in Sections C1 and C2 below.

The HCV genotype 3 subjects receiving 24 weeks of SOF+RBV had an 84% SVR rate (Table 3). Furthermore, the SVR rates were 93% in the genotype 3 treatment-naïve subjects and 77% in the genotype 3 treatment-experienced subjects. As expected, the 24-week treatment duration resulted in better SVR rates than seen with the shorter treatment durations (i.e., 12 and 16 weeks) in Studies 1231, 107 and 108. The detailed discussion of the SVR12 rates for different treatment durations of SOF+RBV treatment in HCV genotype 3 subjects are presented in Sections C3 and C4 below.

For the group of the HCV genotype 3 subjects receiving 12-week SOF+RBV, the sample size was too small to make an informative conclusion.

Table 3: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)
SVR12	93% (68/73)	84% (210/250)	27% (3/11)
95% CI[1]	(85%, 98%)	(79%, 88%)	(6%, 61%)

Source: Table 3 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]based on the Clopper-Pearson method

Table 4: Applicant's Results for SVR12 Rates by Treatment Experience in Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)
Treatment-naïve	97% (31/32)	93% (98/105)	0% (0/2)
95% CI[1]	(84%, 99.9%)	(87%, 97%)	(0%, 84%)
Treatment-experienced	90% (37/41)	77% (112/145)	33% (3/9)
95% CI[1]	(77%, 97%)	(70%, 84%)	(7%, 70%)

Source: Table 5 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]based on the Clopper-Pearson method

Of note, the study was a non-IND European trial. Study 1231 was the only Phase 3 study consisting of subjects in European sites. Although the study only included 24 genotype 3

treatment-naïve subjects from Europe and the sample size was small, the US subjects tended to have numerically better SVR12 rates than European subjects in both 12-week SOF+RBV (i.e., 60% in US vs. 27% in Europe) and 24-week PEG+RBV (62% in US vs. 56% in Europe) treatment arms. This may alleviate the concern that the European study may have overestimated SVR rate.

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

In the analysis of the on-treatment virologic responses, the reviewer used the noncompleter=failue (NC=F) approach to impute the missing data. This approach was applied in the phase 3 studies previously reviewed. The following rules were used in the NC=F analysis.

1) subjects who prematurely discontinued the study drugs were considered as failures regardless of the reasons for discontinuation;

2) the viral load at the next visit was carried backward to impute the intermittent missing value.

Figure 1: and Table 5 display the reviewer's results for the on-treatment virologic responses. Like other SOF studies, the SOF+RBV treatment rapidly suppressed HCV viral load in both HCV genotypes 2 and 3 subjects. Almost all subjects had HCV RNA below LLOQ after receiving the treatment for 4 weeks. The high response rates were sustained through the end of treatment (EOT) in the genotype 2 subjects receiving 12 weeks of SOF+RBV and genotype 3 subjects receiving 24 weeks of SOF+RBV. The response rates for the 11 HCV genotype 3 subjects who received 12 weeks of SOF+RBV dropped from 100% at Week 4 to 73% at the EOT. The sample size in this group was too small to be conclusive.

Figure 1: Reviewer's Results for On-Treatment Response Rates for 12-Week SOF+RBV for Genotype 2 Subjects and 24-Week SOF+RBV for Genotype 3 Subjects in Study 133 (NC=F)

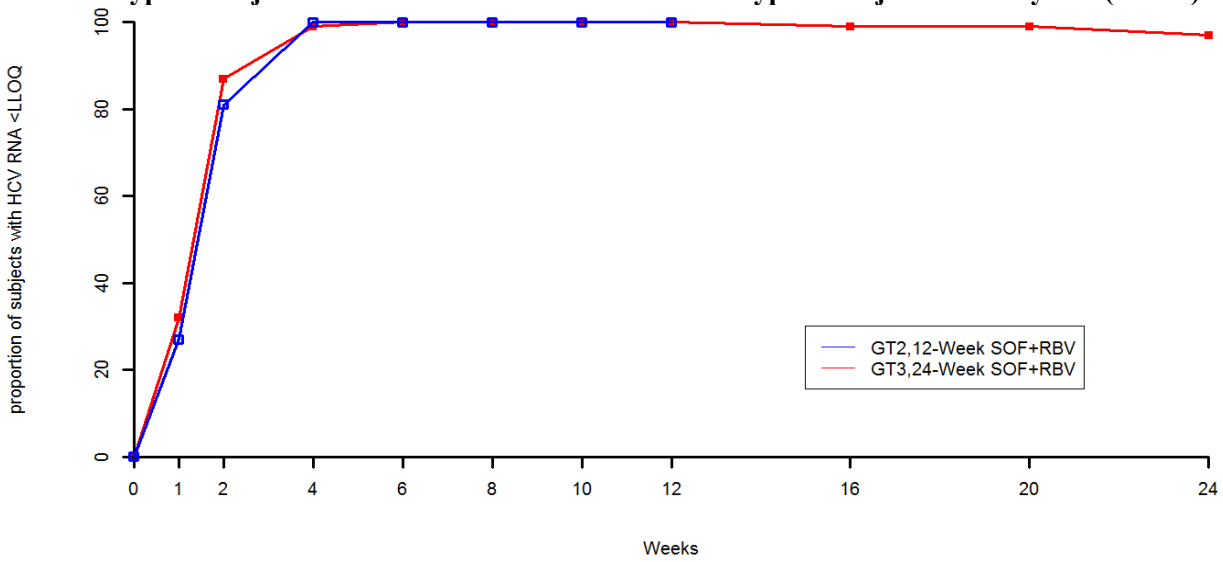


Table 5: Reviewer's Results for on-Treatment Virologic Responses in Study 133 (NC=F)

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)
Week 1	37% (27)	32% (80)	36% (4)
Week 2	81% (59)	87% (217)	55% (6)
Week 4	100% (73)	99% (247)	100% (11)
Week 6	100% (73)	100% (250)	91% (10)
Week 8	100% (73)	100% (250)	82% (9)
Week 10	100% (73)	100% (250)	82% (9)
Week 12	100% (73)	100% (250)	73% (8)
Week 16	n/a	99% (248)	n/a
Week 20	n/a	99% (248)	n/a
Week 24	n/a	97% (243)	n/a

Also, among the subjects who received SOF-containing regimen, only one HCV genotype 3 subject who received 24 weeks of SOF+RBV experienced on-treatment virologic failure.

B2. Post-Treatment Relapses

Table 6 summarizes the post-treatment relapse rates at the follow-up visits. The relapses usually occurred 4 weeks after the end of treatment. The relapse rates in the treatment-experienced subjects were higher compared with the treatment-naïve subjects. Also, the relapse rate at Week 12 post-treatment in the HCV genotype 3 subjects receiving 24 weeks of SOF+RBV was as high as 20%.

Table 6: Reviewer's Results for Post-Treatment Relapse in Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)
Overall			
by 4 weeks post-treatment	7% (5/73)	11% (27/249)	45% (5/11)
by 12 weeks post-treatment	7% (5/73)	14% (34/249)	55% (6/11)
Treatment-naïve			
by 4 weeks post-treatment	3% (1/32)	5% (5/105)	100% (2/2)
by 12 weeks post-treatment	3% (1/32)	5% (5/105)	100% (2/2)
Treatment-experienced			
by 4 weeks post-treatment	10% (4/41)	15% (22/144)	33% (3/9)
by 12 weeks post-treatment	10% (4/41)	20% (29/144)	44% (4/9)

B3. Virologic Responses at End of Treatment (EOT) and Sustained Virologic Response (SVR) after Treatment

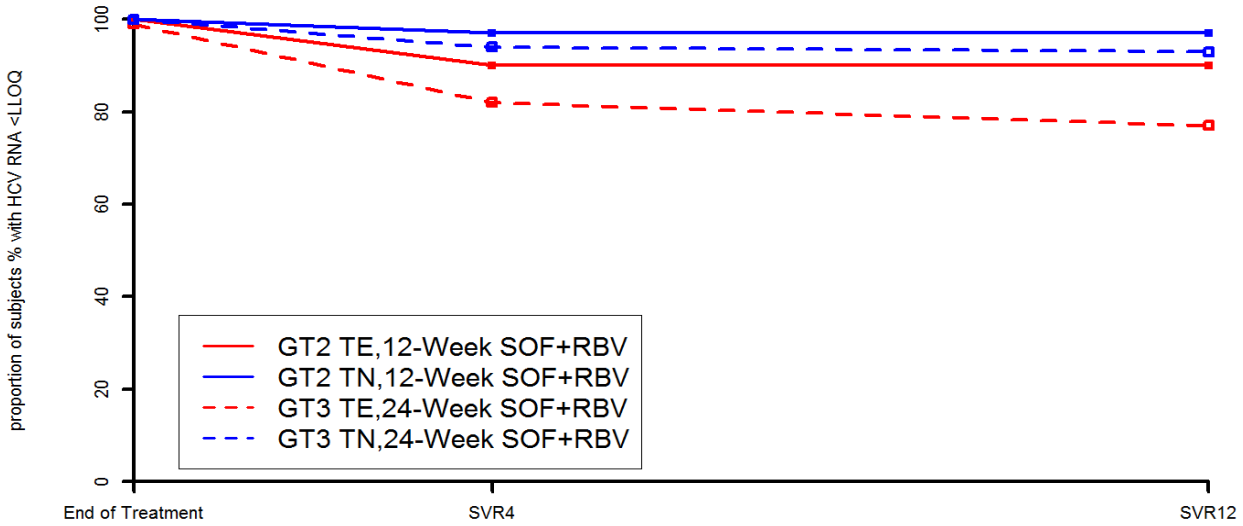
As shown in Table 7 below, almost all subjects achieved HCV RNA below LLOQ at the EOT. For the HCV genotype 2 subjects in the 12-week SOF+RBV treatment group, the SVR rates remained above 90% regardless of prior PEG+RBV treatment history. For the HCV genotype 3 subjects in the 24-week SOF+RBV treatment group, the SVR rates were higher in the treatment-naïve subjects compared to the treatment-experienced subjects. Also, the relapses described in the previous section attributed to most treatment failures.

Table 7: Reviewer's Results for Response Rates at EOT and Post-Treatment Visits in Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)
Overall[1]			
EOT	100% (73/73)	99.6% (249/250)	100% (11/11)
SVR4	93% (68/73)	87% (218/250)	45% (5/11)
SVR12	93% (68/73)	84% (210/250)	27% (3/11)
Treatment-naïve			
EOT	100% (32/32)	100% (105/105)	100% (2/2)
SVR4	97% (31/32)	94% (99/105)	0% (0/2)
SVR12	97% (31/32)	93% (98/105)	0% (0/2)
Treatment-experienced			
EOT	100% (41/41)	99% (144/145)	100% (9/9)
SVR4	90% (37/41)	82% (119/145)	56 % (5/9)
SVR12	90% (37/41)	77% (112/145)	33% (3/9)

[1]also reported in Table 3 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013

Figure 2: Reviewer's Results for Response Rates at EOT and Post-Treatment Visits for 12-Week SOF+RBV for Genotype 2 Subjects and 24-Week SOF+RBV for Genotype 3 Subjects



C. Exploratory Analysis Examining SVR12 rates for SOF+RBV Treatment Regimen Among Studies 1231, 108 and 133

Study 1231 evaluated the 12 weeks of SOF+RBV treatment regimen in treatment-naïve subjects with genotype 2 or 3 HCV infection, while Study 108 investigated 12 and 16 weeks of SOF+RBV in treatment-experienced subjects with genotype 2 or 3 HCV infection. Statistical review of both studies was presented in the original review of the NDA. In this section, the reviewer performed exploratory analyses to examine the SVR12 rates for different treatment durations of SOF+RBV observed in HCV genotype 2 or 3 subjects in Studies 1231, 108 and 133.

C1. SOF+RBV Regimen in HCV Genotype 2 Treatment-Naïve Subjects in Studies 1231 and 133

The 12 weeks of SOF+RBV treatment in HCV genotype 2 treatment-naïve subjects was evaluated in Studies 1231 and 133. Both studies resulted in high SVR12 rates (Table 8). The rates were also similar in all the subgroups in the two studies (Table 32 in Section 6.1).

Table 8: Reviewer's Results for SVR12 in HCV Genotype 2 Treat-Naïve Subjects Receiving 12 Weeks of SOF+RBV in Studies 1231 and 133

	GT2 TN 12-Week SOF+RBV	
	Study 1231 (N=73)	**Study 133 (N=32)**
SVR12 - % (n) **95% CI[1]**	95% (69) (87%, 98%)	97% (31) (84%, 99.9%)

[1]based on Clopper-Pearson method

C2. SOF+RBV Regimen in HCV Genotype 2 Treatment-Experienced Subjects in Studies 108 and 133

The 12 and 16 weeks of SOF+RBV treatment regimens were investigated in HCV genotype 2 treatment-experienced subjects in Study 108, and the 12-week treatment duration was also evaluated in Study 133. The SVR12 rates for the 12-week SOF+RBV treatment in both studies were comparable to the 16 weeks of SOF+RBV regimen (Table 9). Similar results were observed for the rates in the subgroups shown in Table 33 in Section 6.1. The analysis results suggested that the 12-week SOF+RBV may be sufficient to treat the treatment-experienced subjects infected with genotype 2 HCV.

Table 9: Reviewer's Results for SVR12 in HCV Genotype 2 Treat-Experienced Subjects Receiving SOF+RBV in Studies 108 and 133

	Study 108		Study 133
	12-Week SOF+RBV	**16-Week SOF+RBV**	**12-Week SOF+RBV**
SVR12 - % (n) **95% CI[1]**	82% (32/39) (66%, 92%)	89% (31/35) (73%, 97%)	90% (37/41) (77%, 97%)

[1]Clopper Pearson 95% CI

C3. SOF+RBV Regimen in HCV Genotype 3 Treatment-Naïve Subjects in Studies 1231 and 133

The 12 weeks of SOF+RBV in the treatment-naïve subjects infected with genotype 3 HCV was evaluated in Study 1231 and the 24-week treatment duration was assessed in Study 133. As discussed in the previous statistical review for the original submission, use of 12-week SOF+RBV treatment appeared insufficient for the HCV genotype 3 treatment-naïve subjects. In Study 133, 24 weeks of SOF+RBV resulted in a better SVR12 rate than that seen with the 12 week treatment duration, i.e., 93% vs. 56% (Table 10). This may imply that the HCV genotype 3 treatment-naïve subjects should use SOF+RBV for 24 weeks.

Table 10: Reviewer's Results for SVR12 in HCV Genotype 3 Treatment-Naïve Subjects Receiving SOF+RBV in Studies 1231 and 133

	Study 1231 12-Week SOF+RBV (N=183)	**Study 133 24-Week SOF+RBV (N=105)**	**12-Week SOF+RBV vs. 24-Week SOF+RBV Prop Diff (95% CI)**
SVR12 - % (n)	56% (102)	93% (98)	-38% (-46%, -29%)
95% CI[1]	(48%, 63%)	(87%, 97%)	

[1]Clopper Pearson 95% CI

Since the 12-week and 24-week SOF+RBV treatment regimens were not evaluated in the same study, there was a concern that the observed difference in SVR12 rates may be due to the different baseline characteristics in the two studies. Hence, the reviewer developed a logistic regression model to evaluate whether the prolonged treatment duration had an improved impact on SVR12 after adjusting for the baseline covariates using the data from both Studies 133 and 1231. Besides the indicator for the treatment duration, the following baseline covariates were included in the model: age (<50 years, ≥50 years), sex (female, male), BMI (<30 kg/m^2, ≥30 kg/m^2), cirrhotic status (yes, no), IL28B (CC, non-CC), baseline HCV RNA (<6 $\log_{10}$ IU/mL, ≥6 $\log_{10}$ IU/mL), baseline ALT (≤1.5xULN, >1.5xULN). Moreover, the reviewer used a stepwise procedure to select the variables at the significant level of 0.05.

The parsimonious model included sex, cirrhotic status, baseline HCV RNA and treatment duration. The odds ratio adjusted by sex, cirrhotic status and baseline HCV RNA was estimated to be approximately 12 with a 95% CI of (5, 28). That is, after considering sex, baseline cirrhotic status and HCV viral load, the odds of achieving SVR12 for the subjects receiving 24 week of SOF+RBV was 12 times higher than that for the subjects receiving 12 weeks of SOF+RBV.

C4. SOF+RBV Regimen in HCV Genotype 3 Treatment-Experienced Subjects in Studies 108 and 133

The 12 and 16 week SOF+RBV regimens in treatment-experienced subjects were investigated in Study 108, and the 24 week duration was evaluated in Study 133. As shown in Table 11, the SVR12 rates increased with the treatment duration. The 24-week SOF+RBV regimen had a higher SVR12 rate than that seen for the16-week SOF+RBV regimen (Table 12).

Table 11: Reviewer's Results for SVR12 in HCV Genotype 3 Treatment-Experienced Subjects Receiving SOF+RBV in Studies 108 and 133

	Study 108		Study 133
	12-Week SOF+RBV (N=64)	16-Week SOF+RBV (N=63)	24-Week SOF+RBV (N=145)
SVR12 - % (n) **95% CI[1]**	30% (19) (19%, 42%)	62% (39) (49%, 74%)	77% (112) (70%, 84%)

[1]Clopper Pearson 95% CI

Table 12: Reviewer's Results for SVR12 for 16-Week and 24-Week SOF+RBV in HCV Genotype 3 Treatment-Experienced Subjects in Studies 108 and 133

	Study 108 16-Week SOF+RBV (N=63)	Study 133 24-Week SOF+RBV (N=145)	16-Week SOF+RBV vs. 24-Week SOF+RBV Prop Diff (95% CI)
SVR12 - % (n) **95% CI[1]**	62% (39) (49%, 74%)	77% (112) (70%, 84%)	-15% (-29%, -2%)

[1]Clopper Pearson 95% CI

Similar to the analysis described in Section C3, the reviewer employed logistic regression using the data from Studies 108 and 133 to evaluate the difference in SVR12 rates between 24-week SOF+RBV and 16-week SOF+RBV in HCV genotype 3 treatment-experienced subjects adjusted for the baseline characteristics. Besides the variables listed in Section C3 for the HCV genotype 3 treatment-naïve subjects, the PEG+RBV treatment experience (i.e., IFN intolerant/relapse/breakthrough, null response) and study (Study 108, Study 133) were included in the model selection as well.

The parsimonious model included sex, cirrhotic status, and treatment duration. The odds ratio of 24-week SOF+RBV over 16-week SOF+RBV adjusted by sex and cirrhotic status was approximately 2.1 with a 95% CI of (1.1, 4.1).

In summary, use of SOF+RBV for 24 weeks in HCV genotype 3 treatment-experienced resulted in a higher SVR12 rate than the 16 week treatment duration. However, as discussed in Section B2, the 24-week SOF+RBV still had an approximate 20% relapse rate in the HCV genotype 3 treatment-experienced subjects.

3.2.2 Study 123

3.2.2.1 Study Design and Endpoints

Study 123 was a Phase 3, open-label, multicenter trial to evaluate the efficacy and safety of SOF+RBV in the subjects with genotype 1, 2 or 3 HCV infection and HIV-1 co-infection. There was no pre-specified hypothesis testing in the study. A total of 223 subjects were enrolled in the following three groups depending on their HCV genotypes and prior treatment experience with PEG+RBV:

1) 12-week SOF+RBV treatment-naïve HCV genotype 2 or 3 (Group 1): treatment-naïve subjects with genotype 2 or 3 HCV infection received SOF 400 mg administered once daily + RBV total daily dose of 1000 or 1200 mg administered in a divided daily dose for 12 weeks;

2) 24-week SOF+RBV treatment-experienced HCV genotype 2 or 3 (Group 2): treatment-experienced subjects with genotype 2 or 3 HCV infection received SOF 400 mg administered once daily + RBV total daily dose of 1000 or 1200 mg administered in a divided daily dose for 24 weeks;

3) 24-week SOF+RBV treatment-naïve HCV genotype 1 (Group 3): treatment-naïve subjects with genotype 1 HCV infection received SOF 400 mg administered once daily + RBV total daily dose of 1000 or 1200 mg administered in a divided daily dose for 24 weeks.

The study procedures are displayed in Table 37, Table 38 and Table 39 in Section 6.2. The total time to complete all study visits was approximately 40 weeks including:

- 28 day (4 week) screening period
- 12 week treatment period
- Up to 24 week post-treatment period

All subjects completed screening, on-treatment and post-treatment assessments. Screening assessments were completed within 28 days of the Baseline/Day 1 visit. All subjects completed a 4-Week Post-Treatment visit regardless of treatment duration. Subjects with HCV RNA < LLOQ at the 4-Week Post-Treatment Visit completed 12-Week and 24-Week Post-Treatment visits unless confirmed viral relapse occurred.

The following on-treatment HCV virologic response-based treatment stopping criteria were utilized for all subjects:

- Confirmed HCV RNA ≥LLOQ after 2 consecutive HCV RNA <LLOQ
- Confirmed >1 log10 increase from nadir
- HCV RNA ≥LLOQ through 8 weeks of treatment

Confirmation should be performed as soon as possible but within 2 weeks after determination of initial observation.

Subjects who met the criteria listed below were considered to have HIV virologic rebound:

- At any visit, have at least two consecutive plasma HIV-1 RNA levels ≥ 50 copies/mL (at least two weeks apart)

Following the unconfirmed HIV virologic rebound, subjects were asked to return to the clinic for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV

virologic rebound was confirmed at the scheduled or unscheduled visit, then the blood samples from this visit were used for HIV-1 genotype/phenotype testing if the HIV-1 RNA was ≥ 400 copies/mL. Plasma samples with < 400 copies/mL of HIV-1 RNA were analyzed as the protease/reverse transcriptase genotype/phenotype assays used in this study were not validated when plasma HIV-1 RNA levels are < 400 copies/mL.

These criteria only applied to subjects currently on ARV treatment and have HIV-1 RNA levels < 50 copies/ml. These did not apply to subjects meeting the ARV untreated parameters outlined in the inclusion criteria of the protocol.

The primary efficacy endpoint was SVR12 rate. The secondary efficacy endpoints were the same as those in Study 133 listed in Section 3.2.1.1.

3.2.2.2 Statistical Methodologies

The statistical approach to analyze efficacy endpoint, the definition of visit windows and the approach to handle the missing data were similar to those in Study 133 in Section 3.2.1.2.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 13 displays patient disposition in Study 123. Approximately 10% of the subjects discontinued the study drug in the two groups for the treatment-naïve subjects, i.e., Group1 of 12-week SOF+RBV in HCV genotype 2 or 3 treatment-naïve subjects and Group 3 of 24-week SOF+RBV in HCV genotype 1 treatment-naïve subjects. The most common reason for discontinuation in the two groups was due to adverse events. For Group 2 of 24 weeks of SOF+RBV in HCV genotype 2 or 3 treatment-experienced subjects, only one subject discontinued the study medicine. Meanwhile, approximately 20% subjects in Groups 1 and 3 withdrew from the study due to lack of efficacy.

Of note, as of the data collection for this interim synoptic clinical study report, all subjects completed treatment or prematurely discontinued treatment. All treatment-naïve HCV genotype 1, 2 or 3 subjects in Groups 1 and 3 completed post-treatment follow-up through the timing of the primary efficacy endpoint of SVR12 or prematurely discontinued the study. Among the 41 HCV genotype 2 or 3 treatment-experienced subjects in Group 2, 28 completed the post-treatment follow-up through post-treatment Week 12 or prematurely discontinued the study. These 28 subjects were included in the efficacy analysis; however, all 41 subjects were included in the safety analysis.

Table 13: Patient Disposition in Study 123 (All Treated)

	Group 1 12-Week SOF+RBV GT 2/3 TN[1]	Group 2 24-Week SOF+RBV GT 2/3 TE[1]	Group 3 24-Week SOF+RBV GT 1 TN[1]
Number of enrolled and treated	68 (100%)	41 (100%)	114 (100%)
Discontinued study treatment	6 (9%)	1 (2%)	11 (10%)
Efficacy failure	0	0	1 (1%)
Adverse event	3 (4%)	1 (2%)	3 (3%)
Protocol violation	0	0	4 (4%)
Investigator decision	1 (1%)	0	1 (1%)
Subject withdrew consent	1 (1%)	0	2 (2%)
Lost to follow-up	1 (1%)	0	0
Discontinued study[2]	21 (31%)	2 (5%)	27 (24%)
Death	1 (1%)	0	0
Efficacy failure	13 (19%)	1 (2%)	24 (21%)
Subject withdrew consent	2 (3%)	0	1 (1%)
Lost to follow-up	5 (7%)	1 (2%)	2 (2%)

Source: Table 1 in Study GS-US-334-0123 Second Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
[2]summarized by the statistical reviewer

Table 40 in Section 6.2 displays patient demographics in the study. The three groups shared similar patient demographics and baseline characteristics with two exceptions. There was a slightly higher percent of male subjects in Group 2 and a greater proportion of African-American subjects in Group 3. Overall, the mean (SD) age of the subjects in the study was 49 (9) years. The majority of the subjects in the study were male (83%), white (69%), non-Hispanic (76%), from US sites (97%) and had baseline BMI < 30 kg/m^2 (77%).

Table 41 in Section 6.2 shows the baseline disease characteristics. The three groups had similar disease characteristics with respect to baseline HCV viral load, cirrhosis status, IL28B genotype, ART treatment, baseline HIV viral load and CD4 counts. Overall, the majority of the subjects in the study had a baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL (78%), did not have cirrhosis (90%), had non-CC IL28B genotype (66%), were on ART treatment (95%), had a baseline HIV RNA < 50 copies/mL (93%). The average (SD) CD4 count was 625 (267) cells/mm^3. The majority of the HCV genotype 1 treatment-naïve subjects in Group 1 did not have cirrhosis at baseline, and the majority of the HCV genotype 2 or 3 treatment-experienced subjects in Group 2 were breakthrough/relapsers.

3.2.2.4 Results and Conclusions

A. Primary Efficacy Endpoint

Table 14 shows the overall SVR12 rates for the three groups as well as the rates by HCV genotype for Study 123 provided by the applicant. The reviewer verified and agreed with the

results. Meanwhile, Table 15 displays the SVR12 rate by HCV genotype and prior PEG+RBV treatment experience in Studies 1231, 107, 108, 133 and 123. These results were also presented by the applicant in the clinical study report for the individual studies and were verified by the reviewer.

In Group 1 consisting of HCV genotype 2 or 3 treatment-naïve subjects receiving 12 weeks of SOF+RBV, the overall SVR12 rate was 75%. The SVR12 rate was lower in HCV genotype 3 treatment-naïve subjects as compared to HCV genotype 2 treatment-naïve subjects, i.e., 67% vs. 88% (Table 14). The findings were consistent with what had been observed in Studies 1231, 107 and 133 where SOF+RBV for 12 weeks was evaluated in treatment-naïve subjects mono-infected with genotype 2/3 HCV (Table 15).

In Group 2 consisting of HCV genotype 2 or 3 treatment-experienced subjects receiving 24 weeks of SOF + RBV, only two-thirds of the subjects had their SVR12 data available in this submission including 15 HCV genotype 2 and 13 HCV genotype 3 subjects. The overall SVR12 rate was 93% for the 28 subjects. Although the sample size for each genotype was small, the SVR12 rate in the 15 genotype 2 subjects was 93% which was comparable to the rate seen in Study 133. In addition, the SVR12 rate for the 13 genotype 3 subjects was 92% which was numerically larger than the 77% SVR12 rate in the treatment-naïve subjects mono-infected with genotype 3 HCV in Study 133. Thirteen subjects in Group 2 did not have SVR12 data in the submission. Of the 13 subjects, 12 of them achieved SVR4 while one subject did not have SVR4 data available.

In Group 3 including HCV genotype 1 treatment-naïve subjects receiving 24 weeks of SOF+RBV, the overall SVR12 rate was 76%. Furthermore, 90 (79%) subjects in Group 1 were infected with genotype 1a HCV and 24 (21%) subjects were infected with genotype 1b HCV. The SVR12 rates were 82% in HCV genotype 1a subjects and 54% in HCV genotype 1b subjects. In Study 110 where the 12-week SOF+PEG+RBV was evaluated in the subjects mono-infected with genotype 1, genotype 1a subjects had 10% higher SVR12 rates than genotype 1b subjects.

Table 14: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 123

	Group 1 12-Week SOF+RBV GT2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT2/3 TE[1] (N=28)	Group 3 24-Week SOF+RBV GT1 TN[1] (N=114)
Overall **SVR12** **95% CI[2]**	75% (51) (63%, 85%)	93% (26) (77%, 99%)	76% (87) (67%, 84%)
Genotype 1a **SVR12** **95% CI[2]**	n/a	n/a	82% (74/90) (73%, 89%)
Genotype 1b **SVR12** **95% CI[2]**	n/a	n/a	54% (13/24) (33%, 74%)
Genotype 2 **SVR12** **95% CI[2]**	88% (23/26) (70%, 98%)	93% (14/15) (68%, 99.8%)	n/a
Genotype 3 **SVR12** **95% CI[2]**	67% (28/42) (50%, 80%)	92% (12/13) (64%, 99.8%)	n/a

Source: Table 3 in Study GS-US-334-0123 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
[2]based on the Clopper-Pearson method

Table 15: Reviewer's Analysis for SVR12 Rate for SOF+RBV by HCV Genotype and Prior PEG+RBV Treatment Experience in Studies 1231, 107, 108, 133 and 123

	Genotype 2		Genotype 3	
	TN[1]	**TE[1]**	**TN[1]**	**TE[1]**
Study 1231 **12-week SOF+RBV** **SVR12** **95% CI[2]**	95% (69/73) (87%, 98%)	n/a	56% (102/183) (48%, 63%)	n/a
Study 107 **12-week SOF+RBV** **SVR12** **95% CI[2]**	92% (86/93) (85%, 97%)	94% (15/16) (70%, 99.8%)	70% (54/77) (59%, 80%)	29% (6/21) (11%, 52%)
Study 108 **12-week SOF+RBV** **SVR12** **95% CI[2]** **16-week SOF+RBV** **SVR12** **95% CI[2]**	n/a n/a	86% (31/36) (71%, 95%) 94% (30/32) (79%, 99%)	n/a n/a	30% (19/64) (19%, 42%) 62% (39/63) (49%, 74%)

[1]TN = treatment-naïve, TE = treatment-experienced
[2]based on the Clopper-Pearson method

(to be continued)

Table 15: Reviewer's Analysis for SVR12 Rate for SOF+RBV by HCV Genotype and Prior PEG+RBV Treatment Experience in Studies 1231, 107, 108, 133 and 123 (continued)

	Genotype 2		Genotype 3	
	TN[1]	TE[1]	TN[1]	TE[1]
Study 133				
12-week SOF+RBV				
SVR12	97% (31/32)	90% (37/41)	n/a	n/a
95% CI[2]	(84%, 99.9%)	(71%, 95%)		
24-week SOF+RBV				
SVR12	n/a	n/a	93% (98/105)	77% (112/145)
95% CI[2]			(87%, 97%)	(70%, 84%)
Study 123				
12-week SOF+RBV				
SVR12	88% (23/26)	n/a	67% (28/42)	n/a
95% CI[2]	(70%, 98%)		(50%, 80%)	
24-week SOF+RBV				
SVR12		93% (14/15)	n/a	92% (12/13)
95% CI[2]		(68%, 99.8%)		(64%, 99.8%)

[1]TN = treatment-naïve, TE = treatment-experienced
[2]based on the Clopper-Pearson method

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

Figure 3 and Table 16 display on-treatment virologic responses in the study. Similar to what has been observed in other Phase 3 studies, the HCV viral load was rapidly suppressed after the subjects received the SOF+RBV treatment in all groups. Among the HCV genotype 2 or 3 subjects in Groups 1 and 2, greater than 90% achieved HCV RNA below LLOQ two weeks after treatment. For the HCV genotype 1 treatment-naïve subjects in Group 3, almost all of them had HCV RNA below LLOQ four weeks after receiving SOF+RBV. The high response rates were maintained through the end of the treatment. Also, only two subjects experienced on-treatment virologic failure, one in Group 1 and one in Group 3.

Figure 3: Reviewer's Results for On-Treatment Response Rates by Treatment and Genotype in Study 123 (NC=F)

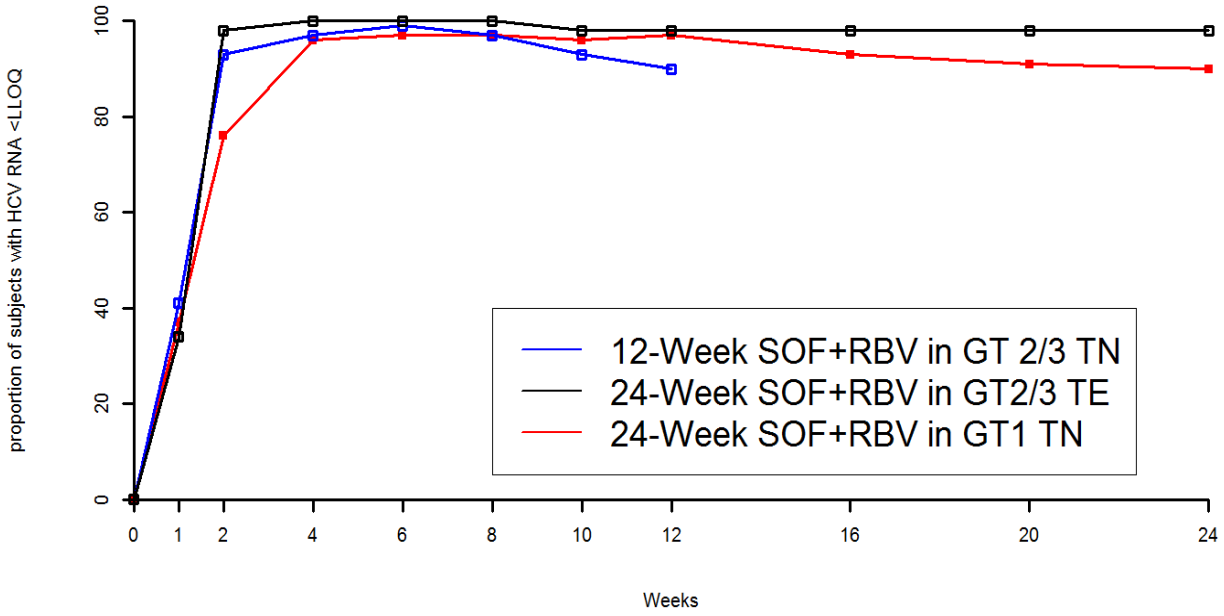


Table 16: Reviewer's Results for on-Treatment Virologic Responses in Study 123 (NC=F)

	Group 1 12-Week SOF+RBV GT 2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT 2/3 TE[1] (N=41)	Group 3 24-Week SOF+RBV GT 1 TN[1] (N=114)
Week 1	41% (28)	34% (14)	37% (42)
Week 2	93% (63)	98% (40)	76% (87)
Week 4	97% (66)	100% (41)	96% (110)
Week 6	99% (67)	100% (41)	97% (111)
Week 8	97% (66)	100% (41)	97% (111)
Week 10	93% (63)	98% (40)	96% (110)
Week 12	90% (61)	98% (40)	97% (111)
Week 16	n/a	98% (40)	93% (106)
Week 20	n/a	98% (40)	91% (104)
Week 24	n/a	98% (40)	90% (103)

B2. Post-Treatment Relapses

Table 17 below summarizes the post-treatment relapse. Relapses usually occurred 4 weeks after the end of the study treatment. The relapse rate at Week 12 post-treatment in genotype 3 treatment-naïve subjects who received 12-week SOF+RBV was still 29%. The relapse rate in genotype 1b treatment-naïve subjects who received 24 weeks of SOF+RBV was high (42%).

Table 17: Reviewer's Results for Post-Treatment Relapse in Study 123

	Group 1 12-Week SOF+RBV GT2/3 TN[1]	Group 2 24-Week SOF+RBV GT2/3 TE[1]	Group 3 24-Week SOF+RBV GT1 TN[1]
Overall			
by 4 weeks post-treatment	15% (10/67)	4% (1/28)	17% (19/113)
by 12 weeks post-treatment	18% (12/67)	7% (2/28)	22% (25/113)
Genotype 1a	n/a	n/a	
by 4 weeks post-treatment			11% (10/89)
by 12 weeks post-treatment			17% (15/89)
Genotype 1b	n/a	n/a	
by 4 weeks post-treatment			38% (9/24)
by 12 weeks post-treatment			42% (10/24)
Genotype 2			n/a
by 4 weeks post-treatment	0% (0/25)	0% (0/15)	
by 12 weeks post-treatment	0% (0/25)	7% (1/15)	
Genotype 3			n/a
by 4 weeks post-treatment	24% (10/42)	8% (1/13)	
by 12 weeks post-treatment	29% (12/42)	8% (1/13)	

[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced

B3. Virologic Responses at EOT and SVR

Figure 4 and Table 18 display virologic response rate at EOT and post-treatment visits. Almost all subjects had HCV RNA below LLOQ at the end of treatment regardless of different HCV genotypes and prior PEG+RBV treatment experience. However, the SVR rates varied with the different HCV genotype and prior PEG+RBV treatment experience. Also, the relapses attributed to the decrease in the response rates from the EOT to post-treatment visits.

Figure 4: Reviewer's Results for Response Rates at EOT and Post-Treatment Visits by Treatment Group and Genotype in Study 123

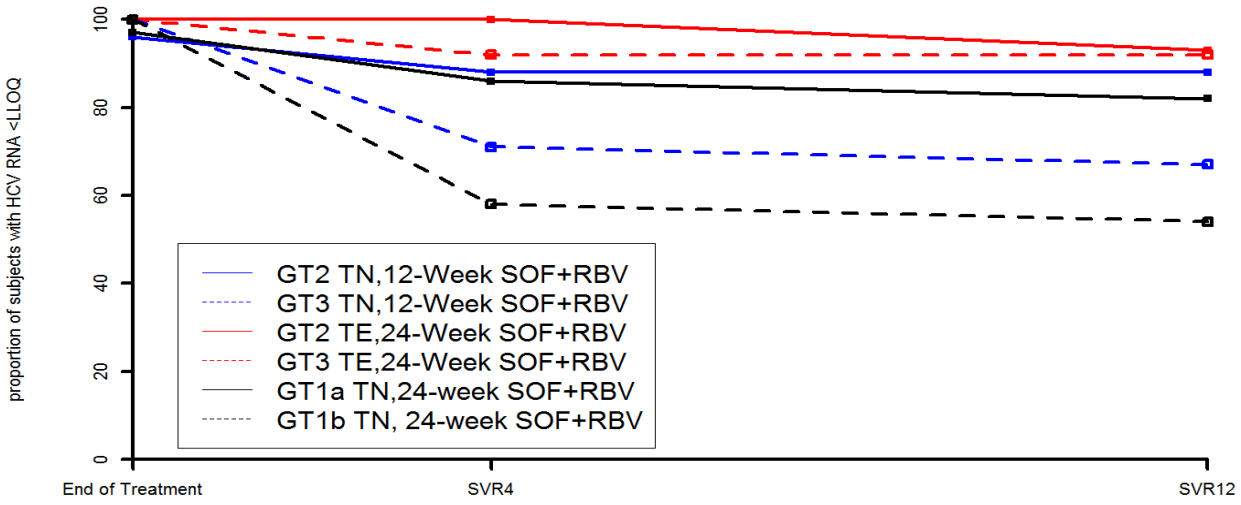


Table 18: Reviewer's Results for Response Rates at EOT and Post-Treatment Visits in Study 123

	Group 1 12-Week SOF+RBV GT2/3 TN[1]	Group 2 24-Week SOF+RBV GT2/3 TE[1]	Group 3 24-Week SOF+RBV GT1 TN[1]
Overall			
EOT	99% (67/68)	100% (28/28)	99% (113/114)
SVR4	78% (53/68)	96% (27/28)	80% (91/114)
SVR12	75% (51/68)	93% (26/28)	76% (87/114)
Genotype 1a	n/a	n/a	
EOT			97% (89/90)
SVR4			86% (77/90)
SVR12			82% (74/90)
Genotype 1b	n/a	n/a	
EOT			100% (24/24)
SVR4			58% (14/24)
SVR12			54% (13/24)
Genotype 2			n/a
EOT	96% (25/26)	100% (15/15)	
SVR4	88% (23/26)	100% (15/15)	
SVR12	88% (23/26)	93% (14/15)	
Genotype 3			n/a
EOT	100% (42/42)	100% (13/13)	
SVR4	71% (30/42)	92% (12/13)	
SVR12	67% (28/42)	92% (12/13)	

[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced

C. Safety

The study consisted of subjects co-infected with HIV-1 and HCV. The safety assessments included the HIV viral load and CD4 counts. This section summarizes the reviewer's analyses for HIV viral load and CD4 counts.

C1. HIV Viral Load at Baseline and EOT

The majority of the subjects in the study had HIV RNA < 50 copies/mL at baseline. Also, almost all the subjects with baseline HIV RNA < 50 copies/mL were on HIV antiretroviral therapy (ARV). The reviewer applied the FDA's snapshot algorithm to calculate the proportion of subjects with HIV RNA <50 copies/mL at EOT. The snapshot algorithm is usually used to compute the primary efficacy endpoint of percent of subjects with HIV RNA < 50 copies/mL in HIV trials. The algorithm classifies the subjects into virologic responders, virologic non-responders and other depending on their HIV viral load and the reasons for discontinuation at a given time. Table 19 shows the HIV viral load at EOT by the baseline viral load (< 50 or ≥ 50 copies/mL). In all three treatment groups, greater than 90% of the subjects who had baseline viral load below 50 copies/mL maintained their viral load suppressed below 50 copies/mL at EOT.

Table 19: Reviewer's Results for HIV Viral Load at Baseline and EOT in Study 123

	Group 1 12-Week SOF+RBV GT2/3 TN[1] (N=68)	**Group 2 24-Week SOF+RBV GT2/3 TE[1] (N=41)**	**Group 3 24-Week SOF+RBV GT1 TN[1] (N=114)**
Baseline HIV RNA < 50 copies/mL	60 (100%)	40 (100%)	108 (100%)
HIV RNA at EOT			
Virologic success – HIV RNA <50 copies/mL	54 (90%)	38 (95%)	99 (92%)
Virologic failure[2]	3 (5%)	1 (3%)	5 (5%)
No virologic data at EOT window	3 (5%)	1 (3%)	4 (4%)
Discontinued SOF+RBV due to AE or death	1 (2%)	1 (3%)	1 (1%)
Discontinued SOF+RBV for other reasons	1 (2%)	0	2 (2%)
Missing data during window but on SOF+RBV	1 (2%)	0	1 (1%)
Baseline HIV RNA ≥ 50 copies/mL	8 (100%)	1 (100%)	6 (100%)
HIV RNA at EOT			
Virologic success – HIV RNA <50 copies/mL	2 (25%)	1 (100%)	4 (67%)
Virologic failure[2]	5 (63%)	0	1 (17%)
No virologic data at EOT window	1 (13%)	0	1 (17%)
Discontinued SOF+RBV due to AE or death	0	0	1 (17%)
Discontinued SOF+RBV for other reasons	0	0	0
Missing data during window but on SOF+RBV	1 (13%)	0	0

[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced

[2]including subjects who discontinued study drug due to lack of efficacy and subjects who had HIV RNA ≥ 50 copies in the EOT window

C2. HIV Virologic Rebound

According to the protocol, the subjects who met the following criteria were considered to have HIV virologic rebound:

- at any visit, having at least two consecutive plasma HIV RNA ≥ 50 copies/mL (at least two weeks apart)
- currently on ARV treatment and had HIV RNA < 50 copies/mL

The majority of the subjects did not experience the protocol-specified HIV virologic rebound. Only two subjects met the rebound criteria including Subject GS-US-334-0123-4262-8725 in Group 1 and Subject GS-US-334-0123-0843-8852 in Group 3. Subject GS-US-334-0123-1692-8915 in Group 2 had HIV RNA < 50 copies/mL at baseline, but had ≥ 50 copies/mL at Weeks 20 and 24 visits. However, the subject was not on ARV treatment. Therefore, the subject was not considered having virologic rebound.

Of note, the two subjects having protocol-specified virologic rebound were included as the virologic failure in the snapshot analysis in the study. Seven more subjects who had baseline HIV RNA < 50 copies/mL were classified as virologic failure at the end of treatment based on the snapshot algorithm but did not experience the protocol-specified virologic rebound. This was mainly because the criteria for the virologic rebound required the subjects had at least two consecutive plasma HIV RNA ≥ 50 copies/mL at any visit, except if the plasma HIV RNA >50 copies/mL occurred at the last available visit which will be counted as virologic rebound as well. In the reviewer's opinion, the protocol-specified virologic rebound is more informative to evaluate the safety of the SOF regimen because the majority of the subjects in the study had their HIV viral load below 50 copies/mL at baseline.

C3. Total CD4 Counts

Table 20 displays the total CD4 counts at baseline and the change from baseline in the total CD4 cells at EOT and post-treatment follow-up visits in the three treatment groups. The CD4 count at EOT was the last available CD4 count before the end of the treatment, while the CD4 counts at Weeks 4 and 12 post-treatment were the last measurements available within the visit windows for post-treatment Week 4 (i.e., between 21 and 69 days after EOT) and Week 12 (i.e., between 70 and 146 days after EOT). Some subjects have not completed their post-treatment follow-up visits as of the data collection for this interim synoptic clinical study report, or discontinued the study; therefore, their CD4 measurements were not available.

Overall, the total CD4 counts decreased at the end of SOF+RBV treatment in all three groups. The applicant attributed the decrease to RBV. The CD4 count increased after the treatments were terminated.

Table 20: Reviewer's Analysis for Total CD4 Cell Counts in Study 123

	Group 1 12-Week SOF+RBV GT 2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT 2/3 TE[1] (N=41)	Group 3 24-Week SOF+RBV GT 1 TN[1] (N=114)
Baseline			
n	68	41	114
Mean (SD)	585 (246)	658 (333)	636 (251)
Median (Q1, Q3)	562 (395, 723)	579 (482, 744)	583 (455, 812)
Change from baseline at EOT			
n	68	41	114
Mean (SD)	-94 (141)	-99 (156)	-79 (175)
Median (Q1, Q3)	-81 (-167, 5)	-73 (-161, -13)	-88 (-186, -4)
Change from baseline at 4 weeks post-treatment			
n	64	39	111
Mean (SD)	-71 (175)	-64 (153)	-35 (173)
Median (Q1, Q3)	-65 (-158, 26)	-55 (-161, 34)	-52 (-131, 34)
Change from baseline at 12 weeks post-treatment			
n	51	27	93
Mean (SD)	-4 (134)	-46 (138)	64 (171)
Median (Q1, Q3)	-13 (-111, 106)	-52 (-129, 45)	52 (-56, 164)

[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced

C4. Percentages of CD4 Cells

Table 21 summarizes the percentages of CD4 cells at baseline and the change in percentages of CD4 cells from baseline at EOT, 4- and 12-week visits after EOT. The percentages of CD4 cells stayed fairly consistent at EOT and post-treatment follow-up visits.

Table 21: Reviewer's Analysis for Percentages of CD4 Cells in Study 123

	Group 1 12-Week SOF+RBV GT 2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT 2/3 TE[1] (N=41)	Group 3 24-Week SOF+RBV GT 1 TN[1] (N=114)
Baseline			
n	68	41	114
Mean (SD)	31 (9)	34 (10)	33 (9)
Median (Q1, Q3)	32 (24, 35)	34 (28, 41)	34 (28, 40)
Change from baseline at EOT			
n	68	41	114
Mean (SD)	1 (3)	2 (3)	2 (4)
Median (Q1, Q3)	2 (-1, 4)	2 (1, 3)	3 (-0.2, 5)

(to be continued)

Table 21: Reviewer's Analysis for Percentages of CD4 Cells in Study 123 (continued)

	Group 1 12-Week SOF+RBV GT 2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT 2/3 TE[1] (N=41)	Group 3 24-Week SOF+RBV GT 1 TN[1] (N=114)
Change from baseline at 4 weeks post-treatment			
n	64	39	111
Mean (SD)	-0.1 (4)	1 (3)	1 (4)
Median (Q1, Q3)	0.3 (-2, 3)	1 (-1, 4)	1 (-2, 3)
Change from baseline at 12 weeks post-treatment			
n	51	27	93
Mean (SD)	-1 (3)	-1 (3)	1 (4)
Median (Q1, Q3)	-1 (-4, 1)	-0.2 (-3, 2)	1 (-1, 4)

[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced

3.2.3 Bridging Analysis to Estimate SVR12 Rate for 12-Week SOF+PEG+RBV for Genotype 1 Treatment-Experienced Subjects

3.2.3.1 Background and Objective for Bridging Analysis

Study 110 showed that 12 weeks of SOF+PEG+RBV treatment resulted in a high SVR12 rate (i.e., 89%) and limited toxicities in HCV genotype 1 treatment-naïve subjects. However, there are no available data from SOF studies that investigate the regimen in the HCV genotype 1 PEG+RBV treatment-experienced population. Since the regimen may offer an important treatment option for HCV genotype 1 PEG+RBV treatment-experienced patients, the Division explored the predicted SVR rate for the 12-week SOF+PEG+RBV in the HCV genotype 1 treatment-experienced population.

The pharmacometrics reviewer, Dr. Jeff Florian, conducted the initial exploratory analysis. His analysis used the SVR rate in the harder-to-treat subset in Study 110 to predict the SVR rate for the SOF+PEG+RBV regimen in prior PEG+RBV partial and null responders. The harder to treat subset was identified by baseline characteristics commonly associated with a response to PEG+RBV. The analysis assumed that the prior PEG+RBV partial and null responders were included in the treatment-naïve population as the harder-to-treat subset. Refer to Dr. Florian's review for details of the analysis.

The statistical team also conducted two exploratory analyses to predict the SVR rate for the SOF+PEG+RBV treatment regimen in HCV genotype 1 treatment-experienced population. The first analysis used the SVR rate for the PEG+RBV treatment regime observed in historical trials. The second analysis extrapolated the predicted SVR rate for the prior PEG+RBV null responders based on the assumption of equivalent odds ratios or relative risks between the treatment-naïve subjects and prior PEG+RBV null responders in the SOF regimen and previous HCV programs. The two analyses are described in the next two sections.

Of note, the prediction approaches based on the observed historical SVR rate for PEG+RBV treatment the harder-to-treat subset were presented at the AC meeting on October 25, 2013.

3.2.3.2 Predicting SVR Rate in HCV Genotype 1 PEG+RBV Treatment-Experienced Subjects Based on Historical SVR Rate on PEG+RBV Treatment

Across the PEG+RBV arms in multiple historical studies, the observed SVR rates on PEG+RBV treatment in the HCV genotype 1 treatment-naïve subjects ranged from 40% to 50%. Those subjects who did not achieve SVR were classified as PEG+RBV treatment failures and became the PEG+RBV treatment-experienced population. As a conservative assessment, we assumed that 50% of the HCV genotype 1 treatment-naïve subjects in Study 110 could be PEG+RBV treatment failures and that the 11% of subjects who failed to respond SOF+PEG+RBV in Study 110 were also PEG+RBV treatment failures. This implied that 39% (i.e., 50% - 11%) of the potential PEG+RBV treatment failures responded to the SOF+PEG+RBV treatment. Then, the predicted SVR rate in the HCV genotype 1 treatment-experienced population would be 78% (i.e., 39/50). Table 22 illustrates the approach.

Table 22: Predicted SVR Rate in HCV Genotype 1 PEG+RBV Treatment-Experienced Subjects Based on Historical SVR Rate on PEG+RBV Treatment

	SOF+PEG+RBV non-response	**SOF+PEG+RBV response**	
percent of potential PEG+RBV treatment failures based on historical trial	11%	39% = 50% - 11%	50%

The predicted SVR rate in genotype 1 treatment-experienced population = 39/50 = 78%

There were two additional assumptions in this approach. First, the approach assumed that the 50% of potential PEG+RBV treatment failures would not have their response to the SOF+PEG+RBV treatment impacted by first failing a treatment course of PEG+RBV. This assumption was supported by a lack of identified resistance to PEG+RBV treatment, similarity between on-treatment responses following initial or subsequent course of PEG/RBV treatment (Liu et al. CID 2012), and previous FDA analyses bridging observations between treatment naïve and prior PEG/RBV treatment failures (Liu et al. Hepatology 2013, Florian et al. Hepatology 2013).

In addition, the approach assumed that the baseline characteristics were similar between HCV genotype 1 treatment-naïve subjects in the historical PEG+RBV studies and those in Study 110. Table 23 below summarizes selected baseline characteristics. However, the subjects in Study 110 seemed more difficult to treat with respect to the baseline characteristics. Specifically, Study 110 consisted of an older demographic, more subjects with HCV genotype 1a, cirrhosis and higher baseline HCV RNA compared to the historical PEG+RBV studies.

Table 23: Selected Baseline Characteristics between HCV Genotype 1 Treatment-Naïve Subjects Who Received PEG+PEG in Historical Studies and Who Were Enrolled in Study 110

	Historical studies[1] (N=3374)	**Study 110** (N=292)
Age		
mean (SD)	47 (9)	52 (10)
median (Q1, Q3)	49 (43, 53)	54 (48, 59)
Male	59%	65%
Black	15%	17%
Genotype 1a	62%	77%
Cirrhosis	5%	18%
Baseline HCV viral load >=800K	76%	83%

[1]including PEG+RBV treatment arms in ACHIEVE-1 IDEAL, PROVE 1, PROVE 2, ADVANCE, SPRING-II studies

3.2.3.3 Extrapolating SVR Rates for Prior PEG+RBV Partial and Null Responders based on Assumption of Equivalent Odds Ratios and Relative Risk between SOF Regimen and Previous HCV Programs

The statistical team also performed an analysis extrapolating the SVR rate for the SOF+PEG+RBV regimen in prior PEG+RBV null responders. This analysis was based on the assumption that the odds ratio or relative risk between the treatment naïve population and prior null responders was the same in the SOF+PEG+RBV regimen as that observed in previous HCV programs including telaprevir, boceprevir and simeprevir (Table 24). The odds ratios between treatment-naïve and prior PEG+RBV null responders were different among the other three HCV drug programs, but the relative risks were fairly consistent. Also, the PEG+RBV null responders were chosen for the analysis because they represented the most difficult to treat subset in the PEG+RBV treatment failures.

Table 24: SVR in Genotype 1 Treatment-Naïve Subjects and Prior PEG+RBV Null Responders in Telaprevir, Boceprevir and Simeprevir

Drug	**SVR rate in Genotype 1 treatment-naïve**	**SVR rate in Genotype 1 prior PEG+RBV null responders**	**Odds ratio between treatment-naïve and null responders**	**Relative risk between treatment-naïve and null responders**
Telaprevir[1]	79% (285/363)	32% (47/147)	7.8	0.3
Boceprevir[1]	66% (242/366)	38% (20/52)	3.1	0.5
Simeprevir[2]	80% (419/521)	49% (49/101)	4.9	0.4

[1]obtained from drug label
[2]obtained from AC backgrounder

The following illustrates how we calculated the predicted SVR rate for the SOF+PEG+RBV regimen in the PEG+RBV null responders using the observed rates in simeprevir as an example.

Let $P_{SOF, NR}$ = the estimated SVR12 rate for 12 weeks of SOF+PEG+RBV treatment in the HCV genotype 1 prior PEG+RBV null responders;

$P_{SOF, TN}$ = the observed SVR12 rate for 12 weeks of SOF+PEG+RBV treatment in the HCV genotype 1 treatment-naïve subjects in Study 110;

$P_{TMC, NR}$ = the observed SVR12 rate for simeprevir-containing treatment regimen in the HCV genotype 1 prior PEG+RBV null responders;

$P_{TMC, TN}$ = the observed SVR12 rate for simeprevir-containing treatment regimen in the HCV genotype 1 treatment-naïve subjects.

The extrapolation used the observed SVR12 rates for the HCV genotype 1 subjects from the simeprevir studies and Study 110 to derive the SVR12 rate for the 12-week SOF+PEG+RBV treatment in the genotype 1 prior PEG+RBV null responders (Table 25).

Table 25: Predicted SVR Rate for 12-Week SOF+PEG+RBV in HCV Genotype 1 Prior PEG+RBV Null Responders based on Extrapolation

Study 110: HCV Genotype 1 Treatment-Naïve

Treatment	SVR12 rate
12-week SOF+PEG+RBV in treatment-naïve	$P_{SOF, TN}$ = 89% (261/292)
12-week SOF+PEG+RBV in prior PEG+RBV null responders	**? $P_{SOF, NR}$**

Simeprevir (TMC) in HCV Genotype 1

Treatment	SVR12 rate
TMC in treatment-naive	$P_{TMC, TN}$ = 80% (419/521)
TMC in prior PEG+RBV null responders	$P_{TMC, NR}$ = 49% (49/101)

Specifically, the extrapolation of the SVR12 rate for the 12 weeks of SOF+PEG+RBV treatment in prior PEG+RBV null responders was performed by solving the following equations which assumed the same OR for the treatment-naïve subjects and prior PEG+RBV null responders in the SOF- and TMC- regimens:

$$\frac{P_{SOF,TN}/(1-P_{SOF,TN})}{P_{SOF,NR}/(1-P_{SOF,NR})} = \frac{P_{TMC,TN}/(1-P_{TVR,TN})}{P_{TMC,NR}/(1-P_{TVR,NR})}$$

When the extrapolation was based on the relative risk, the following equation was used:

$$\frac{1-P_{SOF,TN}}{1-P_{SOF,NR}} = \frac{1-P_{TVR,TN}}{1-P_{TVR,NR}}$$

Table 26 summarizes the analysis results. The extrapolation based on equivalent odds ratios resulted in lower predicted SVR rates ranging from 52% to 73%, compared with 66% to 81% predicted SVR rates based on equivalent relative risks.

Table 26: Predicted SVR Rates for 12-Week SOF+PEG+RBV in Prior PEG+RBV Null Responders based on Extrapolation

Comparator drug	Predicted SVR rate for 12-week SOF+PEG+RBV in prior PEG+RBV null responders based on odds ratio (95% CI)	Predicted SVR rate for 12-week SOF+PEG+RBV in prior PEG+RBV null responders based on relative risk (95% CI)
Telaprevir	52% (38%, 66%)	66% (50%, 76%)
Boceprevir	73% (57%, 85%)	81% (71%, 87%)
Simeprevir	63% (43%, 79%)	70% (52%, 82%)

A merit of the analyses was that they were easy to understand. However, the analyses assumed that the SOF-containing regimen worked similar to other HCV regimens in HCV genotype 1 subjects. This may not be biologically plausible since SOF is a nucleotide analogue inhibitor, but telaprevir, boceprevir and simeprevir are protease inhibitors. Another limitation of the approach was that it did not consider the treatment duration for treatment-naïve and prior PEG+RBV null responders in the comparator drugs which may be different. A response-guided therapy was used in the treatment-naïve trials in telaprevir, boceprevir and simeprevir but not in the prior PEG+RBV null responder studies. In other words, the treatment-naïve subjects may have shorter treatment duration compared with the prior PEG+RBV null responders in the comparator drugs. As a result, the predicted SVR rates for the SOF regimen in the prior PEG+RBV null responders may be inflated.

3.3 Evaluation of Safety

The reviewer evaluated the safety related to HIV endpoints in Study 123 which consisted of the HIV and HCV co-infected patients. Please refer to Section 3.2.2.4. The medical officer, Dr. Poonam Mishra, reviewed the safety data for the two studies in detail. Based on her review, there were no major safety issues related to the use of SOF. For a detailed safety evaluation, please refer to Dr. Poonam Mishra's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Study 133

The study was not placebo-controlled after the second amendment of the protocol. The subgroup analyses were conducted to assess the consistency of the SVR12 rates across different subgroups for the 12-week SOF+RBV treatment regimen in the HCV genotype 2 subjects and the 24-week SOF+RBV regimen in the HCV genotype 3 subjects. The subgroups were defined by the following baseline measures: age (< 50 years, ≥ 50 years), gender, baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2), cirrhosis status at baseline (absence, presence), IL28B (CC, non-CC), baseline HCV RNA (< 6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL), and baseline ALT level (≤ 1.5 x ULN, > 1.5 x ULN). Of note, a subgroup analysis by geographic region was not conducted because the study was

conducted in Europe. Also, almost all subjects were white. Therefore, the subgroup analysis by race was not performed either.

Within each treatment group, the reviewer also investigated the SVR12 rates for the treatment-naïve and treatment-experienced subjects separately across the subgroups defined by the baseline measures. The results are shown in Table 34 and Table 35 in Section 6.1.

4.1.1 Subgroup Analysis for HCV Genotype 2 Subjects Receiving 12-Week SOF+RBV Treatment

Among the HCV genotype 2 subjects who received 12 weeks of SOF+RBV, the SVR12 rates were above 89% in most of the subgroups except for subjects with BMI $\geq$ 30 kg/m^2 at baseline and subjects with baseline HCV viral load < 6 $\log_{10}$ IU/mL. The SVR12 rate for the subset of subjects with baseline BMI $\geq$ 30 kg/m^2 was 75%, and rate for the subset of subjects with baseline HCV viral load < 6 $\log_{10}$ IU/mL was 81%. The sample sizes in both groups were smaller than 20 subjects, which was too small to be conclusive.

Further analyses to assess the SVR12 rates across the subgroups for the treatment-naïve and treatment-experienced subjects separately revealed that the majority of the subgroups for both treatment-naïve and treatment-experienced subjects had high SVR12 rates.

4.1.2 Subgroup Analysis for HCV Genotype 3 Subjects Receiving 24-week SOF+RBV Treatment

The subgroup analyses in the HCV genotype 3 subjects receiving 24 weeks of SOF+RBV treatment demonstrated that subjects below 50 years old had better SVR12 rate than those 50 and older (i.e., 91% vs. 78%), females had better rate than males (i.e., 93% vs. 79%), the subjects with lower HCV viral load had better rate than those with higher viral load (i.e., 96% vs. 79%), and non-cirrhotic subjects had higher rate than cirrhotic subjects (i.e., 89% vs. 67%). The SVR12 rates did not differ much between IL28B CC and non-CC subjects (87% vs. 82%) or between prior PEG+RBV relapse/breakthrough and null responders (77% vs. 73%).

Further analyses demonstrated that the SVR12 rates for 24-week SOF+RBV treatment in all subgroups were above 90% in the HCV genotype 3 treatment-naïve subjects, whereas the rates were lower in the subgroups with poor baseline characteristics in the HCV genotype 3 treatment-experienced subjects. Specifically, among the HCV genotype 3 treatment-experienced subjects, subjects younger than 50 had better SVR12 rates than those 50 and older (i.e., 85% vs. 73%), females had higher rate than males (i.e., 91% vs. 71%), the subjects with lower HCV viral load had better rate than those with higher viral load (i.e., 91% vs. 73%), and non-cirrhotic subjects had higher rate than cirrhotic subjects (i.e., 85% vs. 60%). The low SVR rates observed in these subgroups in the genotype 3 treatment-experienced subjects attributed to the low SVR rates for the subsets in the overall genotype 3 subjects described in the previous paragraph.

Finally, it is of clinical interest to evaluate the SVR rates by prior PEG+RBV treatment history and baseline cirrhosis status in HCV genotype 3 subjects receiving 24-week SOF+RBV. Table

36 summarizes the results. As expected, the prior PEG+RBV relapsers and null responders with cirrhosis at baseline had worse response rates compared to those who did not have cirrhosis.

4.2 Study 123

There was not a control group in the study. The reviewer and the applicant conducted subgroup analyses to evaluate the consistency of the SVR12 rates for the three treatment regimens across the different subgroups defined by the following baseline measures: age (< 50 years, ≥ 50 years), gender, race (black, non-black), baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2), cirrhosis status at baseline (absence, presence), IL28B (CC, non-CC), baseline HCV RNA (< 6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL), and baseline ALT level (≤ 1.5 x ULN, > 1.5 x ULN). In addition, the subgroup analyses stratified by interferon (IFN) class (eligible, ineligible) was conducted for the treatment-naïve subjects, while the subgroup analysis defined by prior PEG+RBV treatment history (IFN intolerant, prior PEG+RBV relapse/breakthrough, prior PEG+RBV null responders) was performed for the treatment-experienced subjects. Of note, the subgroup analysis by geographic region was not conducted because the majority of the subjects in the study were from the US sites.

As shown in Table 42 in Section 6.2, the SVR12 rates were fairly consistent across the subgroups for all three treatment regimens. Of note, it was of clinical interest to explore the use of the 24-week SOF+RBV treatment regimen for HCV genotype 1 treatment-naïve subjects who were ineligible to IFN treatment. In this HIV/HCV co-infection study, approximately 25% of the 114 subjects were in Group 3 (24-week SOF+RBV in HCV genotype 1 treatment-naïve, IFN ineligible), and the SVR12 rate was 76%.

The SVR12 rates by HCV genotype, prior PEG+RBV treatment history and cirrhosis status were also computed (Table 43 in Section 6.2). Overall, the sample sizes for cirrhotic subjects in each genotype and treatment arm were too small to be conclusive.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was no statistical issue in Studies 133 and 123.

Late in the review cycle, the review team discussed extensively whether the high SVR rate observed in Study 110 could be utilized as evidence to support use of the SOF regimen in HCV genotype 1 treatment-experienced population even though no data was included in the submission to evaluate the regimen in that population. Several exploratory analyses were performed by the pharmacometric and statistical teams to predict the SVR rate for 12-week SOF+PEG+RBV in genotype 1 PEG+RBV treatment-experienced population. The exploratory analyses resulted in high predicted SVR rates in HCV genotype 1 prior PEG+RBV treatment-experienced population and the more difficult-to-treat subsets in the population. However, these analyses were based on assumptions. Two of the analyses were presented at the AC meeting. The AC members had a spectrum of responses with varying opinions. Some AC members

expressed concern that there was no clinical data to support the use in the treatment-experienced population and that the exploratory analyses were based on assumptions requiring validation via clinical studies. However other AC members commented that the exploratory analyses were convincing and that the SVR rate in the HCV genotype 1 treatment-experienced patients was expected to be between 70% to 80%, therefore they supported the use of 12-week SOF+PEG+RBV in HCV genotype 1 PEG+RBV treatment-experienced population.

5.2 Collective Evidence

The reviewer evaluated two additional phase 3 studies submitted late in the review cycle. The treatment effects of the SOF-involved treatments evaluated in the two studies were similar to those investigated in the four phase 3 studies in the original NDA submission. The SOF-containing regimen rapidly suppressed the HCV virus shortly after treatment regardless of the HCV genotype, and the high response rates were maintained through the end of treatment period. Very few subjects had a protocol-defined on-treatment virologic failure. Also, the relapses usually occurred four weeks after the end of treatment. The relapse rates varied among the treatment regimens and HCV genotypes, and the variation was attributed to the different SVR rates.

In Study 133, the 12 weeks of SOF+RBV treatment regimen resulted in a high SVR12 rate in HCV genotype 2 subjects. This was consistent with the conclusions in Studies 1231 and 108. The study also resulted in better SVR12 rates and lower relapse rates in the HCV genotype 3 subjects receiving treatment for a longer duration than the rates seen with the 12- and 16-week treatment durations evaluated in Studies 1231 and 108. This provided evidence that longer treatment duration could benefit the genotype 3 subjects.

Study 123 investigated the SOF+RBV regimen in subjects with genotype 1, 2 or 3 HCV infection and HIV-1 co-infection. The study results were consistent with those observed in other Phase 3 trials for the HCV mono-infection. The 12 weeks of SOF+RBV treatment led to an 88% SVR12 rate in the genotype 2 treatment-naïve subjects, but only a 67% SVR12 rate in the genotype 3 treatment-naïve subjects with a 29% relapse rate. The SVR12 rate for the 24 weeks SOF+RBV treatment in genotype 1a treatment-naïve subjects was 82%, whereas the SVR12 rate was only 54% in genotype 1b treatment-naïve subjects with a 42% relapse rate. For the partial data submitted for the 24 week of SOF+RBV in genotype 2 or 3 treatment-experienced subjects, the SVR12 rates were above 90% for both genotypes. In the study, the SOF+RBV regimen appeared to not have an impact on HIV viral load since the majority of the subjects who had baseline viral load below 50 copies/mL maintained their viral suppression at the end of treatment. However, the SOF+RBV regimens resulted in decreased CD4 counts.

Finally, several analyses were conducted to explore bridging the use of 12 weeks of SOF+PEG+RBV in the HCV genotype 1 treatment-naïve subjects to the HCV genotype 1 PEG+RBV treatment-experienced population. The exploratory analyses resulted in high predicted SVR rates in HCV genotype 1 prior PEG+RBV treatment-experienced population and the more difficult-to-treat subsets in the population.

5.3 Conclusions and Recommendations

After reviewing the submitted data, the reviewer makes the following conclusions:

1) The 12-week SOF+RBV regimen demonstrated efficacy in treatment of the subjects with genotype 2 HCV infection.

2) The 24-week SOF+RBV regimen demonstrated efficacy in treatment of the subjects with genotype 3 HCV infection.

3) The 12 week SOF+RBV regimen demonstrated efficacy in treatment of the subjects co-infected with genotype 2 HCV and HIV-1.

4) The 24-week SOF+RBV regimen demonstrated efficacy in treatment of the subjects co-infected with genotype 3 HCV and HIV-1.

5) The 24-week SOF+RBV regimen demonstrated efficacy in treatment of treatment-naïve subjects co-infected with genotype 1 HCV and HIV-1.

6) The results from the bridging analyses suggested that the 12 weeks of SOF+PEG+RBV would have high SVR12 rates in HCV genotype 1 PEG+RBV treatment-experienced population. However, there is no clinical data to confirm the efficacy of the regimen in this population. The collective review team will need to weigh the benefits and risks of the use of the regimen in genotype 1 treatment-experienced patients.

5.4 Labeling Recommendations

The reviewer has the following two comments regarding the label which was submitted on November 1, 2013 and located in \\CDSESUB1\evsprod\NDA204671\0047.

1) The relapse rate at post-treatment Week 12 by the prior PEG+RBV treatment history (i.e., treatment-naïve, or treatment-experienced) in Study 133 should be presented in the label because the rates differed greatly between the two subsets.

2) The results from Study 123 should be presented in the label.

6 APPENDICES

6.1 Study 133

Table 27: Study Procedures for 12-Week SOF+RBV and Placebo in Study 133

			Visit identified by on-treatment study week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X									
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Quality of Life Surveys[f]		X			X				X	X
Review of Study s Medication Compliance			X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X			

			Visit identified by on-treatment study week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12	Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA1c	X									
TSH	X									
Pharmacogenomic		X[e]								

a Vital signs include blood pressure, pulse, respiratory rate and temperature
b The IWRS will provide direction on the specifics of each subject's study drug dispensing.
c Baseline/ Day 1 assessments must be performed prior to dosing
d Plasma samples will be collected and stored for potential HCV sequencing and other virology studies
e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.
f Quality of Life Surveys will be collected from all subjects at Day 1, Week 4, Week 12, Early Termination, Week-4 Post-Treatment and Week-12 Post-Treatment visit if a site is approved to use the survey.

Source: Appendix Table 1 in Appendix 2 in SAP

Table 28: Study Procedures for 24-Week SOF+RBV in Study 133

			Visit identified by on-treatment study week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12, 16, 20,	Week 24 or Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X								X
Height	X									
Weight	X	X								X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X									
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X								X
Quality of Life Surveys[f]		X			X				X	X
Review of Study s Medication Compliance			X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X		X	

			Visit identified by on-treatment study week							
	Screening	Baseline/Day 1[c]	1	2	4	6	8	10	12, 16, 20,	Week 24 or Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X								X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA1c	X									
TSH	X									
Pharmacogenomic		X[e]								

a Vital signs include blood pressure, pulse, respiratory rate and temperature

b The IWRS will provide direction on the specifics of each subject's study drug dispensing.

c Baseline/ Day 1 assessments must be performed prior to dosing

d Plasma samples will be collected and stored for potential HCV sequencing and other virology studies

e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.

f Quality of Life Surveys will be collected from all subjects at Day 1, Week 4, Week 12, Week 24, Early Termination, Week-4 Post-Treatment and Week-12 Post-Treatment visit if a site is approved to use the survey.

Source: Appendix Table 1B in Appendix 2 in SAP for Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013

Table 29: Scheduled Posttreatment Visits in Study 133

	4 Weeks Post Treatment	12 Weeks Post Treatment	24 Weeks Post Treatment
Clinical Assessments			
Vital Signs	X	X	X
Weight		X	X
AEs	X		
Concomitant Medications	X		
Quality of Life Surveys	X	X	
Laboratory Assessments			
Hematology, Chemistry	X	X	
HCV RNA	X	X	X
Viral Sequencing	X	X	X
Urine Pregnancy Test	X	X	X
Pregnancy Prevention Counseling	X	X	X

Source: Appendix Table 2 in Appendix 2 in SAP for Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013

Table 30: Patient Demographics and Baseline Characteristics for Study 133 (All Treated)

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)	Genotype 2/3 Placebo (N=85)	Total (N=419)
Age (years)					
Mean (SD)	58 (10)	48 (10)	46 (9)	49 (10)	50 (11)
Median (Q1, Q3)	60 (53, 65)	50 (44, 55)	44 (40, 56)	51 (45, 56)	51 (45, 57)
<50 years old	13 (18%)	117 (47%)	8 (73%)	37 (44%)	175 (42%)
>= 50 years old	60 (82%)	133 (53%)	3 (27%)	48 (56%)	244 (58%)
Sex					
Male	40 (55%)	155 (62%)	6 (55%)	59 (58%)	250 (60%)
Female	33 (45%)	95 (38%)	5 (45%)	36 (42%)	169 (40%)
Race					
Black	5 (7%)	0	0	1 (1%)	6 (1%)
White	65 (89%)	236 (94%)	11 (100%)	81 (95%)	393 (94%)
Asian	1 (1%)	9 (4%)	0	3 (4%)	13 (3%)
Not permitted	2(3%)	5 (2%)	0	0	7 (2%)
Ethnicity					
Hispanic	6 (8%)	36 (14%)	1 (9%)	10 (12%)	53 (13%)
Non-Hispanic	65 (89%)	203 (81%)	10 (91%)	71 (84%)	349 (83%)
Not permitted	2 (3%)	11 (4%)	0	4 (5%)	17 (4%)
Country[1]					
Austria	2 (3%)	12 (5%)	0	4 (5%)	18 (4%)
Germany	8 (11%)	46 (18%)	1 (9%)	14 (16%)	69 (16%)
Spain	5 (7%)	31 (12%)	1 (9%)	11 (13%)	48 (11%)
Estonia	2 (3%)	6 (2%)	4 (36%)	3 (4%)	15 (4%)
France	15 (21%)	53 (21%)	0	13 (15%)	81 (19%)
England	3 (4%)	31 (12%)	4 (36%)	17 (20%)	55 (13%)
Italy	25 (34%)	27 (11%)	1 (9%)	9 (11%)	62 (15%)
Netherlands	6 (8%)	14 (6%)	0	5 (6%)	25 (6%)
Poland	0	18 (7%)	0	4 (5%)	22 (5%)
Sweden	7 (10%)	12 (5%)	0	5 (6%)	24 (6%)
Baseline body mass index (kg/m^2)					
Mean (SD)	26 (4)	25 (4)	28 (8)	26 (5)	26 (4)
Median (Q1, Q3)	25 (23, 29)	25 (22, 28)	23 (22, 36)	25 (23, 30)	25 (23, 28)
< 30 $kg/m^{2,1}$	61 (84%)	220 (88%)	7 (64%)	66 (78%)	354 (84%)
≥ 30 $kg/m^{2,1}$	12 (16%)	30 (12%)	4 (36%)	19 (22%)	65 (16%)

Source: Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]summarized by the statistical reviewer

Table 31: Baseline Disease Characteristics for Study 133

	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Genotype 3 12-Week SOF+RBV (N=11)	Genotype 2/3 Placebo (N=85)	Total (N=419)
HCV genotype					
Genotype 2	73 (100%)		0	18 (21%)	91 (22%)
2a/2c[1]	28 (28%)	0	0	8 (9%)	36 (9%)
2b[1]	18 (25%)	0	0	4 (5%)	22 (5%)
Genotype 3		250 (100%)	11 (100%)	67 (79%)	328 (78%)
3a[1]	0	243 (97%)	11 (100%)	65 (76%)	319 (76%)
Prior HCV treatment experience and interferon (IFN) classification					
Experienced	41 (56%)	145 (58%)	9 (82%)	50 (59%)	245 (58%)
IFN intolerant	3 (4%)	10 (4%)	0	0	13 (3%)
Non-response	10 (14%)	41 (16%)	4 (36%)	18 (21%)	73 (17%)
Relapse/Breakthrough	28 (38%)	94 (38%)	5 (45%)	32 (38%)	159 (38%)
Naïve	32 (44%)	105 (42%)	2 (18%)	35 (41%)	174 (42%)
IFN-eligible	27 (37%)	94 (38%)	2 (18%)	30 (35%)	153 (37%)
IFN-ineligible	5 (7%)	11 (4%)	0	5 (6%)	21 (5%)
Baseline cirrhosis					
No	63 (86%)	192 (77%)	9 (82%)	67 (79%)	331 (79%)
Yes	10 (14%)	58 (23%)	2 (18%)	18 (21%)	88 (21%)
IL28B					
CC	24 (33%)	86 (34%)	4 (36%)	22 (26%)	136 (32%)
non-CC	49 (67%)	164 (66%)	7 (64%)	63 (74%)	283 (68%)
Baseline HCV RNA (log_{10} IU/mL)					
Mean (SD)	6.5 (0.7)	6.3 (0.7)	6.2 (0.8)	6.5 (0.7)	6.4 (0.7)
Median (Q1, Q3)	6.7 (6.1, 7.0)	6.5 (5.9, 6.9)	6.2 (5.6, 7.1)	6.7 (6.1, 7.0)	6.6 (5.9, 6.9)
< 6 log_{10} IU/mL	16 (22%)	72 (29%)	4 (36%)	21 (25%)	113 (27%)
≥ 6 log_{10} IU/mL	57 (78%)	178 (71%)	7 (64%)	64 (75%)	306 (73%)
Baseline ALT					
≤ 1.5 x ULN	39 (53%)	64 (26%)	4 (36%)	32 (38%)	139 (33%)
> 1.5 x ULN	34 (47%)	186 (74%)	7 (64%)	53 (62%)	280 (67%)

Source: Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]summarized by the statistical reviewer

Table 32: Reviewer's Results for SVR12 Rates in Selected Subgroups for Genotype 2 Treatment-Naïve Subjects Receiving SOF+RBV in Studies 1231 and 133

	Genotype 2 TN 12-Week SOF+RBV	
	Study 1231 (N=73)	**Study 133 (N=32)**
Age (years)		
< 50 years old	96% (22/23)	100% (6/6)
≥ 50 years old	94% (47/50)	96% (25/26)
Sex		
Male	93% (43/46)	92% (11/12)
Female	96% (26/27)	100% (20/20)
Ethnicity		
Hispanic	88% (15/17)	100% (1/1)
Non-Hispanic	96% (54/56)	97% (29/30)
Baseline body mass index		
< 30 kg/m^2	96% (51/53)	100% (28/28)
≥ 30 kg/m^2	90% (18/20)	75% (3/4)
HCV subgenotype		
2	100% (9/9)	100% (12/12)
2a or 2c	100% (9/9)	91% (10/11)
2b	93% (51/55)	100% (9/9)
Cirrhosis		
No	97% (59/61)	97% (29/30)
Yes	83% (10/12)	100% (2/2)
IL28 B		
CC	97% (32/33)	100% (14/14)
CT or TT	93% (37/40)	94% (17/18)
Baseline HCV RNA (log_{10} IU/mL)	100% (25/25)	88% (7/8)
< 6 log_{10} IU/mL	92% (44/48)	100% (24/24)
≥ 6 log_{10} IU/mL		
Baseline ALT		
≤ 1.5 x ULN	95% (35/37)	94% (15/16)
> 1.5 x ULN	94% (34/36)	100% (16/16)

Table 33: Reviewer's Results for SVR12 Rate in Selected Subgroups in Genotype 2 Treatment-Experienced Subjects Receiving SOF+RBV in Studies 108 and 133

	Study 108		Study 133
	12-Week SOF+RBV (N=39)	16-Week SOF+RBV (N=35)	12-Week SOF+RBV (N=41)
Age (years)			
< 50 years old	83% (5/6)	75% (3/4)	71% (5/7)
≥ 50 years old	82% (27/33)	90% (28/31)	94% (32/34)
Sex			
Male	72% (18/25)	84% (21/25)	93% (26/28)
Female	100% (14/14)	100% (10/10)	85% (11/13)
Ethnicity			
Hispanic	80% (4/5)	100% (1/1)	80% (4/5)
Non-Hispanic	82% (28/34)	88% (30/34)	91% (32/35)
Baseline body mass index			
< 30 kg/m^2	86% (24/28)	94% (16/17)	94% (31/33)
≥ 30 kg/m^2	73% (8/11)	83% (15/18)	75% (6/8)
HCV subgenotype			
2	80% (4/5)	100% (3/3)	80% (12/15)
2a or 2c	50% (2/4)	100% (16/17)	100% (5/5)
2b	87% (26/30)	85% (23/27)	100% (9/9)
Treatment experience classification			
INF intolerant	0	0	100% (3/3)
Relapse/breakthrough	86% (25/29)	89% (24/27)	89% (25/28)
Null response	70% (7/10)	88% (7/8)	90% (9/10)
Cirrhosis			
No	90% (26/29)	92% (24/26)	91% (30/33)
Yes	60% (6/10)	78% (7/9)	88% (7/8)
IL28 B			
CC	88% (7/8)	71% (10/14)	100% (10/10)
CT or TT	81% (25/31)	100% (21/21)	87% (27/31)
Baseline HCV RNA (log_{10} IU/mL)			
< 6 log_{10} IU/mL	89% (8/9)	100% (3/3)	75% (6/8)
≥ 6 log_{10} IU/mL	80% (24/30)	88% (28/32)	94% (31/33)
Baseline ALT			
≤ 1.5 x ULN	83% (20/24)	91% (20/22)	91% (21/23)
> 1.5 x ULN	80% (12/15)	85% (11/13)	89% (16/18)

Table 34: Reviewer's Analysis for SVR12 Rates for Selected Subgroups in Genotype 2 Subjects Receiving 12 Weeks of SOF+RBV in Study 133

	All Genotype 2 (TN+TE)		Genotype 2 TN		Genotype 2 TE	
	SVR12	**95% CI[1]**	**SVR12**	**95% CI[1]**	**SVR12**	**95% CI[1]**
Overall	93% (68/73)	(85%, 98%)	97% (31/32)	(84%, 100%)	90% (37/41)	(77%, 97%)
Age						
<50 years old	85% (11/13)	(55%, 98%)	100% (6/6)	(54%, 100%)	71% (5/7)	(29%, 96%)
≥50 years old	95% (57/60)	(86%, 99%)	96% (25/26)	(80%, 100%)	94% (32/34)	(80%, 99%)
Sex						
Female	94% (31/33)	(80%, 99%)	100% (20/20)	(83%, 100%)	85% (11/13)	(55%, 98%)
Male	93% (37/40)	(80%, 98%)	92% (11/12)	(62%, 100%)	93% (26/28)	(77%, 99%)
Baseline BMI						
<30 kg/m^2	97% (59/61)	(89%, 100%)	100% (28/28)	(88%, 100%)	94% (31/33)	(80%, 99%)
≥30 kg/m^2	75% (9/12)	(43%, 95%)	75% (3/4)	(19%, 99%)	75% (6/8)	(35%, 97%)
Baseline HCV RNA						
< 6 log_{10} IU/mL	81% (13/16)	(54%, 96%)	88% (7/8)	(47%, 100%)	75% (6/8)	(35%, 97%)
≥ 6 log_{10} IU/mL	97% (55/57)	(88%, 100%)	100% (24/24)	(86%, 100%)	94% (31/33)	(80%, 99%)
ALT						
≤ 1.5 x ULN	92% (36/39)	(79%, 98%)	94% (15/16)	(70%, 99.8%)	91% (21/23)	(72%, 99%)
>1.5 x ULN	94% (32/34)	(80%, 99%)	100% (16/16)	(79%, 100%)	89% (16/18)	(65%, 99%)
IL28B						
CC	100% (24/24)	(86%, 100%)	100% (10/10)	(69%, 100%)	100% (14/14)	(77%, 100%)
Non-CC	90% (44/49)	(78%, 97%)	94% (17/18)	(73%, 100%)	87% (27/31)	(70%, 96%)
Cirrhosis						
No	94% (59/63)	(85%, 98%)	97% (29/30)	(83%, 100%)	91% (30/33)	(76%, 98%)
Yes	90% (9/10)	(56%, 100%)	100% (2/2)	(16%, 100%)	88% (7/8)	(47%, 100%)
Treatment experience classification						
IFN Intolerant	100% (3/3)	(29%, 100%)	n/a	n/a	100% (3/3)	(29%, 100%)
Relapse/ breakthrough	89% (25/28)	(72%, 98%)	n/a	n/a	89% (25/28)	(72%, 98%)
Null response	90% (9/10)	(56%, 100%)	n/a	n/a	90% (9/10)	(56%, 100%)

[1]based on Clopper-Pearson method

Table 35: Reviewer's Analysis for SVR12 Rates for Selected Subgroups in Genotype 3 Subjects Receiving 24 Weeks of SOF+RBV in Study 133

	All Genotype 3 (TN+TE)		Genotype 3 TN		Genotype 3 TE	
	SVR12	**95% CI[1]**	**SVR12**	**95% CI[1]**	**SVR12**	**95% CI[1]**
Overall	84% (210/250)	(79%, 88%)	93% (98/105)	(87%, 97%)	77% (112/145)	(70%, 84%)
Age						
<50 years old	91% (106/117)	(84%, 95%)	94% (65/69)	(86%, 98%)	85% (41/48)	(72%, 94%)
≥50 years old	78% (104/133)	(70%, 85%)	92% (33/36)	(78%, 98%)	73% (71/97)	(63%, 82%)
Sex						
Female	93% (88/95)	(85%, 97%)	96% (43/45)	(85%, 99%)	90% (45/50)	(78%, 97%)
Male	79% (122/155)	(71%, 85%)	92% (55/60)	(82%, 97%)	71% (67/95)	(60%, 79%)
Baseline BMI						
<30 kg/m^2	84% (184/220)	(78%, 88%)	94% (87/93)	(86%, 98%)	76% (97/127)	(68%, 83%)
≥30 kg/m^2	87% (26/30)	(69%, 96%)	92% (11/12)	(62%, 100%)	83% (15/18)	(59%, 96%)
Baseline HCV RNA	96% (69/72)	(88%, 99%)	100% (38/38)	(91%, 100%)	91% (31/34)	(76%, 98%)
< 6 log_{10} IU/mL						
≥ 6 log_{10} IU/mL	79% (141/178)	(73%, 85%)	90% (60/67)	(80%, 96%)	73% (81/111)	(64%, 81%)
ALT						
≤ 1.5 x ULN	89% (57/64)	(79%, 95%)	94% (29/31)	(79%, 99%)	85% (28/33)	(68%, 95%)
>1.5 x ULN	82% (153/186)	(76%, 87%)	93% (69/74)	(85%, 98%)	75% (84/112)	(66%, 83%)
IL28B						
CC	87% (75/86)	(78%, 93%)	95% (41/43)	(84%, 99%)	79% (34/43)	(64%, 90%)
Non-CC	82% (135/164)	(76%, 88%)	92% (57/62)	(82%, 97%)	76% (78/102)	(67%, 84%)
Cirrhosis						
No	89% (171/192)	(84%, 93%)	93% (86/92)	(86%, 98%)	85% (85/100)	(77%, 91%)
Yes	67% (39/58)	(54%, 79%)	92% (12/13)	(64%, 100%)	60% (27/45)	(44%, 74%)
Treatment experience classification						
IFN Intolerant	100% (10/10)	(69%, 100%)	n/a	n/a	100% (10/10)	(69%, 100%)
Relapse/ breakthrough	77% (72/94)	(67%, 85%)	n/a	n/a	77% (72/94)	(67%, 85%)
Null response	73% (30/41)	(57%, 86%)	n/a	n/a	73% (30/41)	(57%, 86%)

[1]based on Clopper-Pearson method

Table 36: Reviewer's Analysis for SVR Rates by Treatment Experience Classification and Baseline Cirrhosis Status in Genotype 3 Subjects Receiving 24 Weeks of SOF+RBV in Study 133

	Genotype 3 TE, 24-Week SOF+RBV	
	SVR12	**95% CI[1]**
Treatment experience classification and cirrhotic status		
IFN intolerant,		
non-cirrhotic	100% (5/5)	(48%, 100%)
cirrhotic	100% (5/5)	(48%, 100%)
Relapse/breakthrough		
non-cirrhotic	84% (56/67)	(73%, 92%)
cirrhotic	59% (16/27)	(39%, 78%)
Null response		
non-cirrhotic	86% (24/28)	(67%, 96%)
cirrhotic	46% (6/13)	(19%, 75%)

[1]based on Clopper-Pearson method

6.2 Study 123

Table 37: Study Procedures during Treatment Phase for Genotype 2 or 3 Treatment-Naïve Subjects in Study 123

	Screening	Baseline/Day 1[c]	Visit identified by on-treatment study week							
			1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X									
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Quality of Life Surveys[f]		X			X				X	X
Review of Study Medication Compliance			X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X			

	Screening	Baseline/Day 1[c]	Visit identified by on-treatment study week							
			1	2	4	6	8	10	12	Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X
FibroTest® / APRI	X									
HCV RNA	X	X	X	X	X	X	X	X	X	X
HIV RNA	X	X	X	X	X	X	X	X	X	X
CD4 T-lymphocyte Count and %	X	X	X	X	X	X	X	X	X	X
HCV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
HIV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									

	Screening	Baseline/Day 1[c]	Visit identified by on-treatment study week							
			1	2	4	6	8	10	12	Early Termination
HCV, HIV, HBV Serology	X									
HbA1c	X									
TSH	X									
Pharmacogenomic[e]		X								

a Vital signs include blood pressure, pulse, respiratory rate and temperature

b The IWRS will provide direction on the specifics of each subject's study drug dispensing. Subjects to dose in-clinic at baseline/day1 after all assessments are completed. On subsequent visit days (after baseline/day 1) subjects can dose in the AM prior to the visit, this will not affect PK.

c Baseline/ Day 1 assessments must be performed prior to dosing

d Plasma samples will be collected and stored for potential HCV and HIV sequencing and other virology studies

e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.

f Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

Source: Appendix Table 1 in GS-US-334-0123 study protocol amendment 1 on 07 August 2012 submitted in IND 106739/SDN185

Table 38: Study Procedures during Treatment Phase for Genotype 1, 2 or 3 Treatment-Experienced Subjects in Study 123

			Visits identified by on-treatment study week										
	Screening	Baseline/Day 1	1	2	4	6	8	10	12	16	20	24	Early Termination
Clinical Assessments													
Informed Consent	X												
Determine Eligibility	X	X											
Medical History	X												
Physical Examination	X	X										X	X
Height	X												
Weight	X	X										X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X												
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X			X	X
Quality of Life Surveys[f]		X			X				X			X	X
Review of Study Medication Compliance			X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing[b]		X			X		X		X	X	X		

			Visits identified by on-treatment study week										
	Screening	Baseline/Day 1	1	2	4	6	8	10	12	16	20	24	Early Termination
Laboratory Assessments													
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X			X	X
FibroTest® / APRI	X												
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4 T-lymphocyte Count and %	X	X	X	X	X	X	X	X	X	X	X	X	X
HCV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X	X	X	X
HIV Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X	X	X	X
Urinalysis	X												
Urine Drug Screen	X												

			Visits identified by on-treatment study week										
	Screening	Baseline/Day 1	1	2	4	6	8	10	12	16	20	24	Early Termination
HCV Genotyping, IL28B	X												
HCV, HIV, HBV Serology	X												
HbA1c	X												
TSH	X												
Pharmacogenomic[e]		X											

a Vital signs include blood pressure, pulse, respiratory rate and temperature

b The IWRS will provide direction on the specifics of each subject's study drug dispensing. Subjects to dose in-clinic at baseline/day1 after all assessments are completed. On subsequent visit days (after baseline/day 1) subjects can dose in the AM prior to the visit, this will not affect PK.

c Baseline/ Day 1 assessments must be performed prior to dosing

d Plasma samples will be collected and stored for potential HCV and HIV sequencing and other virology studies

e Only for subjects who have consented to this testing. If not obtained at Baseline/Day, the sample may be drawn at any time during the study.

f Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

Source: Appendix Table 2 in GS-US-334-0123 study protocol amendment 1 on 07 August 2012 submitted in IND 106739/SDN185

Table 39: Study Procedures during Post-Treatment Phase for All Groups in Study 123

	4 Weeks Post Treatment	12 Weeks Post Treatment	24 Weeks Post Treatment
Clinical Assessments			
Vital Signs	X	X	X
Weight		X	X
AEs	X		
Concomitant Medications	X		
Quality of Life Surveys[a]	X	X	X
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
HIV RNA	X	X	X
CD4 T-lymphocyte Count and %	X	X	X
Viral Sequencing	X	X	X
Urine Pregnancy Test[b]	X	X	X
Pregnancy Prevention Counseling	X	X	X

a Quality of life surveys will be collected from all subjects if a site is approved to use the survey.

b Refer to Section 6.3.1 and Section 6.4.11 for details on Post-Treatment pregnancy tests.

Source: Appendix Table 3 in GS-US-334-0123 study protocol amendment 1 on 07 August 2012 submitted in IND 106739/SDN185

Table 40: Demographics and Baseline Characteristics in Study 123

	Group 1 12-Week SOF+RBV GT 2/3 TN[1]	Group 2 24-Week SOF+RBV GT 2/3 TE[1]	Group 3 24-Week SOF+RBV GT 1 TN[1]	Total
	N=68	N=41	N=114	N=223
Age (years)				
Mean (SD)	49 (10)	54 (6)	48 (8)	49 (9)
Median (Q1, Q3)	50 (44, 56)	54 (51, 57)	49 (45, 53)	51 (45, 55)
Sex				
Male	55 (81%)	37 (90%)	93 (82%)	185 (83%)
Female	13 (19%)	4 (10%)	21 (18%)	38 (17%)
Race				
Black	8 (12%)	7 (17%)	37 (32%)	52 (23%)
White	52 (76%)	32 (78%)	69 (61%)	153 (69%)
Asian	1 (1%)	1 (2%)	1 (1%)	3 (1%)
Other	6 (9%)	1 (2%)	6 (5%)	13 (6%)
Ethnicity				
Hispanic	19 (28%)	10 (24%)	25 (22%)	54 (24%)
Non-Hispanic	49 (72%)	31 (76%)	89 (78%)	169 (76%)
Country[2]				
USA	65 (96%)	39 (95%)	113 (99%)	217 (97%)
Puerto Rico	3 (4%)	2 (5%)	1 (1%)	6 (3%)
Baseline body mass index (kg/m^2)				
Mean (SD)	27 (4)	27 (5)	27 (5)	27 (5)
Median (Q1, Q3)	27 (25, 30)	26 (24, 30)	26 (24, 29)	26 (24, 30)
< 30 kg/m^2	53 (78%)	31 (76%)	88 (77%)	172 (77%)
≥ 30 kg/m^2	15 (22%)	10 (24%)	26 (23%)	51 (23%)

Source: Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
[2]summarized by the statistical reviewer

Table 41: Baseline Disease Characteristics in Study 123

	Group 1 12-Week SOF+RBV GT 2/3 TN[1]	Group 2 24-Week SOF+RBV GT 2/3 TE[1]	Group 3 24-Week SOF+RBV GT 1 TN[1]	Total
	N=68	N=41	N=114	N=223
HCV genotype				
1	0	0	114 (100%)	114 (51%)
1a	0	0	90 (79%)	90 (40%)
1b	0	0	24 (21%)	24 (11%)
2	26 (38%)	24 (59%)	0	50 (22%)
3	42 (62%)	17 (41%)	0	59 (26%)
Baseline HCV RNA				
< 6 $\log_{10}$ IU/mL	21 (31%)	7 (17%)	22 (19%)	50 (22%)
≥ 6 $\log_{10}$ IU/mL	47 (69%)	34 (83%)	92 (81%)	173 (78%)
Cirrhosis				
No	61 (90%)	31 (76%)	109 (96%)	201 (90%)
Yes	7 (10%)	10 (24%)	5 (4%)	22 (10%)
IL28B genotype				
CC	25 (37%)	20 (49%)	30 (26%)	75 (34%)
CT	37 (54%)	17 (41%)	57 (50%)	111 (50%)
TT	6 (9%)	4 (10%)	26 (23%)	36 (16%)
Missing	0	0	1 (1%)	1 (<1%)
Prior PEG+RBV Treat				
Naïve	68 (100%)	0	114 (100%)	182 (82%)
Experienced	0	41 (100%)	0	41 (18%)
Breakthrough/relapse[3]	0	25 (61%)	0	25 (11%)
Partial/null responders[3]	0	7 (17%)	0	7 (3%)
Interferon intolerant[3]	0	9 (22%)	0	9 (22%)
Interferon classification				
Interferon eligible	49 (72%)	0	85 (75%)	134 (60%)
Interferon ineligible	19 (28%)	0	29 (25%)	48 (22%)
On ARV treatment at enrollment				
No	7 (10%)	2 (5%)	2 (2%)	11 (5%)
Yes	61 (90%)	39 (95%)	112 (98%)	212 (95%)
Tenofovir/Emtricitabine +				
Efavirenz	20 (29%)	16 (39%)	42 (37%)	78 (35%)
Atazanavir/ritonavir	7 (10%)	8 (20%)	24 (21%)	39 (17%)
Darunavir/ritonavir	17 (25%)	2 (5%)	15 (13%)	34 (15%)
Raltegravir	8 (12%)	7 (17%)	21 (18%)	36 (16%)
Other[3]	9 (13%)	6 (15%)	10 (9%)	25 (11%)
Baseline HIV RNA[3]				
< 50 copies/mL	60 (88%)	40 (98%)	108 (95%)	208 (93%)
≥ 50 copies/mL	8 (12%)	1 (2%)	6 (5%)	15 (7%)
Baseline CD4 (Cells/mm^3)[3]				
Mean (SD)	585 (246)	658 (333)	636 (251)	625 (267)
Median (Q1, Q3)	562 (395, 723)	579(482, 744)	583 (455, 812)	579 (442, 753)

Source: Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
[2]summarized by the statistical reviewer
[3]other ART regimens included tenofovir/emtricitabine/atazanavir/raltegravir/ritonavir, tenofovir/emtricitabine/atazanavir, tenofovir/emtricitabine/darunavir/raltegravir/ritonavir, tenofovir/emtricitabine/darunavir/raltegravir/ritonavir/rilpivirine, tenofovir/darunavir/raltegravir/ritonavir, tenofovir/emtricitabine/rilpivirine

Table 42: Applicant's Results for SVR12 Rates for Selected Subgroups in Study 123

	Group 1 12-Week SOF+RBV GT2/3 TN		Group 2 24-Week SOF+RBV GT2/3 TE		Group 3 24-Week SOF+RBV GT1 TN	
	SVR12	**95% CI[1]**	**SVR12**	**95% CI[1]**	**SVR12**	**95% CI[1]**
Age[2]						
< 50 years	70% (23/33)	(51%, 84%)	100% (3/3)	(29%, 100%)	76% (48/63)	(64%, 86%)
≥ 50 years	80% (28/35)	(63%, 92%)	92% (23/25)	(74%, 99%)	76% (39/51)	(63%, 87%)
Sex						
Female	69% (9/13)	(39%, 91%)	100% (4/4)	(40%, 100%)	86% (18/21)	(64%, 97%)
Male	76% (42/55)	(63%, 87%)	92% (22/24)	(73%, 99%)	74% (69/93)	(64%, 83%)
Race[2]						
Black	75% (6/8)	(35%, 97%)	80% (4/5)	(28%, 99%)	65% (24/37)	(47%, 80%)
non-Black	75% (45/60)	(62%, 85%)	96% (22/23)	(78%, 99.9%)	82% (63/77)	(71%, 90%)
Baseline BMI						
<30 kg/m^2	75% (40/53)	(62%, 86%)	95% (21/22)	(77%, 99.9%)	76% (67/88)	(66%, 85%)
≥30 kg/m^2	73% (11/15)	(45%, 92%)	83% (5/6)	(36%, 99.6%)	77% (20/26)	(56%, 91%)
Baseline HCV RNA						
< 6 $\log_{10}$ IU/mL	76% (16/21)	(53%, 92%)	100% (4/4)	(40%, 100%)	77% (17/22)	(55%, 92%)
≥ 6 $\log_{10}$ IU/mL	74% (35/47)	(60%, 86%)	92% (22/24)	(73%, 99%)	76% (70/92)	(66%, 84%)
ALT[2]						
≤1.5 x ULN	65% (15/23)	(43%, 84%)	86% (12/14)	(57%, 98%)	73% (47/64)	(61%, 84%)
>1.5 x ULN	80% (36/45)	(65%, 90%)	100% (14/14)	(77%, 100%)	80% (40/50)	(66%, 90%)
IL28B						
CC	68% (17/25)	(47%, 85%)	92% (11/12)	(62%, 99.8%)	80% (24/30)	(61%, 92%)
Non-CC	79% (34/43)	(64%, 90%)	94% (15/16)	(70%, 99.8%)	75% (62/83)	(64%, 84%)
Cirrhosis						
No	75% (46/61)	(63%, 86%)	95% (20/21)	(76%, 99.9%)	77% (84/109)	(68%, 85%)
Yes	71% (5/7)	(29%, 96%)	86% (6/7)	(42%, 99.6%)	60% (3/5)	(15%, 95%)

Source: Table 6 in Study GS-US-334-0123 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]based on the Clopper-Pearson method
[2]summarized by statistical reviewer

(to be continued)

Table 42: Applicant's Results for SVR12 Rates for Selected Subgroups in Study 123 (continued)

	Group 1 12-Week SOF+RBV GT2/3 TN		Group 2 24-Week SOF+RBV GT2/3 TE		Group 3 24-Week SOF+RBV GT1 TN	
	SVR12	95% CI[1]	SVR12	95% CI[1]	SVR12	95% CI[1]
Interferon (IFN) classification[2]						
IFN eligible	73% (36/49)	(59%, 85%)	n/a	n/a	76% (65/85)	(66%, 85%)
IFN ineligible	79% (15/19)	(54%, 94%)	n/a	n/a	76% (22/29)	(56%, 90%)
PEG+RBV Treatment history classification	n/a	n/a	80% (4/5)	(28%, 99.5%)	n/a	n/a
IFN Intolerant						
Relapse/ breakthrough	n/a	n/a	100% (6/6)	(54%, 100%)	n/a	n/a
Null response	n/a	n/a	94% (16/17)	(71%, 99.9%)	n/a	n/a

Source: Table 6 in Study GS-US-334-0123 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]based on the Clopper-Pearson method
[2]summarized by statistical reviewer

Table 43: Applicant's Results for SVR12 by HCV Genotype, Prior PEG+RBV Treatment History and Cirrhosis Status in Study 123

	HCV Genotype 1[1]		HCV Genotype 2		HCV Genotype 3	
	24-Week SOF+RBV GT1a TN	24-Week SOF+RBV GT1b TN	12-Week SOF+RBV TN	24-Week SOF+RBV TE	12-Week SOF+RBV TN	24-Week SOF+RBV TE
Cirrhosis						
No	82% (73/89)	57% (13/23)	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Yes	75% (3/4)	0% (0/1)	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

Source: Table 6 in Study GS-US-334-0123 Interim Synoptic Clinical Study Report submitted on 9 October 2013
[1]summarized by the statistical reviewer

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/s/

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WEN ZENG
11/20/2013

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concur with overall conclusions

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	204671
Supplement #:	0000
Drug Name:	Sofosbuvir
Indication(s):	Treatment of chronic hepatitis C for adults
Applicant:	Gilead Sciences, Inc.
Date(s):	Submitted date: April 8, 2013
	PDUFA date: October 8, 2013
Review Priority:	Priority

Biometrics Division:	DB4
Statistical Reviewer:	Karen Qi, Ph.D.
Concurring Reviewers:	Wen Zeng, Ph.D.
Medical Division:	Antiviral
Clinical Team:	Poonam Mishra, MD
Project Manager:	Linda Onaga, M.P.H.

Keywords:

Bayesian analysis, closed-test procedures, Cochran-Mantel-Haenszel, Clopper-Person exact confidence interval, intent-to-treat, interaction, logistic regression, odds ratio, relative risk, Breslow Day test

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1 EXECUTIVE SUMMARY

Gilead submitted four pivotal Phase 3 trials in this NDA to support the use of a Sofosbuvir (SOF)-involved treatment regimen for the treatment of subjects infected with genotype 1, 2, 3, 4, 5, or 6 hepatitis C virus (HCV). The four studies had different patient populations but the same primary efficacy endpoint which was the SVR12 rate defined as the proportion of subjects who had HCV RNA below the lower limit of quantitation (LLOQ) 12 weeks after the end of treatment. Study US-334-0110 (i.e. Study 110) evaluated 12 weeks of SOF in combination with a Pegylated Interferon (PEG) and Ribavirin (RBV) in treatment-naive subjects with genotype 1, 4, 5 or 6 HCV infection. Study P7977-1231 (i.e., Study 1231) assessed 12 weeks of SOF plus RBV for the treatment of the HCV genotype 2 or 3 treatment-naïve subjects. Study US-334-0107 (i.e., Study 107) evaluated 12 weeks of SOF combined with RBV in the subjects with genotype 2 or 3 HCV infection who were interferon (IFN) intolerant, IFN ineligible or unwilling to take IFN. Study US-334-0108 (i.e., Study 108) investigated 12 and 16 weeks of SOF plus RBV in treatment-experienced subjects with genotype 2 or 3 HCV infection.

Study 110 demonstrated the efficacy of 12 weeks of SOF combined with PEG and RBV in treatment-naïve subjects with genotype 1 or 4 HCV infection. However, there were only seven HCV genotype 5 or 6 subjects in the study, and the sample size was too small to draw conclusions for these two genotypes.

The SVR12 rates appeared different between the HCV genotypes 2 and 3 subjects based on the results in Studies 1231, 107 and 108. The data from the three studies indicated that 12 weeks of SOF in combination with RBV had adequate efficacy for the treatment of the HCV genotype 2 subjects who were treatment-naïve, treatment-experienced, IFN intolerant, IFN ineligible or unwilling to take IFN. However, the data also suggested that 12 weeks of treatment may be too short for the genotype 3 patients.

Study 108 was the only trial consisting of an arm with the SOF-containing regimen longer than 12 weeks, i.e., 16-week SOF+RBV. This study demonstrated that 16 weeks of SOF+RBV treatment may be sufficient to treat the HCV genotype 3 treatment-experienced subjects because the regimen resulted in a 62% SVR12 rate which was significantly better than the pre-defined 25% historical rate. However, the relapse rate in the 16-week arm was still as high as 38% even though it was much lower than 66% in the 12-week arm. This suggested that the efficacy could potentially be further improved with treatment duration longer than 16 weeks.

Study 1231 suggested the 12-week SOF+RBV regimen was insufficient for the treatment of the HCV genotype 3 treatment-naïve subjects because the treatment regimen had a lower SVR12 rate than the 24 weeks of PEG+RBV treatment (i.e., 56% vs. 63%). Meanwhile, Study 108 revealed that the 16 weeks of SOF+RBV treatment had a SVR12 rate twice as high as the rate for the 12 week of SOF+RBV among the treatment-experienced subjects with genotype 3 HCV infection (i.e., 62% vs. 30%). Therefore, the applicant conducted a bridging analysis to estimate the SVR12 rate for 16 weeks of SOF+RBV in the treatment of HCV genotype 3 treatment-naïve subjects using the genotype 3 data in Studies 1231 and 108. The bridging analysis was based on

the assumption that the odds ratio (OR) between the 12-week and 16-week SOF+RBV among the HCV genotype 3 treatment-naïve subjects was the same as the OR for the HCV genotype 3 treatment-experienced subjects seen in Study 108. The results suggested that the 16-week SOF+RBV regimen would lead to approximately 80% SVR12 rate in HCV genotype 3 treatment-naïve subjects, which was higher than the 56% SVR12 rate for the 12-week SOF+RBV observed in Study 1231. Also, it was anticipated that a longer duration would result in a better SVR12 rate for the genotype 3 subjects from the clinical perspective. The clinically recommended treatment duration for the genotype 3 treatment-naïve subjects was 16 weeks. However, there was no data to validate the assumption of the same ORs between genotype 3 treatment-naïve and treatment-experienced subjects in the bridging analysis. Therefore, it is difficult to recommend the optimal treatment duration for the genotype 3 subjects from the statistical perspective.

One statistical issue was the apparent treatment differences between the HCV genotypes 2 and 3 subjects. In the reviewer's opinion, the observed differences in the SVR12 rates between genotypes 2 and 3 subjects, in particular for the difference in the SOF+RBV treatment regimens in Studies 1231, 107 and 108, were not due to the chance. It was expected that the HCV genotype would have an impact on the SVR12 rate beforehand. Therefore, HCV genotype was one of the stratification factors in the randomization for Studies 1231 and 108, and the subgroup analysis by HCV genotype was one of the pre-defined subgroup analyses in the statistical analysis plan (SAP) in each study. In Study 1231, the 12-week SOF+RBV regime was compared to the 24 weeks PEG+RBV regime and the treatment-by-genotype interaction was significant (p-value = 0.0002). The difference in the SVR12 rate between genotypes 2 and 3 was greater in the 12-week SOF+RBV treatment arm than in the 24-week PEG+RBV treatment arm. In the 12-week SOF+RBV group, 97% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001). On the other hand, 78% and 63% of genotypes 2 and 3 subjects, respectively, achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326). Study 107 compared 12-weeks of SOF+RBV against placebo where no placebo subjects achieved SVR12. In the 12-week SOF+RBV group, the HCV genotype 2 subjects had a significantly higher SVR12 rate than the HCV genotype 3 subjects (i.e., 93% vs. 61%, p-value < 0.0001). In Study 108 where two durations of SOF+RBV were evaluated, the difference in SVR12 rates between the genotypes 2 and 3 subjects were significant within each duration group. In the 12-week SOF+RBV group, 83% of the HCV genotype 2 subjects achieved SVR12 compared with 30% of the HCV genotype 3 subjects (p-value < 0.0001). In the 16-week SOF+RBV group, the SVR12 rates were 82% and 62% for the genotypes 2 and 3 subjects, respectively (p-value = 0.0052). The collective evidence from the three studies strongly suggested that the HCV genotype 2 subjects did have a higher SVR rate than the HCV genotype 3 subjects. The small and consistent p-values could overcome the concern of the lack of a pre-specified plan to control Type 1 error.

Another major statistical issue was the appropriateness of the statistical methods in the applicant's bridging analyses to derive the SVR12 rate for the 16-week SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection based on the observed rates in Studies 1231 and 108. The applicant used the data from all HCV genotype 3 subjects in Studies 1231 and 108 to generate the logistic regression models. They estimated the model parameters using a Bayesian approach and derived the SVR12 rate for the 16 week SOF+RBV regimen in the genotype 3 treatment-naïve subjects based on the assumption that the OR of the 16-week SOF+RBV over

the 12-week SOF+RBV in the genotype 3 treatment-naïve subjects was the same as the OR in the genotype 3 treatment-experienced subjects. The reviewer conducted several analyses to test the sensitivity of the results to various methodologies. First, the reviewer used the maximum likelihood estimation (MLE) approach to estimate the model parameters. The reviewer obtained almost identical results to the applicant's results. Also, the reviewer estimated the SVR12 rate by extrapolating from the observed rates in Studies 1231 and 108 based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. The merit of the extrapolation was that it was relatively easy to follow. The reviewer obtained an 83% SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects based on the extrapolation, which was similar to the applicant's result. The reviewer also used relative risk (RR) and proportion difference (PD) to extrapolate the SVR rate. The estimated SVR12 rate was 76% based on RR and 88% based on PD. All of these post-hoc analyses suggested that 16 weeks of SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects would lead to a higher SVR12 rate than the observed 56% rate for the 12 weeks of SOF+RBV treatment seen in Study 1231. Again, the strong assumptions in the bridging analysis and the lack of Week 16 data made it difficult to determine the optimal treatment duration from the statistical point of view.

Another issue worth noting was the applicant's exclusion of subjects from the efficacy analysis sets in Studies 1231 and 108. There were nine subjects who were misclassified as having genotype 2 HCV infection by the LiPA method at screening but were subsequently found to have genotype 1 infection by population sequencing in the two studies. The LiPA method is currently used to determine the genotype in the clinical practice, whereas population sequencing is not. The applicant excluded these subjects from the efficacy analysis. The inclusion or exclusion of these subjects slightly affected the study results, and the reviewer included the subjects in the analysis in order to follow the intent-to-treat principle.

The final issue was the interpretation of the finding that the HCV genotype 1a treatment-naïve subjects had higher SVR12 rate than the genotype 1b subjects in Study 110 (i.e., 92% vs. 82%). Historically, the subjects infected with genotype 1a HCV are more difficult to treat compared to the subjects with genotype 1b HCV infection. The applicant attributed the observed treatment difference to the findings that the subjects with genotype 1a had a lower percentage of IL28B CC subjects, black subjects, non-cirrhotic subjects and had a lower mean age as compared to the subjects infected with genotype 1b HCV in the study. However, the reviewer compared the SVR12 rates between the two subgenotypes across the subgroups defined by the demographics and baseline characteristics, and found that the genotype 1a subjects had numerically higher SVR12 rate than the genotype 1b subjects in all subgroups. Therefore, the reviewer disagreed with the applicant's interpretation. However, the lack of a control group in the study made it difficult to definitively conclude whether the observed differences between the two subgenotypes were due to chance.

2 INTRODUCTION

2.1 Overview

SOF is a novel nucleotide analogue inhibitor of the HCV NS5B protein to prevent viral replication. It was initially developed by Pharmasset and then acquired by Gilead. The current standard of care (SOC) for the treatment of genotype 1 HCV infection is one protease inhibitor (PI) combined with PEG and RBV. The PIs are Telaprevir and Boceprevir which were approved in 2011. The current SOC improved response rates by 3 to 40% over the old SOC of PEG+RBV alone. However, the safety profile of the SOC is poor. PEG is well known to have many side effects. It is estimated that only 32% of subjects infected with HCV are considered eligible for PEG therapy. Meanwhile, the PIs lead to increased adverse drug reactions. The early phase studies for the SOF-involved regimens demonstrated that SOF in combination with PEG and RBV for 12 weeks was efficacious in treatment of genotype 1 HCV infection. Also the treatment regimen shortened the duration of PEG and RBV and therefore resulted in less adverse events. In contrast, the current SOC for genotype 2 or 3 HCV infection is 24 weeks of PEG and RBV. The early phase studies for SOF also revealed that the PEG-free SOF+RBV regimens resulted in higher cure rates but much less toxicities in treatment of genotype 2 or 3 HCV infection compared with the current SOC.

Since the SOF-containing treatment regimens were shown to be a safe and effective alternative to the current SOC regimens based on the data from the early phase studies, the regimens are considered to be breakthrough therapies. The Division granted Fast Track designation in August of 2010. In this NDA, the applicant submitted the interim clinical study reports for the four pivotal studies including the results of the primary efficacy analysis to support the SOF-involved treatment regimens for the indication of treatment of genotype 1, 2, 3, 4, 5, or 6 HCV infections. The NDA was granted a priority review and will be presented at an advisory committee meeting in October, 2013.

The statistical reviewer focused on reviewing the efficacy of the four Phase 3 trials. These studies had different study designs because they consisted of different patient populations. The summaries of the key elements in the study design in each study are displayed in Table 1.

2.2 Data Sources

The data were submitted electronically and are located in \\Cdsesub1\evsprod\NDA204671\0000. The proposed label discussed in Section 5.4 is located in \\Cdsesub1\evsprod\NDA204671\00004.

Table 1: List of All Phase 3 Studies Included in Review Report

Study Number	Phase and Design	Study Population	Treatment Arms and Number of Randomized/Enrolled Subjects per Arm	Follow-up Period	Primary Hypothesis
P7977-1231 (Study 1231) (Fission)	phase 3, multicenter, open-label, randomized, active-controlled, non-inferiority	treatment-naïve subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week SOF and ribavirin (SOF+RBV), N=263 Arm 2: 24-week pegylated interferon and ribavirin (PEG+RBV), N=264	48 weeks	The SVR12 rate in the12-week SOF+RBV treatment arm was non-inferior to the 24-week PEG+RBV by 15%.
GS-US-334-0107 (Study 107) (Positron)	phase 3, multicenter, randomized, double-blind, placebo-controlled	subjects with chronic genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible or unwilling to take IFN	Arm 1: 12-week SOF+RBV, N=207 Arm 2: placebo, N=71	24 weeks	The SVR12 rate for the 12-week SOF+RBV was superior to placebo.
GS-US-334-0108 (Study 108) (Fusion)	phase 3, multicenter, randomized, double-blind, historical control	treatment-experienced subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week SOF+RBV, N=103 Arm 2: 16-week SOF+RBV, N=99	24 weeks	The SVR12 rate in each of the two treatment arms was no worse than 25%.
GS-US-334-0110 (Study 110) (Neutrino)	phase 3, multicenter, open-label, single-arm, historical control	treatment-naïve subjects with chronic genotype 1, 4, 5 or 6 HCV infection	12-week SOF+PEG+RBV, N=328	24 weeks	The SVR12 rate in the study arm was greater than 60%.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Prior to the NDA submission, the applicant provided the SAP for each study, and each was reviewed. In addition, the reviewers requested sample datasets before the NDA submission and identified data issues which were clarified with the applicant before the submission. In general, the data in this NDA was of high quality, which made it possible for the statistical reviewer to reproduce the applicant's efficacy results easily.

3.2 Evaluation of Efficacy

Because the four studies had different patient populations and primary hypotheses, the reviewer will present the review results for each study individually in the following sections.

3.2.1 Study 1231

3.2.1.1 Study Design and Endpoints

The study was a phase 3, randomized, multicenter, open-label active-controlled, non-inferiority trial conducted among the treatment-naïve subjects with chronic genotype 2 or 3 HCV infection. It aimed to evaluate the efficacy and safety of 12 weeks of SOF in combination with RBV compared with the current SOC, i.e., 24 weeks of PEG plus RBV. The primary hypothesis was that the 12-week SOF+RBV treatment was non-inferior to the 24-week PEG+RBV regimen in the primary efficacy endpoint of SVR12 rate by 15%. Of note, the 15% non-inferiority margin was pre-specified in the protocol. Based on the literature review, the applicant assumed that the SVR rate for the 24-week PEG/weight-based RBV was 70% and that the monotherapy RBV treatment effect was small, and therefore they proposed the non-inferiority margin of 15%. The review team agreed with the margin based on clinical judgment.

The subjects enrolled in the study had chronic genotype 2 or 3 HCV infection, were males or nonpregnant, nonlactating females, were naïve to HCV antiviral treatment, were at least 18 years old, and had a body mass index (BMI) ≤ 18 kg/m^2. Subjects had HCV RNA levels $\geq 10^4$ IU/mL at screening.

The eligible subjects were randomized in a1:1 ratio to either of the following 2 treatment groups:

1) 12-week SOF+RBV: SOF 400 mg plus RBV 1000 to 1200 mg (based on baseline body weight) daily for 12 weeks;
2) 24-week PEG+RBV: PEG 180 ug weekly plus RBV 800 mg daily for 24 weeks

The randomization was stratified by genotype (2 or 3), screening HCV RNA levels (< 6 $\log_{10}$ IU/mL or ≥ 6 $\log_{10}$ IU/mL), and cirrhosis at baseline (present or absent).

All subjects who received at least 1 dose of study medication were followed for 24 weeks after discontinuation or completion of the assigned treatments. Table 35 in Appendix 6.1 provides the study procedures and assessments.

The primary efficacy endpoint was the SVR12 rate defined as the proportion of subjects with HCV RNA < LLOQ 12 weeks after the last dose of study drug.

The secondary efficacy endpoints included the following:

- proportion of subjects with sustained virologic response 24 weeks after stopping therapy, defined as HCV RNA < LLOQ 24 weeks after stopping treatment (i.e., SVR24)
- proportion of subjects with HCV RNA below LLOQ at each visit
- proportion of subjects with ALT normalization (defined as ALT > ULN at baseline and ALT ≤ ULN at each visit) at each visit
- HCV RNA (log10 IU/mL) and change from baseline in HCV RNA (log10 IU/mL) through Week 12
- time to first HCV RNA < LLOQ while on treatment
- time to first HCV RNA < LLOQ target not detected while on treatment
- virologic failure and relapse

The definition of on-treatment virologic failure was as follows:

- 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 value); or
- 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); or
- non-response (HCV RNA persistently ≥ LLOQ through 12 weeks of treatment).

Relapse was defined as a subject with 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.

3.2.1.2 Statistical Methodologies

A. Efficacy Analysis

The efficacy analysis was performed on the full analysis set (FAS) which included subjects with genotype 2, 3 or mixed 2/3 HCV infection who were randomized into the study and received at least one dose of study medication. Subjects with baseline NS5B sequencing that determined the HCV infection was not genotype 2 or 3 were excluded from the FAS.

In the analysis of the primary efficacy endpoint of the SVR12 rate, a closed testing procedure was used. The non-inferiority of SOV+RBV to PEG+RBV was tested first. If the lower limit of the 2-sided 95% CI on the treatment difference (SOF+RBV group minus PEG+RBV group) in the SVR12 rates was > -15%, then it was concluded that SOF+RBV was non-inferior to PEG+RBV. If the non-inferority null hypothesis was rejected, then the p-value associated with the test of superiority was calculated. Superiority would have been demonstrated if the 2-sided p-value was < 0.05.

The point estimate and the 95% CI of the treatment difference in the response rates were constructed based on stratum-adjusted Mantel-Haenszel (MH) proportions to assess non-inferiority. If the null hypothesis for noninferiority was rejected, a Cochran-Mantel-Haenszel (CMH) test stratified by HCV genotype, baseline HCV RNA and cirrhosis status was applied to evaluate the superiority of SOF+RBV group over PEG+RBV.

The point estimates and the 95% exact CIs for the SVR12 rates within each treatment group were calculated based on the Clopper-Pearson method.

For the secondary efficacy endpoints with binary outcome, the proportion and the 95% exact CI using the Clopper-Pearson method were calculated in each treatment group at each scheduled visit.

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 visit windows during the treatment period were calculated from the first dose of study drug (i.e., study day = collection date – date of the first dose; +1 if result is ≥0), while the windows after treatment were from the last study drug dosing date (i.e., follow-up day = collection data – last dose date). The detailed visit windows for all schedule visits are as shown in Table 36 and Table 37 in Appendix 6.1.

C. Handling Missing Data or Dropouts

The applicant described their approach to handling missing data as follows:

> A missing data point for a given study visit may have been due to 1 of the following reasons:
> A visit occurred in the window, but data were not collected or were unusable.
> A visit did not occur in the window.
> A subject permanently discontinued from the study before reaching the visit window.
>
> Values for the missing data (including all safety and health-related quality of life data) were not imputed, with the exception of HCV RNA data.
>
> For the analyses of categorical HCV RNA data, if a data point was missing and was preceded and followed in time by values that were "< LLOQ TND" then the missing data point was set to "< LLOQ TND." If a data point was missing and preceded and followed by values that were "< 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 was set to "< LLOQ detected;" otherwise the data point was considered a failure (ie, ≥ LLOQ detected).

Subjects with missing data due to premature discontinuation of the study had missing data imputed up to the time of their last dose (for on-treatment displays). If study days associated with the last dosing date was greater than the lower bound of a visit window, and the value at the visit was missing, then the value was imputed. If the study days associated with the last dosing date were less than the lower bound of a visit window then the on-treatment value at that visit remained missing. If no HCV RNA values were obtained after the last dose of study drug, the subject was considered a treatment failure for SVR endpoints. However, subjects who were successful for SVR12 and had no further HCV RNA measurements collected were 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 was bracketed by prior and subsequent values of "< LLOQ TND," preceded and followed by "< LLOQ detected," preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected" were set to 24 IU/mL.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows the patient disposition for Study 1231. A total of 527 subjects from 90 study sites in the United States (including Puerto Rico), Australia, New Zealand, Canada, Sweden, Italy and Netherlands were randomized into the study with 263 subjects in the 12-week SOF+RBV group and 264 subjects in the 24-week PEG+RBV group.

Among the randomized subjects who were treated with at least one dose of study medicine (referred to as All Treated hereafter), the percentage of the subjects who discontinued study drug in the 24-week PEG+RBV group was 22%, which was about 5 times as high as the 4% in the 12-week SOF+RBV group. This difference was predominately driven by the lower rate of discontinuations due to AEs or efficacy failure in the 12-week SOF+RBV arm. Specifically, 1% and 0.4% of the subjects treated with SOF+RBV discontinued study drug due to AE and efficacy failure, respectively; while 11% and 7% of the subjects receiving the PEG+RBV treatment discontinued study drug due to AE and efficacy failure, respectively.

Furthermore, the percent of the subjects that withdrew from the study in the 12-week SOF+RBV arm was about 8%, compared with 20% in the 24-week PEG+RBV arm. The major reason for the difference was that none of the subjects in the 12-week SOF+RBV group discontinued the study due to efficacy failure, but 12% in the 24-week PEG+RBV group discontinued due to efficacy failure.

Table 2: Patient Disposition in Study 1231

	12-Week SOF+RBV	24-Week PEG+RBV
Number of screened	677	
Number of randomized	263	264
Number of randomized and treated	256 (100%)	243 (100%)
Discontinued study drug	11 (4%)	54 (22%)
Adverse event	3 (1%)	26 (11%)
Efficacy failure	1 (<1%)	17 (7%)
Death	1 (<1%)	0
Lost to follow-up	2 (1%)	5 (2%)
Consent withdrawn	1 (<1%)	2 (1%)
Other	3 (1%)	4 (2%)
Discontinued study	20 (8%)	48 (20%)
Efficacy failure	0	28 (12%)
Death	1 (<1%)	1 (<1%)
Initiated non-protocol HCV treatment	4 (2%)	0
Lost to follow-up	6 (2%)	9 (4%)
Consent withdrawn	4 (2%)	6 (3%)
Other	5 (2%)	4 (2%)

Source: Table 8-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

The demographics and baseline characteristics for the randomized and treated subjects were well balanced between the two treatment arms (Table 38 in Appendix 6.1). Among the All Treated subjects, the mean (SD) age was approximately 48 (11) years old. The majority of the subjects were male (66%), white (87%), and non-Hispanic (86%). Most subjects were enrolled in U.S. sites (63%).

The baseline disease characteristics were comparable between the two treatment groups (Table 39 in Appendix 6.1). Among the All Treated subjects, the majority (72%) had genotype 3 HCV infection. Approximately 80% of the subjects did not have cirrhosis at baseline. Approximately 57% of the subjects had non-CC IL28B alleles. The mean (SD) of the baseline HCV RNA was 6 (0.8) $\log_{10}$IU/mL with 57% of the subjects having baseline HCV RNA $\geq 6\log_{10}$IU/mL. Approximately 80% of the subjects had baseline ALT above the upper limit of normal range (ULN).

Of note, three subjects in the SOF+RBV arm were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by population sequencing. According to the intent-to-treat principle, these subjects should be included in the efficacy analysis. However, the applicant excluded them. There will be further discussion in Section 3.2.1.4 below.

3.2.1.4 Results and Conclusions

A. Primary Efficacy Endpoint

The applicant's results demonstrated that the SVR12 rates in both treatment groups were around 67% and that the rate in the SOF+RBV group was non-inferior to that in the PEG+RBV group (Table 3).

The applicant's FAS excluded three subjects who were misclassified as having genotype 2 HCV infection by LiPA at screening but were subsequently found to have genotype 1 infection by the population sequencing. In clinical practice, the LiPA assay is used to determine the HCV genotype, whereas the population sequencing is never utilized. Therefore, in the reviewer's opinion, the LiPA assay results should be used to determine HCV genotype, and these three subjects should be included in the analysis in order to follow the intent-to-treat principle. The reviewer conducted the analyses based on the All Treated population including the three subjects with misclassified genotype. Table 4 summarizes the reviewer's results. The inclusion or exclusion of the three subjects had little impact on the results.

Table 3: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 1231 (FAS)

	12-Week SOF+RBV (N=253)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
SVR12 rate (number of subjects with SVR12)	67% (170)	67% (162)	0.3% (-7.5%, 8%)

Source: Table 9-1 in Study GS-US-334-1231 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI are calculated based on Mantel-Haenszel proportions stratified by HCV genotype, cirrhosis status at baseline, and HCV RNA level at screening.

Table 4: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
SVR12 rate (number of subjects with SVR12)	67% (171)	67% (162)	0.1% (-8%, 8%)

[1]based on the Wald asymptotic confidence limits

In addition, the SVR12 rates differed between genotypes 2 and 3 within each treatment group. In the 12-week SOF+RBV group, 95% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001 based on Chi-Square test). In contrast, 78% and 63% of genotypes 2

and 3 subjects achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326 based on Chi-Square test). Furthermore, there was a significant interaction between treatment and HCV genotype for SVR12 rate (p-value based on Breslow-Day test = 0.0002). The SOF+RBV group had a significantly higher SVR12 rate in genotype 2 subjects but numerically lower rate in the HCV genotype 3 subjects. Table 5 displays the applicant's results of the SVR rate by HCV genotype based on the FAS, while Table 6 presents the reviewer's results based on All Treated population. Specifically, the reviewer's analysis demonstrated that the SOF+RBV group had approximately 95% SVR12 rate compared to the 78% SVR12 rate in the PEG+RBV group among genotype 2 subjects (p-value for the treatment difference based on Chi-Squared test = 0.0035). In contrast, the SVR12 rate was 56% in the SOF+RBV group and 63% in the PEG+RBV group among the subjects with genotype 3 HCV infection. These results suggested that the 12 week SOF+RBV treatment was sufficient for the HCV genotype 2 treatment-naïve subjects but not for the HCV genotype 3 treatment-naïve subjects. The subgroup analyses for each genotype to evaluate the treatment effect within the individual genotype were conducted and are presented in Section 4.1.

Of note, patient demographics and the baseline disease characteristics were generally balanced between the two groups within each HCV genotype because genotype was one of the three stratified factors in randomization (Table 40 in Appendix 6.1). Also, the subgroup analysis by genotype was one of the subgroup analyses the applicant planned to conduct as described in their SAP.

Table 5: Applicant's Results for SVR12 Rate by HCV Genotype in Study 1231 (FAS)

	12-Week SOF+RBV	**24-Week PEG+RBV**	**12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]**
Genotype 2			
SVR12 rate (number of SVR12 / number of treated)	97% (68/70)	78% (52/67)	19% (7%, 31%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	56% (102/183)	63% (110/176)	-7% (-17%, 3%)

Source: Table 9-4 in Study GS-US-334-1231 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI are calculated based on Mantel-Haenszel proportions stratified by cirrhosis status at baseline and HCV RNA level at screening.

Table 6: Reviewer's Results for SVR12 Rate by HCV Genotype in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI[1])
Genotype 2[2]			
SVR12 rate (number of SVR12 / number of treated)	95% (69/73)	78% (52/67)	17% (6%, 28%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	56% (102/183)	63% (110/176)	-7% (-17%, 3%)

[1]based on the Wald asymptotic confidence limits
[2]including the 3 subjects who were found to have genotype 2 HCV infection by LiPA assay at screening but later found to have genotype 1 infection by the population sequencing

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

In the analysis of on-treatment virologic responses, the applicant utilized the observed approach, i.e., using all available data without imputing any missing data. Therefore, the analysis set no longer included all randomized and treated subjects. Also, the analysis excluded the subjects who discontinued study drug due to efficacy failure instead of considering them as nonresponders.

The reviewer performed a different analysis based on the All Treated population using the following rules to impute the missing data:

1) the subjects who prematurely discontinued the study drugs were considered as failures regardless of the reasons for discontinuation;

2) the viral load at the next visit was carried backwards to impute the intermittent missing value.

The reviewer's approach will be referred as noncomplete = failure (i.e., NC=F) hereafter. If there were few subjects discontinuing study treatment prematurely, then the reviewer's analysis would lead to similar results as the applicant's observed analysis. However, if there were many discontinuations such as seen in the PEG+RBV treatment group, then the NC=F approach would produce lower response rates.

Figure 1 and Table 7 show the on-treatment responses by genotype in each treatment arm based on the NC=F approach. The SOF+RBV treatment suppressed the viral load quickly. Almost all subjects in the SOF+RBV group achieved HCV RNA < LLOQ around four weeks after receiving the treatment regardless of genotype. The HCV genotype 2 subjects maintained the high response rates thereafter, while the response rates for the genotype 3 subjects dropped slightly at the end of the treatment period because some subjects discontinued study treatment. In the PEG+RBV group, the genotype 2 subjects had higher response rates throughout the treatment phase. The maximum

response rate reached 12 weeks after the start of the treatment for both genotypes, and the response rates decreased slightly towards the end of the treatment due to discontinuations.

Figure 1: Reviewer's Results for On-Treatment Response Rates by Treatment and Genotype in Study 1231 (All Treated, NC=F)

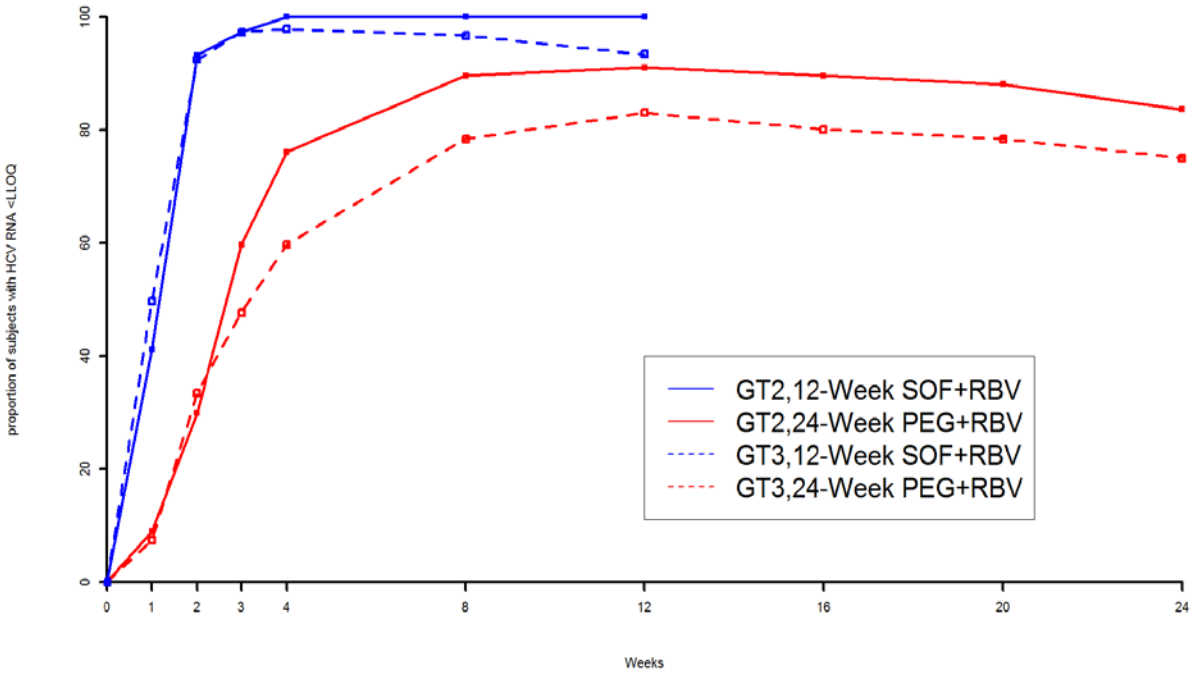


Table 7: Reviewer's Results for On-Treatment Virologic Response at Each Visit in Study 1231 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	**12-Week SOF+RBV (N=256)**	**24-Week PEG+RBV (N=243)**	**12-Week SOF+RBV (N=73)**	**24-Week PEG+RBV (N=67)**	**12-Week SOF+RBV (N=183)**	**24-Week PEG+RBV (N=176)**
Week 1	47% (121)	8% (19)	41% (30)	9% (6)	50% (91)	7% (13)
Week 2	93% (237)	33% (79)	93% (68)	30% (20)	92% (169)	34% (59)
Week 3	97% (249)	51% (124)	97% (71)	60% (40)	97% (178)	48% (84)
Week 4	98% (252)	64% (156)	100% (73)	76% (51)	98% (179)	60% (105)
Week 8	98% (250)	81% (198)	100% (73)	90% (60)	97% (177)	78% (138)
Week 12	95% (244)	85% (207)	100% (73)	91% (61)	93% (171)	83% (146)
Week 16	n/a	83% (201)	n/a	90% (60)	n/a	80% (141)
Week 20	n/a	81% (197)	n/a	88% (59)	n/a	78% (138)
Week 24	n/a	77% (188)	n/a	84% (56)	n/a	75% (132)

In addition, a smaller percentage of subjects in the SOF+RBV group experienced on-treatment virologic failure compared to those in the PEG+RBV group. Specifically, only 0.4% of the subjects

(1/256) receiving the SOF+RBV treatment had on-treatment virologic failure versus 7% (18/243) for the PEG+RBV treatment.

B2. Post-Treatment Relapses

According to the protocol, relapse was defined as subjects with HCV ≥ LLOQ during the post-treatment period after achieving HCV RNA < LLOQ at the end of treatment, confirmed with two consecutive values or the last available post-treatment measurement. As shown in Table 8, the relapses usually occurred at 4 or 8 weeks after the termination of treatment. Overall, higher relapse rates in the 12-week SOF+RBV group were observed compared with the 24-week PEG+RBV group. When the relapse rates were broken down by the different genotypes, it was noticed that the subjects with genotype 2 HCV had lower relapse rates than the subjects with genotype 3 HCV in both treatment groups. As a result, the SVR12 rates were high among genotype 2 subjects in both groups. In addition, compared with the 24-week PEG+RBV, the 12-week SOF+RBV treatment had much lower relapse rates among the subjects with genotype 2 infection but higher relapse rates in the subjects with genotype 3 infection, which caused the significant treatment-by-genotype interaction in SVR12 rate as described above.

Table 8: Reviewer's Results for Post-Treatment Relapse in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV
Overall		
by 4 weeks post-treatment	23% (57/252)	12% (25/217)
by 8 weeks post-treatment	28% (70/252)	20% (44/217)
by 12 weeks post-treatment	30% (76/252)	21% (46/217)
Genotype 2		
by 4 weeks post-treatment	3% (2/73)	6% (4/62)
by 8 weeks post-treatment	3% (2/73)	15% (9/62)
by 12 weeks post-treatment	5% (4/73)	15% (9/62)
Genotype 3		
by 4 weeks post-treatment	31% (55/179)	14% (21/155)
by 8 weeks post-treatment	38% (68/179)	23% (35/155)
by 12 weeks post-treatment	40% (72/179)	24% (37/155)

B3. Virologic Responses at End of Treatment (EOT) and Sustained Virologic Response (SVR) after Treatment

Table 9 displays the virologic responses at the EOT and SVR at 4 and 8 weeks after the EOT (i.e., SVR4 and SVR8). Figure 2 also presents the virologic response rate at the EOT and SVR rates up to post-treatment Week 12 visit. Overall, the 12-week SOF+RBV group had a higher percent of the subjects with virologic response at the EOT than the 24-week PEG+RBV group, but the SVR rates were comparable between the two treatment groups. Moreover, the SVR rates were different between the two genotypes. The SVR rates for the 12-week SOF+RBV treatment were numerically higher in the genotype 2 subjects but lower in the genotype 3 subjects as compared to the rates in the

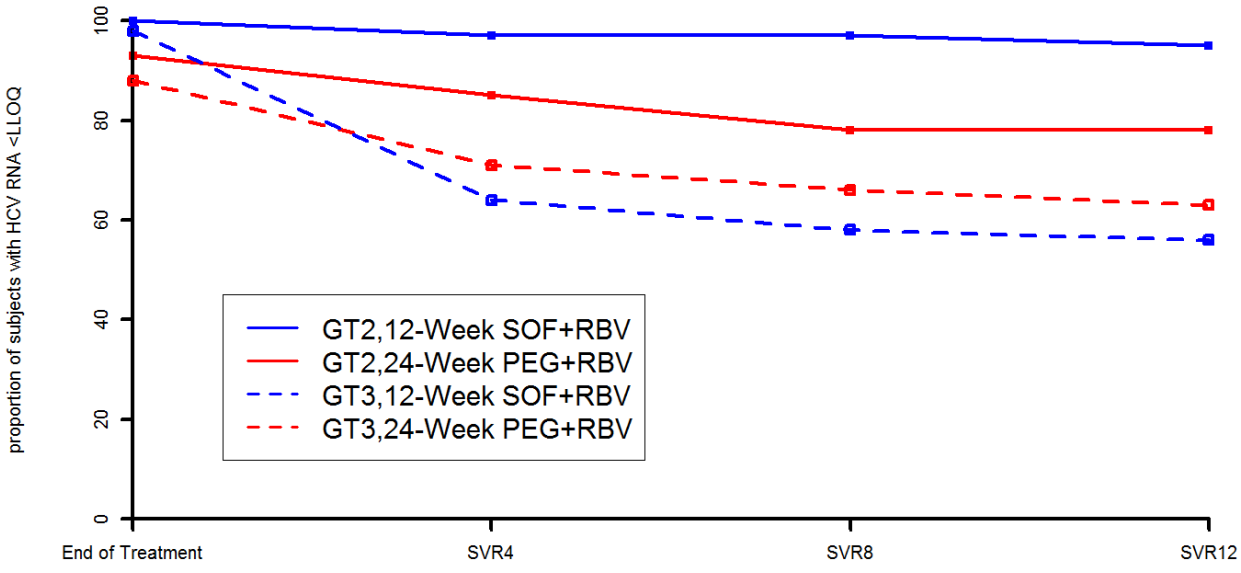
24-week PEG+RBV arm. This was because the SOF+RBV treatment arm had lower relapse rates in the genotype 2 subjects but higher relapse rates in the genotype 3 subjects as mentioned above.

Table 9: Reviewer's Results for EOT Response Rate, SVR4 and SVR8 Rates in Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	12-Week SOF+RBV vs. 24-Week PEG+RBV Proportion Diff (95% CI)[1]
Overall			
EOT response rate	98% (252/256)	89% (217/243)	9% (5%, 13%)
SVR4 rate	73% (188/256)	75% (181/243)	-1% (-9%, 7%)
SVR8 rate	69% (177/256)	68% (165/243)	1% (-7%, 9%)
Genotype 2			
EOT response rate	100% (73/73)	93% (62/67)	7% (1%, 14%)
SVR4 rate	97% (71/73)	85% (57/67)	12% (3%, 22%)
SVR8 rate	97% (71/73)	78% (52/67)	20% (9%, 30%)
Genotype 3			
EOT response rate	98% (179/183)	88% (155/176)	10% (5%, 15%)
SVR4 rate	64% (117/183)	71% (124/176)	-7% (-16%, 3%)
SVR8 rate	58% (106/183)	66% (113/176)	-6% (-16%, 4%)

[1]based on the Wald asymptotic confidence limits

Figure 2: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visits by Treatment and Genotype in Study 1231 (All Treated)



Partial SVR24 data was submitted in this NDA (Table 10). Only one quarter of the subjects in the 24-week PEG+RBV group had the SVR24 data, whereas 95% of the subjects in the 12-week

SOF+RBV group had their SVR24 data available. Specifically, all SVR24 data was available for the HCV genotype 2 subjects and for 93% of the HCV genotype 3 subjects in the 12-week SOF+RBV group. For the HCV genotype 2 subjects receiving the SOF+RBV treatment, the SVR24 rate remained the same as the SVR12 rate. The SVR24 rate was also quite consistent with the SVR12 rate among the HCV genotype 3 subjects.

Table 10: Reviewer's Results for SVR24 Rate by HCV Genotype in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV
Genotype 2		
SVR24 rate	95% (69/73)	21% (14/67)
Not achieving SVR24	5% (4/73)	10% (7/67)
Missing due to discontinuation	0	3% (2/67)
No SVR24 data yet	0	66% (44/67)
Genotype 3		
SVR24 rate	54% (99/183)	7% (13/176)
Not achieving SVR24	35% (64/183)	11% (19/176)
Missing due to discontinuation	4% (7/183)	3% (5/176)
No SVR24 data yet	7% (13/183)	79% (139/176)

3.2.2 Study 107

3.2.2.1 Study Design and Endpoints

This was an ongoing phase 3, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of the 12 weeks of SOF+RBV treatment versus placebo in subjects with chronic genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible or unwilling to take IFN. The primary efficacy hypothesis of the study was that 12-week SOF+RBV was superior to placebo as measured by the SVR12 rate.

The eligible subjects were randomized in a 3:1 ratio to either of the following two treatment groups:

1) 12-Week SOF+RBV: SOF 400 mg plus RBV 1000 to 1200 mg (based on baseline body weight) daily for 12 weeks;

2) placebo: SOF placebo administered once daily plus RBV placebo administered in a divided daily dose for 12 weeks.

The randomization was stratified by the presence or absence of cirrhosis at screening. The treatment duration was 12 weeks. Subjects who had HCV RNA < LLOQ at the post-treatment Week 4 visit were to complete the post-treatment Week 12 and 24 visits unless a confirmed viral relapse had occurred. The detailed study procedures and schedule of assessments are displayed in Table 44 and Table 45 in Appendix 6.2.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- proportion of subjects with HCV RNA < LLOQ by each study visit
- absolute values and HCV RNA and change from baseline in HCV RNA through Week 8
- proportion of subjects with on-treatment virologic failure and relapse.

Of note, the definitions of on-treatment failure and relapse were the same as those for Study 1231 in Section 3.2.1.1.

3.2.2.2 Statistical Methodologies

A. Efficacy Analysis

The efficacy analysis set included all chronic genotype 2 or 3 HCV-infected subjects who were randomized into the study and received at least one dose of study medicine, which was the same as Study 1231. In the primary efficacy analysis, the CMH test stratified by absence or presence of cirrhosis at baseline was applied to compare the SVR12 rates between the two arms (SOF+RBV – placebo). For the secondary efficacy endpoints, the proportion of subjects with HCV RNA < LLOQ and the corresponding 95% CI using the Clopper-Pearson method were calculated for each visit within each treatment group. The CMH test was used for the between treatment comparisons.

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that for Study 1231 described in Section 3.2.1.2, i.e., the half of the duration of time between two consecutive study visits. The visit window for each scheduled visit is provided in Table 46 in Section 6.2.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that in Study 1231 specified in Section 3.2.1.2.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 11 displays patient disposition in Study 107. A total of 280 subjects in 54 study sites in the United States (including Puerto Rico), Canada, Australia and New Zealand were randomized into the study with 209 in the SOF+RBV group and 71 in the placebo arm. There were 2 subjects who were erroneously randomized to the SOF+RBV group but did not receive study drug, and therefore these 2 subjects were excluded from the efficacy analysis.

Among the All Treated subjects, approximately 3% in the 12-week SOF+RBV group and 4% in the placebo group discontinued the study drug. The main reason for discontinuation was AE (2% in the 12-week SOF+RBV group and 4% in the placebo group). However, all of the placebo subjects prematurely terminated the study due to efficacy failure after 12 weeks of the assigned treatment, compared with 21% of the subjects in the SOF+RBV arm.

Table 11: Patient Disposition in Study 107

	12-week SOF+RBV	Placebo
Number of screened	410	
Number of randomized	209	71
Number of randomized and treated	207 (100%)	71 (100%)
Discontinued study drug	6 (3%)	3 (4%)
Adverse event	4 (2%)	3 (4%)
Lost to follow-up	2 (1%)	0
Discontinued study	43 (21%)	71 (100%)
Efficacy failure	38 (18%)	71 (100%)
Death	2 (1%)	0
Lost to follow-up	2 (1%)	0
Withdrew consent	1 (0.5%)	0

Source: Table 8-2 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Overall, the demographics were well balanced between the two treatment groups for most of the baseline measures with the exception of region (Table 48 in Appendix 6.2). Compared with the placebo group, the SOF+RBV group had a lower percent of subjects from North America (88% in the SOF+RBV group vs. 96% in the placebo group), and higher proportion of subjects from Australia/New Zealand (12% in the SOF+RBV group and 4% in the placebo group).

There were no notable imbalances between the two treatment groups for the baseline disease characteristics (Table 49 in Appendix 6.2). Of All Treated subjects in the SOF+RBV arm, slightly more than half of them had genotype 2 HCV infection (51%). They were classified as IFN ineligible (44%), intolerant (9%) or unwilling to take IFN (47%). The majority (81%) had never received HCV treatment previously and did not have cirrhosis at baseline (84%). Also, 45%, 43% and 12% of them had IL28B CC, CT or TT alleles, respectively. Most of them had baseline HCV RNA ≥ 6 $\log_{10}$IU/mL (70%) and ALT > 1xULN (76%).

3.2.2.4 Results and Conclusions

A. Primary Efficacy Endpoint

Since there were no patients with misclassified genotypes, the applicant's FAS was the same as the reviewer's All Treated set. Overall, around 78% of the subjects in the SOF+RBV arm achieved SVR12 while no placebo subjects achieved SVR12 (Table 12). The superiority of 12-week SOF+RBV to placebo was established.

Table 12: Results for Primary Efficacy Endpoint of SVR12 Rate in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs. Placebo Proportion Diff (95% CI)
SVR12 rate (number of subjects with SVR12)	78% (161)	0% (0)	77%[1] (71%, 84%)[1] 78%[2] (72%, 83%)[2]

[1]These were the applicant's results presented in Table 9-1 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA. Difference in proportions between treatment groups and associated 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
[2]These were reviewer's results. The difference in proportions between treatment groups were not adjusted by any baseline covariate. The 95% CI was based on the Wald asymptotic confidence limits.

Furthermore, the SVR12 rates for the SOF+RBV treatment differed between genotype 2 and 3 subjects and showed similar pattern as what was observed in Study 1231. Specifically, the SVR12 rates for the SOF+RBV group among the genotype 2 and 3 subjects were around 93% and 61%, respectively (p-value for difference based on Chi-Square test < 0.0001) (Table 13).

Table 13: Reviewer's Results for SVR12 Rate by HCV Genotype in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs. Placebo Proportion Diff (95% CI)[1]
Genotype 2			
SVR12 rate (number of SVR12 / number of treated)	93% (101/109)	0% (0/34)	93% (88%, 98%)
Genotype 3			
SVR12 rate (number of SVR12 / number of treated)	61% (60/98)	0% (0/37)	61% (52%, 71%)

[1]based on the Wald asymptotic confidence limits

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The reviewer performed the same NC=F analysis as that in Study 1231 to evaluate the virologic response at each scheduled visit during the treatment period. As there were few subjects discontinuing the study medicine in the study, the reviewer's results were close to the applicant's observed analyses. The reviewer's results are displayed in Figure 3 and Table 14 below. Similar to Study 1231, almost all subjects in the SOF+RBV arm achieved their viral load below LLOQ four weeks after receiving the treatment and maintained the high response rates thereafter up to the end of

treatment. On the other hand, no placebo subjects had their viral load suppressed during the 12-week treatment period.

Figure 3: Reviewer's Results for On-Treatment Response Rates by Treatment in Study 107 (All Treated, NC=F)

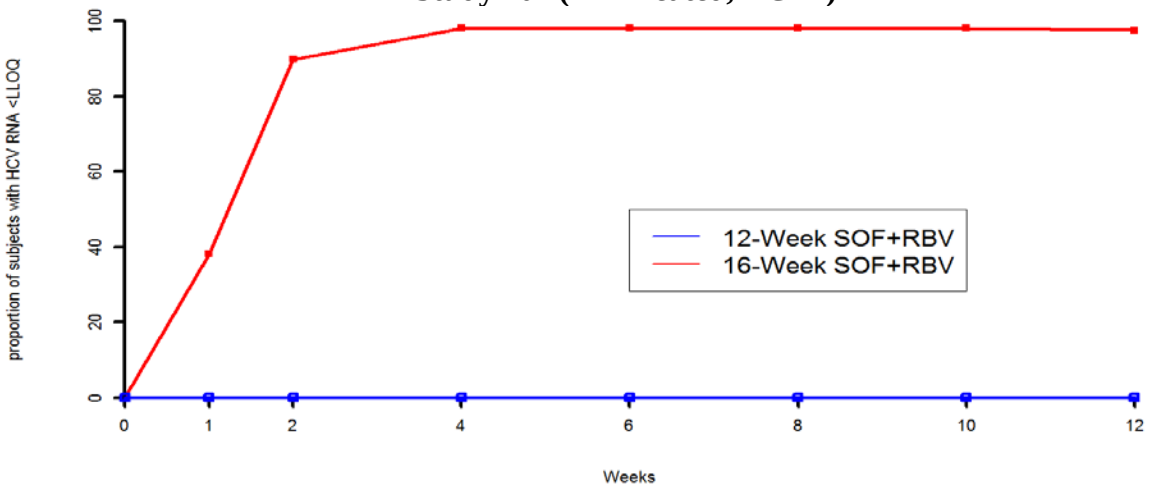


Table 14: Reviewer's Results for On-Treatment Virologic Response at Each Visit in Study 107 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	**12-Week SOF+RBV (N=207)**	**Placebo (N=71)**	**12-Week SOF+RBV (N=109)**	**Placebo (N=34)**	**12-Week SOF+RBV (N=98)**	**Placebo (N=37)**
Week 1	38% (79)	0%	38% (41)	0%	39% (38)	0%
Week 2	90% (186)	0%	90% (98)	0%	90% (88)	0%
Week 4	98% (203)	0%	98% (107)	0%	98% (96)	0%
Week 6	98% (203)	0%	97% (106)	0%	98% (97)	0%
Week 8	98% (203)	0%	98% (107)	0%	98% (97)	0%
Week 10	98% (203)	0%	98% (107)	0%	98% (97)	0%
Week 12	98% (202)	0%	98% (107)	0%	97% (95)	0%

In addition, no subjects in the SOF+RBV arm had on-treatment virologic failure, but almost all placebo subjects (97%) experienced on-treatment virologic failure.

B2. Post-Treatment Relapses

The visit at 4 weeks after the EOT was the only scheduled post-treatment visit before the Week 12 post-treatment visit. Table 15 below depicts relapses at 4 and 12 weeks post-treatment. Overall, 21% of the subjects receiving 12 weeks of SOF+RBV experienced relapse at 12 weeks after the EOT. Furthermore, a lower proportion of HCV genotype 2 subjects had relapses compared with the HCV genotype 3 subjects, which contributed to a higher SVR12 rate for the genotype 2 subjects in

comparison to the genotype 3 subjects. Also, the relapse rate within each genotype was similar to that in the 12-week SOF+RBV group in Study 1231 as shown in Table 8.

Table 15: Reviewer's Results for Post-Treatment Relapses in Study 107 (All Treated)

	12-week SOF+RBV (N=207)	Placebo[1] (N=71)
Overall		
by 4 weeks post-treatment	15% (31/205)	n/a
by 12 weeks post-treatment	21% (42/205)	n/a
Genotype 2		
by 4 weeks post-treatment	2% (2/107)	n/a
by 12 weeks post-treatment	5% (5/107)	n/a
Genotype 3		
by 4 weeks post-treatment	30% (29/98)	n/a
by 12 weeks post-treatment	38% (37/98)	n/a

[1]No subjects in the placebo group achieved HCV RNA < LLOQ at the end of treatment period.

B3. Virologic Responses at EOT and SVR

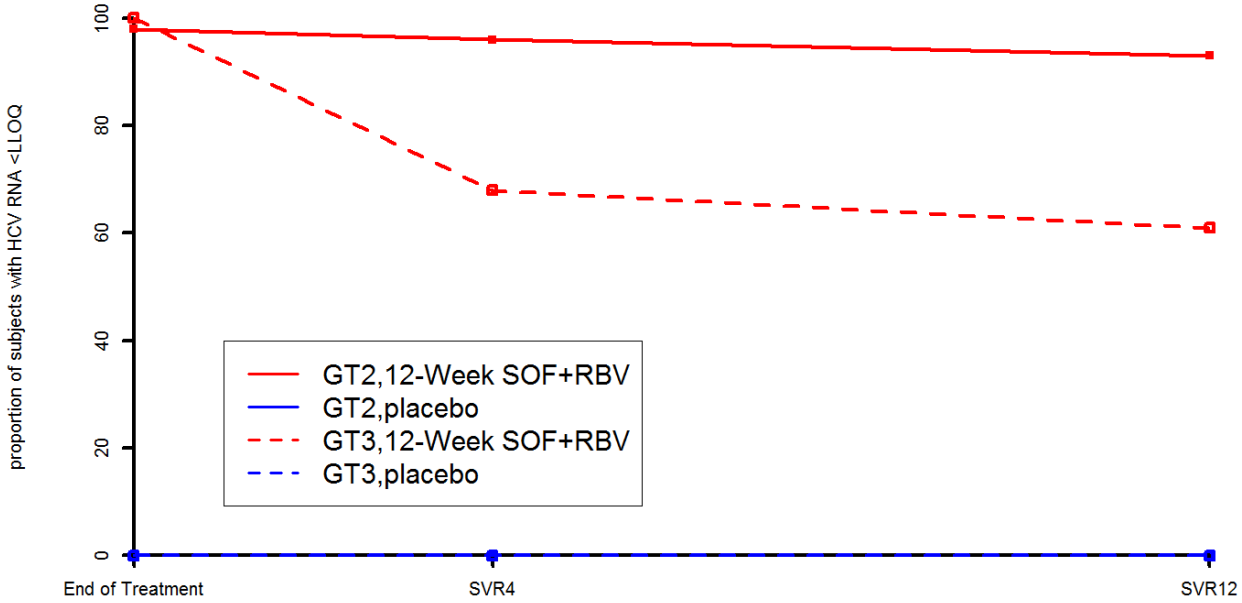
As shown in Table 16, almost all subjects (99%) in the SOF+RBV group achieved HCV RNA < LLOQ at the EOT, but no subjects in the placebo group did. Overall, the SVR4 was observed in 83% of the subjects in the SOF+RBV group. Further analysis demonstrated that 96% of the HCV genotype 2 subjects achieved SVR4 compared to the 68% SVR4 rate in the HCV genotype 3 subjects in the SOF+RBV group. The different relapse rates between genotypes 2 and 3 subjects described earlier contributed to the difference in SVR4 rates in the two genotypes.

Table 16: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	12-Week SOF+RBV vs Placebo Proportion Diff (95% CI)[1]
Overall			
EOT response rate	99% (205/207)	0% (0/71)	99% (98%, 100%)
SVR4 rate	83% (172/207)	0% (0/71)	83% (78%, 88%)
Genotype 2			
EOT response rate	98% (107/109)	0% (0/34)	98% (96%, 100%)
SVR4 rate	96% (105/109)	0% (0/34)	96% (93%, 100%)
Genotype 3			
EOT response rate	100% (98/98)	0% (0/37)	n/a
SVR4 rate	68% (67/98)	0% (0/37)	68% (59%, 78%)

[1]based on the Wald asymptotic confidence limits

Figure 4: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visit by Treatment and Genotype in Study 107 (All Treated)



Finally, the SVR24 data for majority (95%) of subjects was available. Table 17 summarizes the SVR24 rate in the 12-week SOF+RBV treatment group. The SVR24 rates appeared fairly consistent with the SVR12 rates for both genotypes.

Table 17: Reviewer's Results for SVR24 Rate in 12-Week SOF+RBV Group in Study 107 (All Treated)

	12-Week SOF+RBV
Genotype 2	
Achieving SVR24	86% (94/109)
Discontinuation	6% (7/109)
Not having SVR24 data	7% (8/109)
Genotype 3	
Achieving SVR24	60% (59/98)
Discontinuation	37% (36/98)
Not having SVR24 data	3% (3/98)

C. Comparison of SVR12 Rates for 12 weeks of SOF+RBV in Treatment-Naïve Subjects between Study 107 and Study 1231

The reviewer conducted an exploratory analysis to evaluate the consistency of the SVR12 rate for 12 weeks of SOF+RBV in treatment-naïve subjects between Studies 1231 and 107. The reviewer compared the patient demographics and baseline disease characteristics between the subjects who were treatment-naïve and received 12 weeks of SOF+RBV treatment in Study 107 and the subjects

in the 12-week SOF+RBV group in Study 1231 within each genotype (Table 50 in Appendix 6.2). For the HCV genotype 2 subjects, there were not any notable differences in the baseline characteristics between the subjects in the two studies. However, it was noticed that there was a higher proportion of subjects with cirrhosis at baseline in Study 1231 than in Study 107 (21% in Study 1231, and 5% in Study 107) among the HCV genotype 3 subjects.

In theory, the subjects in Study 107 were supposed to be more difficult to treat because they were IFN ineligible, IFN intolerant or unwilling to take IFN. However, it was found that the SVR rates for 12 weeks of SOF+RBV in the two studies were similar among the genotype 2 subjects (95% in Study 1231 vs. 92% in Study 107). Among the genotype 3 subjects, 12 weeks of SOF+RBV treatment in Study 107 even had higher SVR12 rate compared to Study 1231 (56% in Study 1231 vs. 70% in Study 107). The reviewer then compared the SVR12 rates for the genotype 3 subjects between Studies 1231 and 107 across the subsets defined by the baseline measures. Study 1231 had lower SVR12 rates in almost all subsets (Table 51 in Appendix 6.2). In the subgroup of the subjects with cirrhosis at baseline, a lower percent of subjects in Study 1231 achieved SVR12 compared to Study 107 (i.e., 34% [13/38] in Study 1231 vs. 50% [2/4] in Study 107). The findings that Study 1231 had a higher percentage of the HCV genotype 3 subjects with cirrhosis at baseline but had lower SVR12 rate in this subset likely contributed to the treatment difference in genotype 3 subjects between Studies 1231 and 107.

Table 18: Reviewer's Analysis to Compare SVR12 Rates for Treatment-Naïve Subjects Receiving 12 Weeks of SOF+RBV in Study 1231 and Study 107

	12-Week SOF+RBV		
	Study 1231	**Study 107**	**Difference in SVR12 rate (95% CI)**
Genotype 2	95% (69/73)	92% (86/93)	-2% (-10%, 5%)
Genotype 3	56% (102/183)	70% (54/77)	-14% (-27%, -2%)

[1]based on the Wald asymptotic confidence limits

3.2.3 Study 108

3.2.3.1 Study Design and Endpoints

The study was a phase 3, randomized, double-blind, multicenter trial to evaluate the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment regimens among subjects with chronic genotype 2 or 3 HCV infection who failed prior treatment with an IFN-based regimen. The primary hypothesis was that the SVR12 rate of each treatment regimen was no worse than 25%. The treatment guidelines recommend that subjects who fail to achieve SVR after a prior full course of PEG+RBV do not receive retreatment with PEG+RBV. There was no other treatment regimen available for the HCV genotype 2 or 3 treatment-experienced subjects. Therefore, a historical control was used. Assuming the SVR rate would be low had the HCV genotype 3 treatment-experienced subjects been

retreated with PEG+RBV, the 25% historical rate was chosen. The historical rate was based on clinical judgment.

Eligible subjects were randomized in a 1:1 ratio to 1 of the following treatment arms:

1) 12-week SOF+RBV: SOF 400 mg administered once daily plus RBV total daily dose of 1000 to 1200 mg administered in a divided daily dose for 12 weeks; followed by SOF placebo administered once daily plus RBV placebo administered in a divided daily dose for 4 weeks;

2) 16-week SOF+RBV: SOF 400 mg administered once daily plus RBV total daily of 1000 to 1200 mg administered in a divided daily dose for 16 weeks.

The randomization was stratified by two factors at baseline: cirrhosis status (yes vs. no) and HCV genotype (2 vs. 3).

The treatment period duration was 16 weeks in both groups, with the SOF+RBV 12 Week group receiving matching placebo between Weeks 12 and 16. All study subjects were to complete a post-treatment Week 4 visit regardless of their treatment duration. Subjects who had HCV RNA < LLOQ at the post-treatment Week 4 visit were to complete post-treatment Week 8, 12, 20 and 24 visits unless a confirmed viral relapse had occurred. Table 54 and Table 55 in Appendix 6.3 show the details of study procedures and schedule of assessments.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- SVR4 and SVR24
- proportion of subjects with HCV RNA below LLOQ by study visit
- HCV RNA (log_{10}IU/mL) and change from baseline in HCV RNA (log_{10}IU/mL) through Week 8
- proportion of on-treatment failure
- proportion of relapse

3.2.3.2 Statistical Methodologies

A. Efficacy Analysis

Similar to Studies 1231 and 107, the efficacy analyses were performed on the FAS which included subjects with genotype 2 or 3 HCV infection who were randomized into the study and received at least one dose of study medication.

The two-sided exact one-sample binomial test was used to test the primary efficacy hypotheses of whether the SVR12 rates in both treatment groups were greater than 25%. The two-sided exact CI for the SVR12 rate in each group was calculated based on the Clopper-Pearson method. Both hypotheses were tested at a significance level of 0.025 using a Bonferroni method to adjust for multiple testing. If the tests in the primary analysis were statistically significant at the 0.025

significance level, then the secondary analysis of comparing the SVR12 rates between the two groups was performed using the CMH test adjusted by the stratification factors in randomization (i.e., absence or presence of cirrhosis at baseline, HCV genotype 2 or 3).

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that in Study 1231 in Section 3.2.1.2. The visit window for each scheduled visit is provided in Table 56 and Table 57 in Appendix 6.3.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that described in Section 3.2.1.2 for Study 1231.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition is shown in Table 19. A total of 202 subjects from in 57 sites in the United States (including Puerto Rico), Canada and New Zealand were randomized into the study with 103 in the 12-week SOF+RBV arm and 99 in the 16-week SOF+RBV group. One randomized subject in the 16-week SOF+RBV group did not take the study drug. Among the 201 randomized and treated subjects, only one subject in the 12-week SOF+RBV arm discontinued the study medication due to an adverse event. However, approximately half of the subjects in the 12-week treatment arm discontinued the study compared with one third of the subjects in the 16-week arm. The most common reason for premature discontinuation from the study was efficacy failure.

Table 19: Patient Disposition for Study 108

	12-week SOF+RBV	16-week SOF+RBV
Number of screened	277	
Number of randomized	103	99
Number of randomized and treated	103 (100%)	98 (100%)
Discontinued study drug	1 (1%)	0
Adverse event	1 (1%)	0
Discontinued study	52 (50%)	28 (29%)
Efficacy failure	49 (48%)	28 (29%)
Lost to follow-up	2 (2%)	0
Withdrew consent	1 (1%)	0

Source: Table 8-2 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

The patient demographics and baseline characteristics were comparable between the two treatment groups (Table 58 in Appendix 6.3). Among the All Treated subjects, the mean (SD) age for was 54 (8) years. The majority of the subjects were male (70%), white (87%), non-Hispanic (91%), and from US sites (76%). The mean BMI (SD) was around 29 (5) kg/m^2.

The baseline disease characteristics were quite similar between the two treatment arms (Table 59 in Appendix 6.3). In general, the majority of the subjects (63%) had genotype 3 HCV infection. The overall mean (SD) baseline HCV RNA level for the subjects was 6.5 (0.7) $\log_{10}$ IU/mL and most subjects (73%) had baseline HCV RNA $\geq$ 6 $\log_{10}$IU/mL. Approximately 75% of subjects had relapse/breakthrough when receiving the prior HCV treatment, and 25% did not respond to the previous HCV treatment. The majority of the subjects (70%) had non-CC IL28B alleles and did not have cirrhosis (66%) at baseline.

There were six subjects who were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis instead of genotype 2 HCV infection as determined by LiPA at screening. As in Study 1231, the applicant excluded these six subjects from their efficacy analyses, which the reviewer deemed inappropriate due to violation of the intent-to-treat principle.

3.2.3.4 Efficacy Results and Conclusion

A. Primary Efficacy Results

The applicant's results shown in Table 20 demonstrated that about 50% of the subjects in the 12-week group and 73% in the 16-week group achieved SVR12. Both rates were statistically significantly greater than the 25% historical rate. Also, the SVR12 rate for the shorter duration appeared significantly lower than that in the longer duration.

The applicant's analysis excluded the six subjects with misclassified genotype by LiPA assay as done in Study 1231. Again, even though inclusion or exclusion of these subjects only slightly affected the results in this study, the reviewer included these subjects to follow the intent-to-treat principle. The reviewer carried out the analyses on the All Treated population. Table 21 summarizes the reviewer's results.

Similar to Study 1231, it was noticed that the HCV genotype appeared to affect the SVR12 rate in the treatment groups. Based on the reviewer's analysis (Table 23), the SVR12 rate for the HCV genotype 2 subjects was 82% in the 12-week treatment group, which was significantly greater than 30% rate for the genotype 3 subjects in the same group (p-value based on Chi-Square test <0.0001). Similarly, 89% of the genotype 2 subjects in the 16-week treatment arm achieved SVR12, which was significantly higher than 62% of the genotype 3 subjects (p-value based on Chi-Square test = 0.0052). On the other hand, for the HCV genotype 2 subjects, the 12-week and 16-week SOF+RBV had comparable SVR12 rates (i.e., 82% for the 12-week group and 89% for the 16-week group). Both rates were significantly higher than the 25% historical rate (p-value < 0.0001). However, in the HCV genotype 3 subjects, the SVR12 rate for the 12 weeks of treatment was 30%, which was only half of rate for the 16 weeks of treatment. The rate for the 12-week treatment duration did not show superior to the historical rate (p-value=0.4635), while the rate for the 16-week duration did (p-value<0.001). These results suggested that using SOF+RBV for 12 weeks was sufficient for the genotype 2 treatment-experienced subjects but not for the genotype 3 treatment-experienced subjects.

Table 20: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 108 (FAS)

	12-Week SOF+RBV (N=100)	16-Week SOF+RBV (N=95)	12-Week SOF+RBV vs. 16-Week SOF+RBV	
			Proportion Diff (95% CI)[1]	p-value[2]
SVR12	50% (50/100)	73% (69/95)	-23% (-35%, -11%)	<0.001
95% CI[3]	(40%, 60%)	(63%, 81%)		
p-value compared to 25%[3]	<0.001	<0.001		

Source: Table 9-1 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]Difference in proportions between treatment groups and associated 95% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
[2]Between treatment group p-value was from Cochran-Mantel-Haenszel test stratified by randomization stratification factors.
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

Table 21: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week SOF+RBV vs. 16-Week SOF+RBV	
			Proportion Diff (95% CI)[1]	p-value[2]
SVR12	50% (51/103)	71% (70/98)	-22% (-35%, -9%)	0.0015
95% CI[3]	(40%, 60%)	(61%, 80%)		
p-value compared to 25%[3]	<0.001	<0.001		

[1]based on the Wald asymptotic confidence limits
[2]p-value based on Chi-squared test
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

Table 22: Applicant's Results for Primary Efficacy Endpoint of SVR12 Rate by HCV Genotype in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week SOF+RBV vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Genotype 2			
SVR12	86% (31/36)	94% (30/32)	-8% (-24%, 8.5%)
95% CI[2]	(71%, 95%)	(79%, 99%)	
Genotype 3			
SVR12	30% (19/64)	62% (39/63)	-32% (-48%, -15%)
95% CI[2]	(19%, 42%)	(49%, 74%)	

Source: Table 9-4 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]The 95% CI on the difference was based on the exact method (standardized statistic and inverting two 1-sided test).
[2]The exact 95% CI for the proportion within subgroup was based on the Clopper-Pearson method.

Table 23: Reviewer's Results for Primary Efficacy Endpoint of SVR12 Rate by HCV Genotype in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	Proportion Diff (95% CI)[1]
Genotype 2			
SVR12	82% (32/39)	89% (31/35)	-7% (-23%, 9%)
p-value compared to 25%[2]	< 0.001	< 0.001	
Genotype 3			
SVR12	30% (19/64)	62% (39/63)	-32% (-49%, -16%)
p-value compared to 25%[2]	0.4635	< 0.001	

[1]Wald asymptotic confidence intervals
[3]Within treatment group the exact 95% CI was based on the Clopper-Pearson method and the p-value was from the 2-sided exact 1-sample binomial test.

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The reviewer applied the same NC=F approach as that in Study 1231 to assess the on-treatment responses. Similar to Study 107, there were few subjects who discontinued the study medication prematurely. Therefore, the results from NC=F analysis were close to those based on the applicant's observed analysis.

Like the previous two studies, the SOF+RBV treatment quickly suppressed HCV regardless of the HCV genotype. Almost all subjects achieved HCV viral load below LLOQ within four weeks after starting the treatment. The high response rates sustained through the end of the treatment period in both genotypes and both groups (Figure 5 and Table 24). Additionally, no subject in either group experienced on-treatment virologic failure.

Figure 5: Reviewer's Results for On-Treatment Virologic Response by Treatment in Study 108 (All Treated)

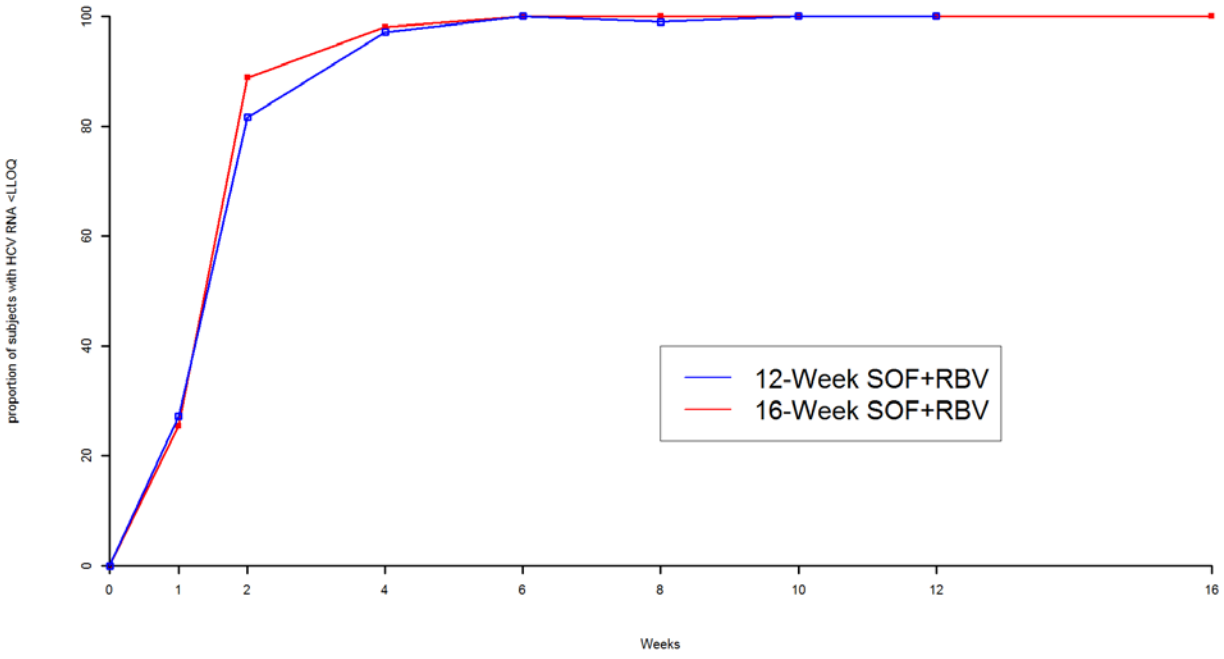


Table 24: Reviewer's Results for On-Treatment Virologic Responses in Study 108 (All Treated, NC=F)

	All		Genotype 2		Genotype 3	
% (# of responders)	**12-Week SOF+RBV (N=103)**	**16-Week SOF+RBV (N=98)**	**12-Week SOF+RBV (N=39)**	**16-Week SOF+RBV (N=35)**	**12-Week SOF+RBV (N=64)**	**16-Week PEG+RBV (N=63)**
Week 1	27% (28)	26% (25)	31% (12)	14% (5)	25% (16)	32% (20)
Week 2	82% (84)	89% (87)	85% (33)	86% (30)	80% (51)	90% (57)
Week 4	97% (100)	98% (96)	100% (39)	100% (35)	95% (61)	97% (61)
Week 6	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 8	99% (102)	100% (98)	100% (39)	100% (35)	98% (63)	100% (63)
Week 10	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 12	100% (103)	100% (98)	100% (39)	100% (35)	100% (64)	100% (63)
Week 16	n/a	100% (98)	n/a	100% (35)	n/a	100% (63)

B2. Post-Treatment Relapses

The relapse pattern was similar to those observed in the SOF+RBV arms in Studies 1231 and 107. Table 25 shows that most relapses occurred 4 weeks following the EOT regardless of treatment duration and the HCV genotype. The HCV genotype 2 subjects had much lower relapse rates than the HCV genotype 3 subjects in both treatment groups. The relapse rates were comparable between

the two durations among the HCV genotype 2 subjects. However, the relapse rates varied between the two groups in the HCV genotype 3 subjects. Around 66% of the genotype 3 subjects in the 12-week group relapsed by 12 weeks after the EOT compared to 38% in the 16-week group. The observed differences in relapse rates between genotypes and between treatment groups within the HCV genotype 3 subjects attributed to the differences in SVR12 rates as discussed in the previous section. Finally, it was important to note that the 38% relapse rate in the 16-week arm was high and therefore the 16 weeks duration may not be long enough for the HCV genotype 3 treatment-experienced subjects.

Table 25: Reviewer's Results for Post-Treatment Relapse in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)
Overall		
by 4 weeks post-treatment	44% (45/103)	24% (24/98)
by 8 weeks post-treatment	46% (47/103)	29% (28/98)
by 12 weeks post-treatment	48% (49/103)	29% (28/98)
Genotype 2		
by 4 weeks post-treatment	15% (6/39)	9% (3/35)
by 8 weeks post-treatment	15% (6/39)	11% (4/35)
by 12 weeks post-treatment	18% (7/39)	11% (4/35)
Genotype 3		
by 4 weeks post-treatment	61% (39/64)	33% (21/63)
by 8 weeks post-treatment	64% (41/64)	38% (24/63)
by 12 weeks post-treatment	66% (42/64)	38% (24/63)

B3. Virologic Responses at EOT and SVR

All subjects had HCV RNA below LLOQ at the EOT but the SVR rates after the EOT were different between the two genotypes and between the two durations among the HCV genotype 3 subjects (Table 26 and Figure 6). The genotype 2 subjects had higher SVR rates than the genotype 3 subjects. The two durations had comparable SVR rates among the genotype 2 subjects, but the rates for the shorter duration appeared much lower than the longer duration in the genotype 3 subjects. The different relapse rates described in the previous section attributed to these different SVR rates.

Table 26: Reviewer's Results for Response Rate at EOT, SVR4 and SVR8 Rates in Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)
Overall			
EOT response rate	100% (103/103)	100% (98/98)	n/a
SVR4 rate	55% (57/103)	76% (74/98)	-20% (-33%, -7%)
SVR8 rate	53% (55/103)	71% (70/98)	-18% (-31%, -5%)

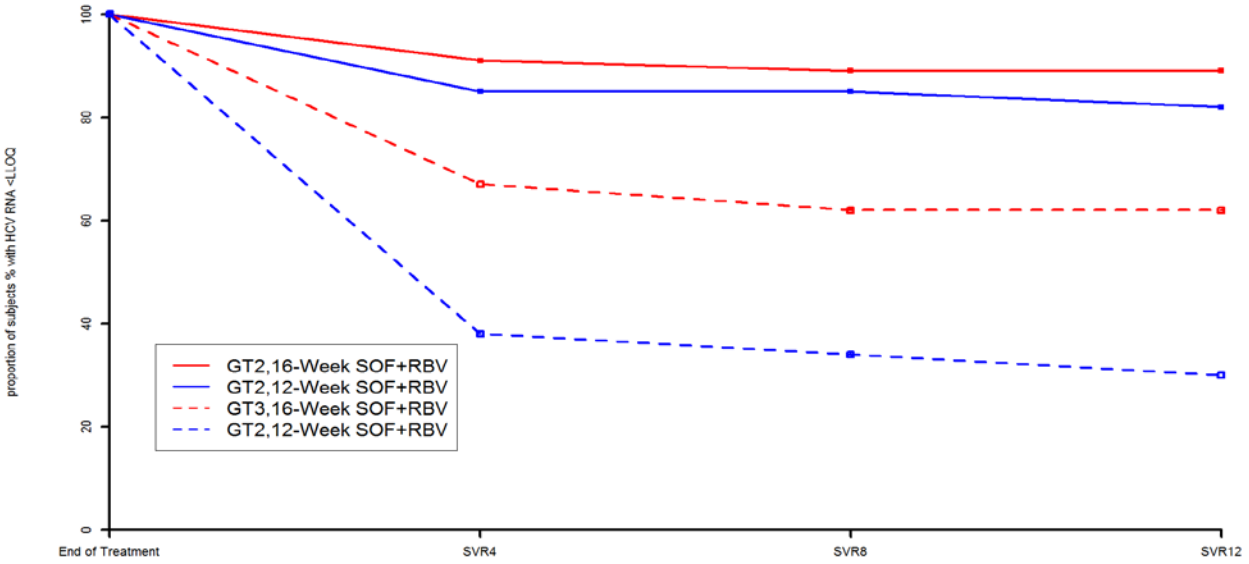
to be continued

Table 32: Reviewer's Results for Response Rate at EOT, SVR4 and SVR8 Rates in Study 108 (All Treated) (Continued)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Genotype 2			
EOT response rate	100% (39/39)	100% (35/35)	n/a
SVR4 rate	85% (33/39)	91% (32/35)	-7% (-21%, 8%)
SVR8 rate	85% (33/39)	89% (31/35)	-4% (-19%, 12%)
Genotype 3			
EOT response rate	100% (64/64)	100% (63/63)	n/a
SVR4 rate	38% (24/64)	67% (42/63)	-29% (-46%, -13%)
SVR8 rate	34% (22/64)	62% (39/63)	-28% (-44%, -11%)

[1]Wald asymptotic confidence intervals

Figure 6: Reviewer's Results for Virologic Responses at EOT and Post-Treatment Visits by Treatment and HCV Genotype in Study 108 (All Treated)



3.2.4 Study 110

3.2.4.1 Study Design and Endpoints

This was a Phase 3, open-label, single arm trial to evaluate the efficacy and safety of SOF in combination of with PEG and RBV in the treatment of treatment-naïve subjects with chronic genotype 1, 4, 5 or 6 HCV infection. The subjects enrolled in the study were treated for 12 weeks with SOF (400 mg once daily) in combination with PEG (180 µg/week) and RBV (1000 or 1200 mg based on baseline body weight). The treatment regimen will be referred as 12-Week

SOF+PEG+RBV hereafter. The primary hypothesis was that the SVR12 rate was greater than the 60% historical rate. The historical rate was based on clinical judgment.

All subjects were to complete a post-treatment Week 4 visit. Subjects with HCV RNA < LLOQ at the post-treatment Week 4 visit completed the post-treatment Week 12 and Week 24 visits unless the confirmed viral relapse occurred. Table 63 and Table 64 in Appendix 6.4 detail the study procedures and schedule of assessments.

The primary efficacy endpoint was the SVR12 rate. The secondary efficacy endpoints included the following:

- SVR4 and SVR24
- proportion of subjects with HCV RNA < LLOQ by study visit
- HCV RNA (log10 IU/mL) and change from baseline in HCV RNA (log10 IU/mL) through Week 8
- proportion of subjects with on-treatment virologic failure and relapse

Of note, the on-treatment virologic failure and relapse were defined the same as in Study 1231.

3.2.4.2 Statistical Methodologies

A. Efficacy Analysis

Two-sided one-sample exact test was performed to determine whether the SVR12 rate was higher than 60%. Also, the Clopper Pearson exact approach was used to construct the 95% CI on the SVR12 rate.

B. Visit Windows

The definition of a visit window for a scheduled visit was the same as that in Study 1231 in Section 3.2.1.2. The visit window for each scheduled visit is provided in Table 65 and Table 66 in Appendix 6.4.

C. Handling Missing Data or Dropouts

The approach to handle missing data or dropouts was the same as that described in Section 3.2.1.2 for Study 1231.

3.2.4.3 Patient Disposition, Demographic and Baseline Characteristics

Table 27 presents the patient disposition. A total of 328 subjects from 55 US sites enrolled in the study, and 327 of them received 12-week SOF 400 mg once daily plus PEG 180 ug/week plus RBV 1000 or 1200 mg /day. Among the 327 enrolled and treated subjects, 2% of them (7 subjects) discontinued study treatment. The most common reason for discontinuation was AE (2%, 5

subjects), following by protocol violation (< 1%, 1 subject) and consent withdrawn (< 1%, 1 subject). After the 12 weeks of treatment, 9% of the treated subjects withdrew from the study mainly due to efficacy failure (8%, 26 subjects).

Table 27: Patient Disposition in Study 110

	12-Week SOF+PEG+RBV
Number of screened	456
Number of enrolled	328
Number of treated	327 (100%)
Discontinued study treatment	7 (2%)
Adverse event	5 (2%)
Protocol violation	1 (0.3%)
Withdrew consent	1 (0.3%)
Discontinued study	29 (9%)
Efficacy failure	26 (8%)
Lost to follow-up	2 (1%)
Withdrew consent	1 (0.3%)

Source: Table 8-2 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Overall the mean age (SD) was 52 years (10). The majority of subjects were male (64%), white (79%), non-Hispanic (86%). The mean (SD) baseline BMI was 29 (7) kg/m^2 (Table 67 in Section 6.4).

The baseline disease characteristics for all enrolled and treated subjects are displayed in Table 68 in Appendix 6.4. The majority of subjects (89%) had genotype 1 HCV infection. There was only one subject infected with genotype 5 HCV and six subjects with genotype 6 HCV infection. Most subjects (83%) did not have cirrhosis at baseline. More than two-third of the subjects had non-CC IL28B allele. The average baseline HCV RNA (SD) was 6.4 $\log_{10}$ (0.67) IU/mL, with majority of the subjects having a baseline HCV RNA $\geq$ 6 $\log_{10}$ IU/mL (78%).

3.2.4.4 Efficacy Results and Conclusion

A. Primary Efficacy Endpoint

Approximately 90% of the treated subjects achieved SVR12, and the rate was significantly greater than the 60% historical rate (Table 28).

Table 28: Applicant's Results for Primary Efficacy of SVR12 Rate in Study 110 (All Treated)

	12-Week SOF+PEG+RBV
SVR12	90% (295/327)
95% CI[1]	(86%, 93%)
p-value compared to 60%[1]	< 0.001

Source: Table 9-1 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA
[1]The exact 95% CI was based on the Clopper-Pearson method and the p-value was from the exact 1-sample binomial test.

Further analysis revealed the SVR12 rates were different between the HCV genotypes 1a and 1b subjects. Historically, the subjects infected with genotype 1a HCV are more difficult to treat than those infected with genotype 1b HCV infection. For the approved Telaprevir regimen, the SVR24 rates were 74% and 86% for the genotype 1a and 1b treatment-naïve subjects, respectively. Of note, the genotype was determined by the LiPA method. Please refer to the statistical review for Telaprevir (NDA 201917) by Dr. Thomas Hammerstrom for the details. For the approved Boceprevir treatment regimen, the SVR24 rate was 59% for the genotype 1a treatment-naïve subjects and 66% for the genotype 1b treatment-naïve subjects. Of note, the genotype was based on the (b) (4) method. Please refer to the statistical review for Boceprevir (NDA 202258) by Dr. Wen Zeng for the details.

The HCV genotype 1a subjects had 10% higher SVR12 rate than the HCV genotype 1b subjects in Study 110 (92% for the subjects with genotype 1a, 82% for the subjects with genotype 1b), and the difference was significant at the significance level of 0.05. The applicant attributed the difference to the higher proportion of IL28B CC subjects, black subjects, subjects with cirrhosis at baseline and mean age among subjects with genotype 1b compared to the subjects with genotype 1a (Table 69 in Section 6.4). The reviewer compared the SVR12 rates between the subjects with genotype 1a and 1b across the subgroups defined by the demographic and baseline characteristics (Table 71 in Section 6.4). The HCV genotype 1a subjects had numerically higher SVR12 rates than the HCV genotype 1b subjects in almost all subgroups. Therefore, the reviewer did not agree with the applicant's interpretation. In the reviewer's opinion, the lack of a control group in the study made it difficult to definitively conclude whether the observed difference in the SVR12 rates between subjects with genotype 1a and 1b was due to chance or not.

Finally, the sample sizes for the HCV genotype 5 and 6 subjects were too small to be conclusive although the 7 genotype 5 and 6 subjects achieved SVR12 in the study.

B. Key Secondary Efficacy Endpoints

B1. On-Treatment Virologic Responses

The HCV viral load was rapidly suppressed after the subjects were treated with SOF+PEG+RBV. Almost all subjects had HCV RNA < LLOQ 4 weeks after the treatment. The high response rate was maintained throughout the rest of the treatment period (Figure 7 and Table 29). Also, no subject experienced the on-treatment virologic failure in the study.

Figure 7: On-Treatment Virologic Responses for Study 110 (All Treated)

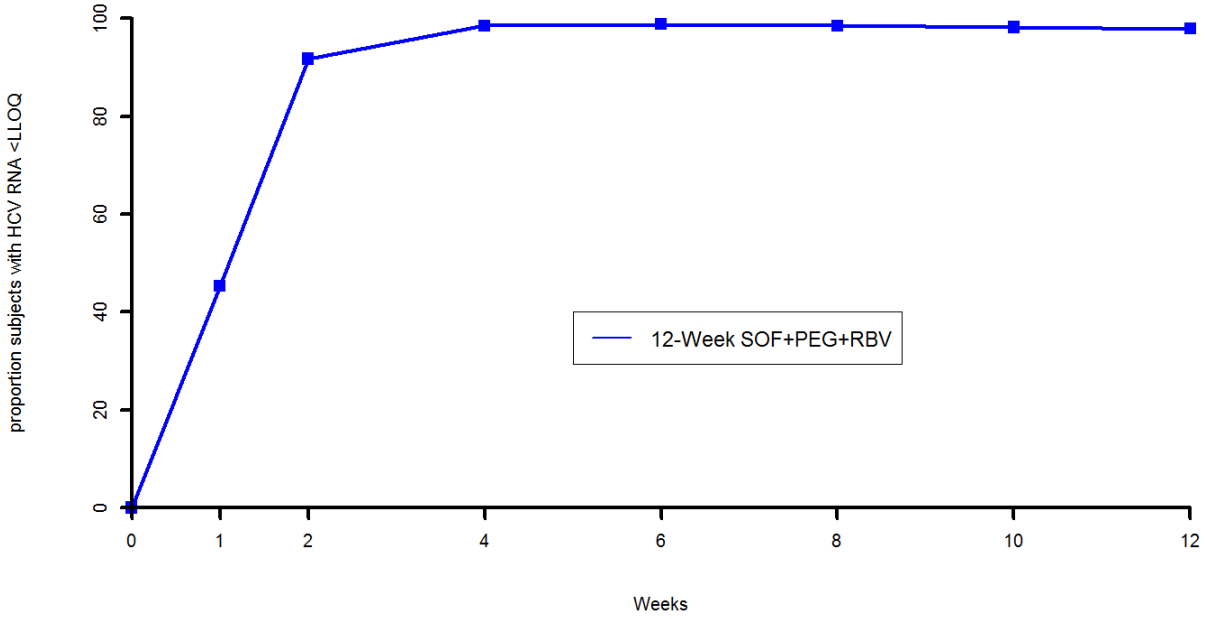


Table 29: Reviewer's Results for On-Treatment Virologic Responses in Study 110 (All Treated, NC=F)

	12-Week SOF+PEG+RBV (N=327)
Week 1	45% (148)
Week 2	92% (300)
Week 4	98% (322)
Week 6	99% (323)
Week 8	98% (322)
Week 10	98% (321)
Week 12	98% (320)

B2. Post-Treatment Relapses

Overall less than 10% of the subjects relapsed 12 weeks after the EOT (Table 30). Also, a higher proportion of the subjects with genotype 1b relapsed compared with the subjects with genotype 1a, which resulted in the lower SVR12 rate for the HCV genotype 1b subjects as described in Section 3.2.4.4 A.

Table 30: Reviewer's Results for Post-Treatment Relapse in Study 110 (All Treated)

	12-Week SOF+PEG+RBV
Overall	
by 4 weeks post-treatment	7% (22/326)
by 12 weeks post-treatment	9% (28/326)
Genotype 1a	
by 4 weeks post-treatment	6% (14/225)
by 12 weeks post-treatment	8% (18/225)
Genotype 1b	
by 4 weeks post-treatment	11% (7/65)
by 12 weeks after EOT	14% (9/65)
Genotype 4	
by 4 weeks post-treatment	4% (1/28)
by 12 weeks post-treatment	4% (1/28)
Genotype 5	
by 4 weeks post-treatment	0% (0/1)
by 12 weeks post-treatment	0% (0/1)
Genotype 6	
by 4 weeks post-treatment	0% (0/6)
by 12 weeks post-treatment	0% (0/6)

B3. Virologic Responses at EOT and Post-Treatment

Almost all subjects in the study achieved virologic suppression at the EOT regardless of the HCV genotype. The response rates remained high for all genotypes after the EOT (Table 31). Figure 9 displays the response rates at the EOT and SVR for the subjects with genotype 1a and 1b HCV.

Table 31: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 110 (All Treated)

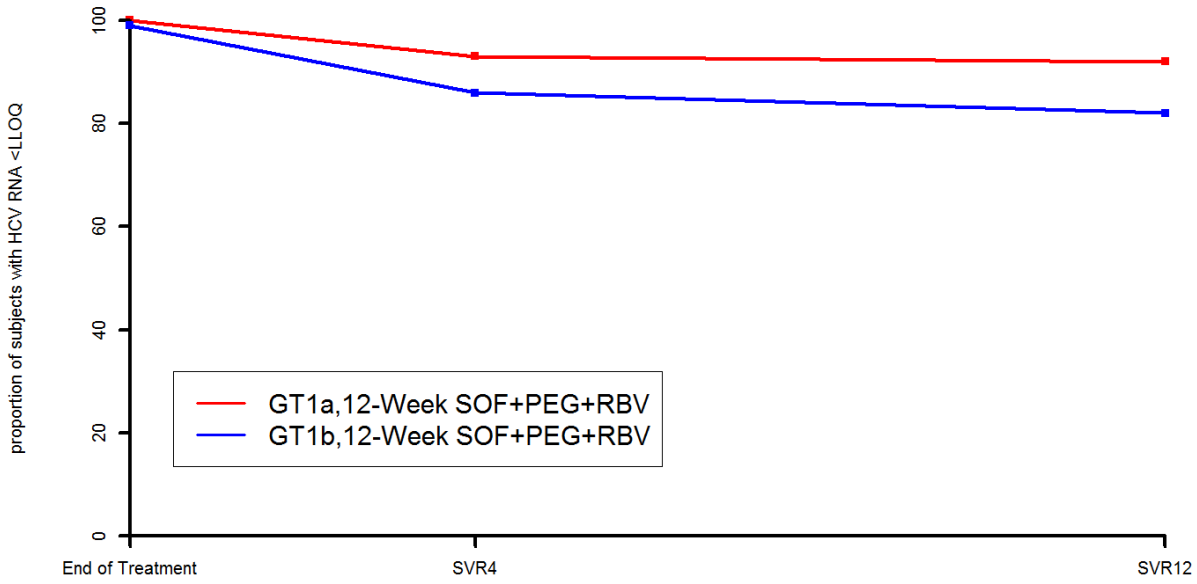
	12-Week SOF+PEG+RBV
Overall	
EOT response rate	99.7% (326/327)
SVR4 rate	92% (302/327)
Genotype 1a	
EOT response rate	100% (225/225)
SVR4 rate	93% (210/225)
Genotype 1b	
EOT response rate	99% (65/66)
SVR4 rate	86% (57/66)

to be continued

Table 40: Reviewer's Results for EOT Response Rate and SVR4 Rate in Study 110 (All Treated) (Continued)

	12-Week SOF+PEG+RBV
Genotype 4	
EOT response rate	100% (28/28)
SVR4 rate	96% (27/28)
Genotype 5	
EOT response rate	100% (1/1)
SVR4 rate	100% (1/1)
Genotype 6	
EOT response rate	100% (6/6)
SVR4 rate	100% (6/6)

Figure 8: Reviewer's Results for Virologic Response Rates at EOT and Post-Treatment by Subgenotype in Subjects with HCV Genotype 1 Infection in Study 110 (All Treated)



3.2.5 Bridging Analysis to Estimate SVR12 Rate for 16-Week SOF+RBV for Genotype 3 Treatment-Naïve Subjects

3.2.5.1 Background and Objective for Bridging Analysis

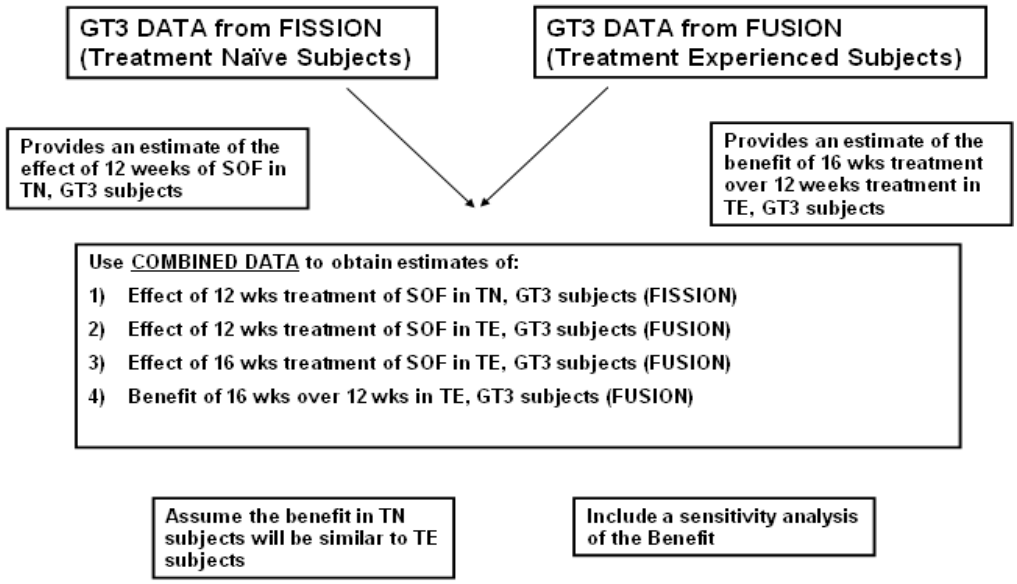
The results in Study 1231 demonstrated that the 12 weeks of SOF+RBV treatment had a lower SVR12 rate than the 24 weeks of PEG+RBV in treatment-naïve subjects with genotype 3 HCV infection (56% in the 12-week SOF+RBV group vs. 62% in the 24-week PEG+RBV group). This suggested that using SOF+RBV for 12 weeks could be insufficient to treat HCV genotype 3 treatment-naïve subjects. Study 108 showed that the 16 weeks of SOF+RBV had a SVR12 rate

twice as high as the 12 weeks of SOF+RBV among HCV genotype 3 treatment-experienced subjects. It implied that genotype 3 treatment-naïve subjects may require 16 weeks of treatment. However, there was no study evaluating the treatment effect of the 16 weeks of SOF+RBV in HCV genotype 3 treatment-naïve subjects. Therefore, the applicant proposed a post-hoc bridging analysis in order to estimate the SVR12 rate for the 16 weeks of treatment in the HCV genotype 3 treatment-naïve subjects based on the SVR12 rates seen in Studies 1231 and 108.

3.2.5.2 Applicant's Bridging Analysis

Figure 9 below displays the applicant's modeling framework for bridging analysis.

Figure 9: Modeling Framework for Bridging Analysis



GT= genotype; TE = treatment-experienced; TN = treatment-naive

Source: Figure 1 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.
Note: Fission Study referred to Study 1231 and Fusion Study referred to Study 108.

(b) (4)

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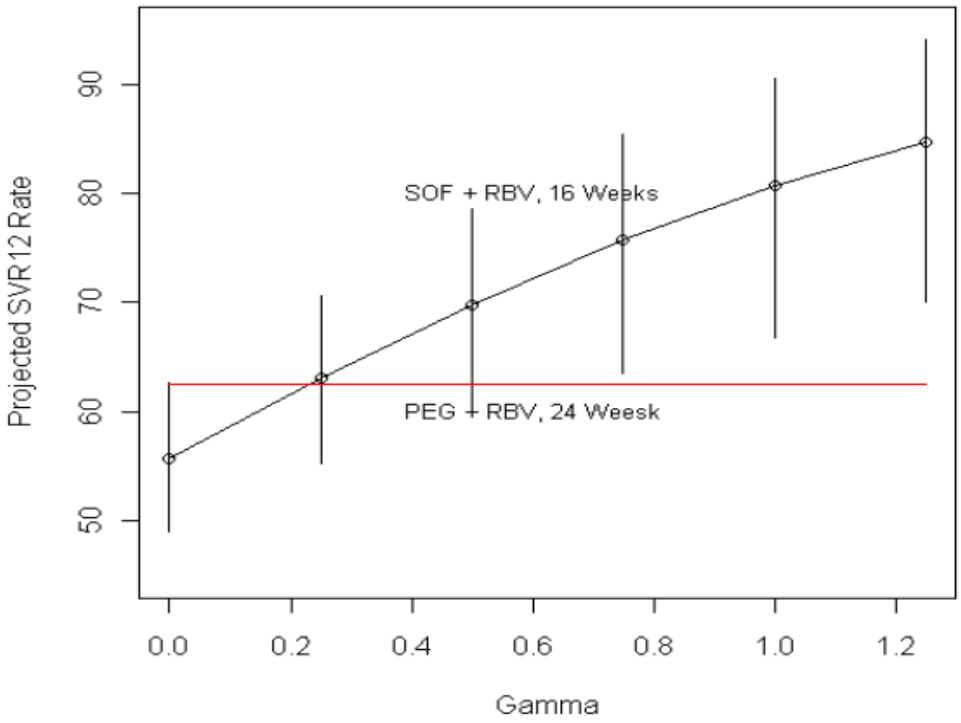
Figure 10: Applicant's Sensitivity Analysis for Impact of 16-Week Treatment Duration of SOF+RBV Using Model 1



Source: Figure 2 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.

3.2.5.3 Reviewer's Sensitivity Analyses

A. Maximum Likelihood Estimation (MLE)

The reviewer assessed whether the MLE approach would produce similar results to those from the Bayesian analysis. Therefore, the reviewer applied the MLE approach to estimate the parameters in the applicant's two logistic models. The reviewer found that the MLE approach led to almost identical SVR12 rates estimated by the Bayesian approach. Specifically, the SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects estimated by MLE was 80.9% based on the first model and was 78.5% based on the second model.

B. Models with Different Covariates

The applicant did not specify how they chose the three baseline covariates of gender, baseline cirrhotic and baseline HCV RNA level in their models. The reviewer used the stepwise procedure to select the important baseline covariates to predict the SVR12 rate. The reviewer found that IL28B status (CC vs. non-CC) was another significant prognostic factor in prediction of the SVR12 rate in addition to gender, baseline cirrhosis and HCV RNA level. Therefore, the reviewer developed a new model with treatment indicators, gender, baseline cirrhosis status, IL28B status and baseline HCV RNA level. Note that the only difference between this model and the applicant's first model was

that this model included IL28 B status. The reviewer used MLE to estimate the model parameters. The estimated SVR12 rate for the 16 weeks of SOF+RBV in treatment-naïve subjects was 80.3%, which was similar to the applicant's result based on their first model without interaction term. Additionally, the reviewer generated another new model which only contained the treatment indicators, gender and baseline cirrhosis status. The estimated SVR12 rate was 80.9%, which again was close to the applicant's result. In summary, models with different covariates resulted in similar estimated SVR12 rates for the 16 weeks of SOF+RBV in the HCV genotype 3 treatment-naïve subjects.

C. Extrapolation

Instead of applying the model to estimate the SVR12 rate for the 16 weeks of SOF+RBV, the reviewer extrapolated the rate using the observed SVR12 rates in Studies 1231 and 108 directly based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. A merit of the extrapolation is that it is easy to understand. The detailed calculation is summarized in the following paragraphs.

Let $P_{TN, 16w}$ = the estimated SVR12 rate for HCV genotype 3 treatment-naïve subjects receiving 16 weeks of SOF+RBV treatment;

$P_{TN, 12w}$ = the observed SVR12 rate for HCV genotype 3 treatment-naïve subjects who received 12 weeks of SOF+RBV treatment in Study 1231;

$P_{TE, 16w}$ = the observed SVR12 rate for HCV genotype 3 treatment-experienced subjects who received 16 weeks of SOF+RBV treatment in Study 108;

$P_{TE, 12w}$ = the observed SVR12 rate for HCV genotype 3 treatment-experienced subjects who received 12 weeks of SOF+RBV treatment in Study 108.

The extrapolation used the observed SVR12 rates for the HCV genotype 3 subjects in Studies 108 and 1231 to derive the SVR12 rate for the 16-week SOF+RBV treatment in genotype 3 treatment-naïve subjects (Figure 11).

Figure 11: Bridging Analysis based on Extrapolation

genotype 3 treatment-experienced (Study 108)

Treatment	SVR12 rate
12-week SOF+RBV	$P_{TE, 12w}$
16-week SOF+RBV	$P_{TE, 16w}$

genotype 3 treatment-naïve (Study 1231)

Treatment	SVR12 rate
12-week SOF+RBV	$P_{TN, 12w}$
16-week SOF+RBV	**? $P_{TN, 16w}$**

Specifically, the extrapolation of the SVR12 rate for the 16 weeks of SOF+RBV treatment was performed by solving the following equation which assumed the same OR of the 16 weeks of treatment over the 12 weeks of treatment in HCV genotype 3 treatment-naïve and treatment-experienced subjects:

$$\frac{P_{TN,16w}/(1-P_{TN,16w})}{P_{TN,12w}/(1-P_{TN,12w})} = \frac{P_{TE,16w}/(1-P_{TE,16w})}{P_{TE,12w}/(1-P_{TE,12w})}.$$

The reviewer also used the relative risk (RR) and proportion difference (PD) to extrapolate the rate. Specifically, the extrapolation was done using the following two equations. The first equation assumed the RR of not achieving SVR12 for the 16 weeks of SOF+RBV treatment over the 12 weeks of SOF+RBV in the HCV genotype 3 treatment-naïve subjects was the same as the RR in the HCV genotype 3 treatment-experienced subjects observed in Study 108. The second equation assumed the treatment difference in the SVR12 rate between the 16 weeks and the 12 weeks of SOF+RBV in HCV genotype 3 treatment-naïve was the same as that in the treatment-experienced subjects seen in Study 108.

$$\frac{1-P_{TN,16w}}{1-P_{TN,12w}} = \frac{1-P_{TE,16w}}{1-P_{TE,12w}}$$

$$P_{TN,16w} - P_{TN,12w} = P_{TE,16w} - P_{TE,12w}$$

Table 32 below summarizes the analysis results. Note that the extrapolation based on OR had similar results to those obtained from the logistic regression.

Table 32: Applicant's Bridging Analysis Results for Estimated SVR12 Rate for 16 Weeks of SOF+RBV in HCV Genotype 3 Treatment-Naïve Subjects based on Extrapolation Approach

Measures	Estimated SVR12 rate for 16-week SOF+RBV in HCV Genotype 3 treatment-naive subjects (95% CI)
Odds ratio	83% (69%, 92%)
Relative risk	76% (65%, 84%)
Proportion difference	88% (70%, 100%)

Similar to the applicant's sensitivity analysis, the reviewer calculated the SVR12 rates for 16 weeks of SOF+RBV in the genotype 3 treatment-naïve subjects based on the different percent of benefit or risk retained (Table 33). The lowest estimated rate was 64% when it was assumed that the RR of 16-week treatment over the 12-week treatment in genotype 3 treatment-naïve subjects was 50% higher than what was observed in genotype 3 treatment-experienced subjects in Study 108. This low rate was about the same as the 63% SVR12 rate for the HCV genotype 3 treatment-naïve subjects receiving the 24 weeks of PEG+RBV treatment in Study 1231.

Table 33: Applicant's Sensitivity Analysis

Measures	% benefit/risk retained	Estimated SVR12 rate for 16-week SOF+RBV in GT3 TN subjects
Odds ratio	50%	71%
	75%	78%
	100%	83%
Relative risk	150%	64%
	125%	70%
	100%	76%
Proportion difference	50%	72%
	75%	80%
	100%	88%

3.3 Evaluation of Safety

The medical officer, Dr. Poonam Mishra, had reviewed the safety data. Based on her review, there were no major safety issues related to the use of SOF. She pooled the safety data from the 12-week SOF+RBV arms in Studies 1231, 107 and 108 in her integrated safety evaluation. In the reviewer's opinion, it was reasonable to combine the data since the proportions of some adverse events were consistent across the three studies even though the randomization ratio in Study 107 was different in Studies 1231 and 108 (Table 77 in Section 6.7). For a detailed safety evaluation, please refer to Dr. Poonam Mishra's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses will be reported by each study individually because the four studies had different patient populations. In all studies, the subgroup analyses were planned in the subsets defined by the following baseline measures: age (< 50 years, ≥ 50 years), gender, race (black, non-black), geographic region (US, non-US), ethnicity (Hispanic, non-Hispanic), baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2), HCV genotype, cirrhosis status at baseline (absence, presence), IL28B (CC, non-CC), baseline HCV RNA (< 6 $\log_{10}$ IU/mL, ≥ 6 $\log_{10}$ IU/mL), and baseline ALT level (≤ 1.5xULN, > 1.5xULN). In Study 107, subgroup analyses by IFN (IFN intolerant, IFN eligible, unwilling to take IFN), and duration of previous HCV treatment (no, ≤ 12 weeks, > 12 weeks) were also planned. In Study 108, an additional pre-specified subgroup analysis included the response to prior HCV treatment (nonresponse, relapse/breakthrough). The Breslow Day test was applied to evaluate whether the odds ratios of achieving SVR12 between the treatment arms were homogeneous

between the subgroups defined by a baseline measure. In other words, the test assessed the consistency of the treatment effect between the subgroups.

4.1 Study 1231

The applicant conducted the subgroup analyses based on the FAS which excluded the three subjects with misclassified genotype, while the reviewer's subgroup analyses were based on the All Treated population. The results from the reviewer's analyses will be presented in this section (also see Table 41, Table 42 and Table 43 in Section 6.1).

4.1.1 Age, Gender, Race, and Geographic Region

The treatment difference (i.e., 12-Week SOF+RBV – 24-week PEG+RBV) was approximately -10% in the subgroup <50 years of age and 10% in the subgroup of ≥ 50 years of age (p-value = 0.0200 based on the Breslow-Day test for the homogeneity of the odds ratios between the 2 age groups).

The interaction between treatment and gender was not obvious. For the subgroup analysis by race, the SOF+RBV arm had a better SVR12 rate than the PEG+RBV arm in Black subjects, but the sample size was too small to be informative. Also, there was not an evident difference between the two treatment groups in the non-Black subjects.

The treatment difference varied between the US and non-US subjects. Specifically, the difference was 6% in the US subjects versus -10% among the non-US subjects (p-value = 0.0718 based on the Breslow-Day test for the homogeneity of the odds ratios between the two geographic regions). However, the fluctuation in treatment difference between the US and non-US subjects was confounded by genotype as the majority of the non-US subjects had a genotype 3 HCV infection.

4.1.2 Other Special/Subgroup Populations

Except for the two genotype groups mentioned earlier, there was not any significant treatment by subgroup interaction. However, the treatment differences in the subgroups defined by cirrhosis, IL28B and baseline HCV RNA level appeared large. The findings are highlighted as follows:

- As compared to the PEG+RBV treatment, the SOF+RBV treatment resulted in 2% lower SVR12 rate in non-cirrhotic subjects but 8% higher among cirrhotic subjects (p-value = 0.3402 based on the Breslow-Day test for the homogeneity of the odds ratios between the two cirrhotic subgroups).

- The SOF+RBV treatment had a 8% higher rate in the subjects with baseline HCV RNA <6 log10 IU/mL and a 6% lower rate in the subjects with baseline HCV RNA ≥ 6 log10 IU/mL (p-value = 0.1045 based on the Breslow-Day test for the homogeneity of the odds ratios between the two subgroups for the baseline HCV RNA level).

- Compared with the subjects in the PEG+RBV group, 8% more subjects in the SOF+RBV group achieved SVR12 among the IL28B CC subjects and 6% less achieved SVR12 among IL28B

non-CC subjects (p-value = 0.0848 based on the Breslow-Day test for the homogeneity of the odds ratios between the two IL28B subgroups).

4.1.3 Subgroup Analysis for Each Genotype

As discussed in Section 3.2.1.4, the HCV genotype appeared to affect the SVR12 rate. The SOF+RBV treatment group had significantly higher SVR12 rates than the PEG+RBV treatment among the genotype 2 subjects, whereas the SOF+RBV treatment resulted in lower SVR12 rates than the PEG+RBV treatment in the genotype 3 subjects. The post-hoc subgroup analyses for each genotype were conducted to examine the consistency of the results for the groups defined by patient demographics and baseline disease characteristics (Table 42 and Table 43). The SOF+RBV treatment group had consistently greater SVR12 rates than the PEG+RBV treatment group across all subgroups in the genotype 2 subjects. Meanwhile, the SOF+RBV regimen led to lower SVR12 rates in most of the subgroups among the genotype 3 subjects.

4.2 Study 107

Because no subject in the placebo group in the study achieved SVR12, the purpose of the subgroup analyses was to check the consistency of the SVR12 rates for 12 weeks of SOF+RBV in the subgroups. Table 52 in Appendix 6.2 summarizes the reviewer's subgroup analyses results for the study.

4.2.1 Age, Gender, Race, Geographic Region

Similar SVR12 rates for the SOF+RBV treatment were observed in the two age subsets. Also, females had a higher SVR12 rate than males (84% for females and 73% for males). In the subgroup analysis for race, a higher proportion of black subjects (89%) achieved SVR12 than the non-black subjects (77%). However, there were only nine black subjects, and the sample size was too small to make a conclusion. Finally, the SVR12 rates were comparable between the US and non-US subjects (77% for the US subjects, and 79% for the non-US subjects).

4.2.2 Other Special/Subgroup Populations

Analyses resulted in similar SVR12 rates for the subgroups defined by most of the baseline measures. However, the SVR12 rates for the 12-week SOF+RBV treatment arm differed for the HCV genotype, duration of prior HCV treatment and cirrhosis subgroups, which are highlighted as follows:

- A higher proportion of genotype 2 subjects receiving 12-week SOF+RBV achieved SVR12 compared to the genotype 3 subjects (93% for the genotype 2 subjects, 61% for the genotype 3 subjects). A detailed discussion regarding different performance between the genotypes 2 and 3 subjects was presented in Section 3.2.2.4.

- The duration of prior HCV treatment appeared to have an impact on the SVR12 rate for 12-week SOF+RBV. The rate was highest in the treatment-naïve subjects (82%), followed by the subjects who had previously received HCV treatment for no longer than 12 weeks (71%). The rate was lowest among subjects who had prior HCV treatment for more than 12 weeks (38%).

- The SVR12 rate in the cirrhotic subjects was approximately 20% lower than the non-cirrhotic subjects (61% for cirrhotic subjects, 81% for non-cirrhotic subjects).

4.2.3 Subgroup Comparisons for 12 Weeks of SOF+RBV between Genotype 2 and 3

The significant difference in the SVR12 rate between the subjects with genotype 2 HCV infection and those with genotype 3 infection as described in Section 3.2.2.4. Of note, the patient demographics and baseline disease characteristics were well balanced between the subjects infected with genotype 2 HCV and those infected genotype 3 HCV (Table 53 in Appendix 6.2). The reviewer compared the SVR12 rates for the 12-week SOF+RBV between the two genotypes in the subgroups defined by the patient demographics and baseline disease characteristics. The results indicated that genotype 2 HCV infected-subjects had consistently higher SVR12 rates than the genotype 3 HCV infected-subjects across all subgroups (Table 53 in Appendix 6.2). Some observations are summarized as follows:

- Females and males had similar SVR12 rates among the subjects with genotype 2 HCV infection (93% for females, 92% for males), but females had a much greater SVR12 rate than males in subjects with genotype 3 HCV infection (76% for females, 49% for males).

- The SVR12 rates were relatively high for the subjects infected with genotype 2 HCV infection regardless of duration of prior HCV treatment (92% for the treatment-naïve subjects, 100% for the subjects who had ≤ 12 weeks of prior treatment, 80% for the subjects who received > 12 weeks of prior treatment). In contrast, the prior treatment duration appeared to affect the SVR12 rates in the subjects infected with genotype 3 HCV. Specifically the SVR12 rates were 70% for treatment-naïve subjects, 40% for the subjects who had ≤ 12 weeks of prior treatment, and 18% for the subjects who had > 12 weeks of prior treatment. However, the sample sizes in the subgroups of the subjects having ≤ 12 weeks of prior treatment and the subjects having > 12 weeks of prior treatment were too small to be conclusive.

- In the genotype 2 HCV infected-subject, the SVR12 rates were unaffected by the cirrhosis status. However, the cirrhotic subjects had notably lower SVR12 rate than the non-cirrhotic subjects among the subjects infected with genotype 3 HCV.

4.3 Study 108

4.3.1 Age, Gender, Race, Geographic Region

As shown in Table 60 in Appendix 6.3, the SVR rates in the SOF+RBV 16-week group were greater than those in the SOF+RBV 12-week group in both age subsets.

For gender, a higher proportion of females than males achieved SVR12 in the 12-week treatment group (70% for females vs. 41% for males) and in the 16-week group (87% for females vs. 64% for males). However, the result from Breslow-Day test for the homogeneity of the odds ratios between gender did not show significant treatment by gender interaction (p=0.8743).

There were only 6 black subjects, and all of them achieved SVR12 in the study. For non-Black subjects, the longer treatment duration again had a better SVR12 rate than the shorter duration.

In both geographic subgroups, the SVR12 rates for the 16-week SOF+RBV were greater than those in the 12-week SOF+RBV. Also, higher SVR12 rates were observed among US subjects compared with non-US subjects in both treatment groups. This was confounded by genotype because US sites enrolled more genotype 2 subjects than non-US sites.

4.3.2 Other Special/Subgroup Populations

The SVR12 rate appeared to be affected by the genotype. The differences in genotype 2 and genotype 3 subjects had been discussed in Section 3.2.3.4. The subgroup analyses the SOF+RBV 16 Week group had consistently higher SVR12 rates than the SOF+RBV 12 Week group for all other subgroups.

4.3.3 Subgroup Analysis for Each Genotype

Because of the apparent treatment by genotype interaction, subgroup analyses for each genotype were performed to evaluate whether the treatment difference between the two treatment durations were consistent across the subgroups stratified by the patient demographics and baseline disease characteristics and to identify whether there was a subgroup of subjects who would benefit from a longer duration of treatment in particular among the genotype 2 subjects. Table 61 summarizes the result for the genotype 2 subjects and Table 62 for the genotype 3 subjects.

It was of clinical interest to investigate whether genotype 2 subjects with poor prognostic factors such as cirrhosis, CC IL28B genotype, or prior lack of response to previous HCV treatment would benefit from longer treatment. Although the 16-week treatment produced numerically higher SVR12 rates compared to the 12-week treatment, the sample sizes in these subsets were approximately 10 subjects, which was too small to be conclusive.

Among genotype 3 subjects, 16 weeks of SOF+RBV showed consistently greater SVR12 rates than the 12 weeks of treatment in almost all subgroups except for black subjects because there were only two black subjects with genotype 3 HCV infection in the study. Also, it was noticed that females had much higher SVR12 rates than males in both durations (i.e., 44% and 25% for females and males in the 12-Week SOF+RBV group, respectively; 81% and 52% for females and males in the 16-Week SOF+RBV group, respectively). A further investigation of the gender difference in genotype 3 subjects in terms of response to the SOF+RBV treatment based on the data from both Studies 1231 and 108 was done, and the results are presented in Section 4.5.

4.4 Study 110

Study 110 was a single arm trial. Therefore, the purpose of the subgroup analyses was to evaluate the consistency of the SVR12 rate for 12-weeks of SOF+PEG+RBV across different subgroups. The results are shown in Table 70 in Section 6.4.

4.4.1 Age, Gender, Race, Geographic Region

The SVR12 rates in the subgroups determined by age, gender, geographic region and ethnicity were at least 87%. There was no any notable difference between the subgroups defined by a covariate.

4.4.2 Other Special/Subgroup Populations

All subgroups defined by baseline characteristics had SVR12 rates greater than 80%. Subgroup analyses demonstrated that the subjects infected with genotype 1a HCV had a higher SVR12 rate than the subjects infected with genotype 1b HCV, (see Section 3.2.4.4). In addition, a higher SVR12 rate was observed in the noncirrhotic subjects than the cirrhotic subjects (92% for noncirrhotic subjects, 80% for cirrhotic subjects). Moreover, subjects with IL28B CC allele had a higher SVR12 rate compared with the subjects with non-CC IL28B CC allele (98% for the CC subjects, 87% for the non-CC subjects).

4.5 Gender Difference in HCV Genotype 3 Subjects

There was a clinical concern regarding the gender difference in response to SOF+RBV in genotype 3 subjects. Therefore, the reviewer compared the SVR12 rates between female and male subjects among the HCV genotype 3 subjects in Studies 1231, 107 and 108. The post-hoc analyses showed that females with genotype 3 infection tended to have better SVR12 rates than males in all of the SOF+RBV groups in the three studies (Table 34). In addition, compared with the 24-week PEG+RBV group, the gender difference was more notable for the 12-week SOF+RBV in Study 1231. The reviewer also found that the females had better SVR12 rates across almost all subsets determined by the baseline measures as shown in the tables in Appendix 6.6. In summary, the post-hoc exploratory analyses showed that gender appeared to affect the SVR rate for SOF+RBV among the HCV genotype 3 subjects.

Table 34: SVR12 Rates by Gender in HCV Genotype 3 Subjects in Study 1231, 107 and 108

	Females	Males	Females vs. Males Proportion Diff (95% CI)
Study 1231			
12-week SOF+RBV	71% (41/58)	49% (61/125)	22% (7%, 37%)
24-week PEG+RBV	69% (41/59)	59% (69/117)	10.5% (-4%, 25%)
Study 107			
12-week SOF+RBV	76% (34/45)	49% (26/53)	27% (8%, 45%)
Placebo	0%	0%	n/a

to be continued

Table 34: SVR12 Rates by Gender in HCV Genotype 3 Subjects in Study 1231, 107 and 108 (Continued)

	Females	Males	Females vs. Males Proportion Diff (95% CI)
Study 108			
12-week SOF+RBV	44% (7/16)	25% (12/48)	19% (-8%, 46%)
16-week SOF+RBV	81% (17/21)	52% (22/42)	29% (6%, 51%)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

One statistical issue was the apparent treatment differences between the HCV genotypes 2 and 3 subjects. In the reviewer's opinion, the observed differences in the SVR12 rates between genotypes 2 and 3 subjects, in particular for the difference in the SOF+RBV treatment regimens in Studies 1231, 107 and 108, were not due to the chance. It was expected the HCV genotype would have an impact on the SVR12 rate beforehand. Therefore, HCV genotype was one of the stratification factors in the randomization for Studies 1231 and 108, and the subgroup analysis by HCV genotype was one of the pre-defined subgroup analyses in the statistical analysis plan (SAP) in each study. In Study 1231, the 12-week SOF+RBV regime was compared to the 24 weeks PEG+RBV regime and the treatment-by-genotype interaction was significant (p-value = 0.0002). The difference in the SVR12 rate between genotypes 2 and 3 was greater in the 12-week SOF+RBV treatment arm than in the 24-week PEG+RBV treatment arm. In the 12-week SOF+RBV group, 97% and 56% of genotypes 2 and 3 subjects achieved SVR12, respectively (p-value < 0.0001). On the other hand, 78% and 63% of genotypes 2 and 3 subjects, respectively, achieved SVR12 in the 24-week PEG+RBV group (p-value = 0.0326). Study 107 compared 12-weeks of SOF+RBV against placebo where no placebo subjects achieved SVR12. In the 12-week SOF+RBV group, the HCV genotype 2 subjects had significantly higher SVR12 rate than the HCV genotype 3 subjects (i.e., 93% vs. 61%, p-value < 0.0001). In Study 108 where two durations of SOF+RBV were evaluated, the difference in SVR12 rates between the genotypes 2 and 3 subjects were significant within each duration group. In the 12-week SOF+RBV group, 83% of the HCV genotype 2 subjects achieved SVR12 compared with 30% of the HCV genotype 3 subjects (p-value < 0.0001). In the 16-week SOF+RBV group, the SVR12 rates were 82% and 62% for the genotypes 2 and 3 subjects, respectively (p-value = 0.0052). The collective evidence from the three studies strongly suggested that the HCV genotype 2 subjects did have a higher SVR rate than the HCV genotype 3 subjects. The small and consistent p values could overcome the concern of the lack of a pre-specified plan to control Type 1 error.

Another major statistical issue was the appropriateness of the statistical methods in the applicant's bridging analyses to derive the SVR12 rate for the 16-week SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection based on the observed rates in Studies 1231 and 108. The applicant used the data from all HCV genotype 3 subjects in Studies 1231 and 108 to generate the logistic regression models. They estimated the model parameters using a Bayesian approach and derived the SVR12 rate for the 16 week SOF+RBV regimen in the genotype 3 treatment-naïve subjects based on the assumption that the OR of the 16-week SOF+RBV over the 12-week SOF+RBV in the genotype

3 treatment-naïve subjects was the same as the OR in the genotype 3 treatment-experienced subjects. The reviewer conducted several analyses to test the sensitivity of the results to various methodologies. First, the reviewer used the maximum likelihood estimation (MLE) approach to estimate the model parameters. The reviewer obtained almost identical results to the applicant's results. Also, the reviewer estimated the SVR12 rate by extrapolating from the observed rates in Studies 1231 and 108 based on the assumption of the same ORs between treatment-naïve and treatment-experienced subjects. The merit of the extrapolation was that it was relatively easy to follow. The reviewer obtained an 83% SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve subjects based on the extrapolation, which was similar to the applicant's result. The reviewer also used relative risk (RR) and proportion difference (PD) to extrapolate the SVR rate. The estimated SVR12 rate was 76% based on RR and 88% based on PD. All of these post-hoc analyses suggested that 16 weeks of SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects would lead to a higher SVR12 rate than the observed 56% rate for the 12 weeks of SOF+RBV treatment seen in Study 1231. Again, the strong assumptions in the bridging analysis and the lack of Week 16 data made it difficult to determine the optimal treatment duration from the statistical point of view.

Another issue worth noting applicant's exclusion of subjects from the efficacy analysis sets in Studies 1231 and 108. There were nine subjects who were misclassified as having genotype 2 HCV infection by the LiPA method at screening but were subsequently found to have genotype 1 infection by population sequencing in the two studies. The LiPA method is currently used to determine the genotype in the clinical practice, whereas population sequencing is not. The applicant excluded these subjects from the efficacy analysis. The inclusion or exclusion of these subjects slightly affected the study results, and the reviewer included the subjects in the analysis in order to follow the intent-to-treat principle.

The final issue was the interpretation of the finding that the HCV genotype 1a treatment-naïve subjects had higher SVR12 rate than the genotype 1b subjects in Study 110 (i.e., 92% vs. 82%). Historically, the subjects infected with genotype 1a HCV are more difficult to treat compared to the subjects with genotype 1b HCV infection. The applicant attributed the observed treatment difference to the findings that the subjects with genotype 1a had a lower percentage of IL28B CC subjects, black subjects, non-cirrhotic subjects and had a lower mean age as compared to the subjects infected with genotype 1b HCV in the study. However, the reviewer compared the SVR12 rates between the two subgenotypes across the subgroups defined by the demographics and baseline characteristics, and found that the genotype 1a subjects had numerically higher SVR12 rate than the genotype 1b subjects in all subgroups. Therefore, the reviewer disagreed with the applicant's interpretation. However, the lack of a control group in the study made it difficult to definitively conclude whether the observed differences between the two subgenotypes were due to chance.

5.2 Collective Evidence

The four Phase 3 studies had different patient populations, study designs and SOF-containing regimens. In all studies, the SOF-involved treatments rapidly suppressed the HCV virus regardless of the HCV genotype. Almost all subjects receiving the SOF-containing regimens achieved HCV RNA < LLOQ approximately four weeks after receiving treatment, and the high response rates were maintained through the end of treatment period. Very few subjects had a protocol-defined on-

treatment virologic failure. Also, the relapses usually occurred four or eight weeks after the end of treatment. The relapse rates varied among the treatment regimens and HCV genotypes, and the variation was attributed to the different SVR rates.

In Study 110, the SVR12 rate for the 12 weeks of SOF+PEG+RBV treatment was 90% for the overall population including the treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection. The rate was statistically significantly better than the pre-specified 60% historical rate. However, the study only recruited one HCV genotype 5 subject and six HCV genotype 6 subjects. The sample size was too small to make conclusions for these two genotypes.

Study 1231 demonstrated that the SVR12 rate for the 12-week SOF+RBV regimen was non-inferior to the 24-week PEG and RBV active control in HCV genotype 2 or 3 treatment-naïve subjects (i.e., 67% vs. 67%). However, the pre-specified subgroup analyses showed a significant interaction between treatment and HCV genotype. Use of SOF+RBV for 12 weeks was sufficient for the HCV genotype 2 treatment-naïve subjects since the 12-week treatment regimen had significantly higher SVR12 rate compared to the 24 weeks of PEG and RBV in the subset (i.e., 97% vs. 78%). However, the 12-week duration was insufficient for the genotype 3 treatment-naïve subjects since it had lower SVR12 rate than the 24-week PEG+RBV in this subpopulation (i.e., 56% vs. 63%).

Study 107 showed the 12 weeks of SOF+RBV had superior efficacy to the placebo with respect to the SVR12 rate (93% vs. 0%) in the genotype 2 or 3 subjects who were IFN intolerant, IFN ineligible or unwilling to take IFN. In addition, the HCV genotype 2 subjects had better SVR12 rate than genotype 3 subjects in the 12-week SOF+RBV group (i.e., 93% vs. 61%).

Study 108 revealed that both 12 and 16 weeks of SOF+RBV regimens had significantly better SVR12 rates than the pre-specified 25% historical rate for the treatment of treatment-experienced subjects infected with genotype 2 or 3 HCV (i.e., 50% for the 12-week SOF+RBV, 73% for the 16-week SOF+RBV). However, the pre-defined subgroup analyses showed an apparent treatment by genotype interaction. The 12-week SOF+RBV regimen was sufficient to treat the HCV genotype 2 treatment-experienced subjects because it had significantly better SVR12 rate than the historical rate, and the SVR12 rate was also comparable to that for the 16-week SOF+RBV in the subpopulation (i.e., 82% for 12-week SOF+RBV, 89% for 16-week SOF+RBV). However, the 12-week duration was not long enough for the genotype 3 treatment-experienced subjects since it only produced 30% SVR12 rate in the subset. Also, although the 16-week SOF+RBV led to a 62% SVR12 rate in the subpopulation, 16 weeks might not be the optimal duration because it still resulted in 38% relapse rate.

Finally, the bridging analyses using the observed rates from Studies 1231 and 108 resulted in an estimated SVR12 rate of approximately 80% for the 16-week SOF+RBV treatment in the HCV genotype 3 treatment-naïve subjects.

5.3 Conclusions and Recommendations

After reviewing the submitted data, the reviewer concludes the following:

1) The 12-week SOF+PEG+RBV treatment regimen demonstrated efficacy in treatment-naïve subjects with genotype 1 or 4 HCV infection.

2) The 12-week SOF+RBV treatment regimen demonstrated efficacy in subjects with genotype 2 HCV infection.

3) The 16-week SOF+RBV treatment regimen has efficacy in treatment-experienced subjects infected with genotype 3 HCV. However, use of SOF+RBV for a duration longer than 16 weeks could potentially improve the efficacy since the 16-week regimen still resulted in approximately 38% relapse rate.

4) The results from the bridging analyses suggested that 16 weeks of SOF+RBV would yield a better SVR12 rate compared with 12 weeks of SOF+RBV in treatment-naïve subjects with genotype 3 HCV infection. However, it is difficult to recommend the 16-week duration from the statistical prospective due to the lack of the data.

5) The sample sizes were too small to support the 12 weeks of SOF+PEG+RBV for the treatment of the subjects with genotype 5 or 6 infection.

5.4 Labeling Recommendations

The Dosage and Administration Section and Section 14 in the label are provided in the following sections and are relevant to the efficacy results in the four pivotal phase 3 studies reviewed in this report.

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

One 400 mg tablet taken once daily with or without food. (2)
Should be used in combination with (b) (4). Recommended combination therapy: (2)
(b) (4)

14 CLINICAL STUDIES

(b) (4)

[redacted] (b) (4)

[redacted]

14.1 Clinical Trials in Subjects with Genotype 1, 4, [redacted] (b) (4) CHC

Treatment-Naïve Adults – NEUTRINO (Study 110)

NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with [TRADENAME] in combination with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection.

Treated subjects (N=327) had a median age of 54 years (range: 19 to 70); 64% of the subjects were male; 79% were White, 17% were Black; 14% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 18 to 56 kg/m^2); 78% had baseline HCV RNA greater than 6 log_{10}IU per mL; 17% had cirrhosis; 89% had HCV genotype 1 [redacted] (b) (4) Table 9 presents the response rates for the treatment group of [TRADENAME] + peginterferon alfa + ribavirin.

Table 9 Response Rates in Study NEUTRINO

	[TRADENAME] + Peg-IFN alfa + RBV 12 weeks
	N=327
Overall SVR	90% (295/327)
[redacted] (b) (4)	
On-treatment virologic failure	0/327
Relapse[a]	9% (28/326)
Other[b]	1% (4/327)

a. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 10.

Table 10 SVR Rates for Selected Subgroups in NEUTRINO

	[TRADENAME] + Peg-IFN alfa + RBV 12 weeks
[redacted] (b) (4)	
Cirrhosis	
No	92% (252/273)
Yes	80% (43/54)
Race	
Black	87% (47/54)
Non-black	91% (248/273)

[redacted] (b) (4)

14.2 Clinical Trials in Subjects with Genotype 2 or 3 CHC

Treatment-Naïve Adults — FISSION (Study 1231)

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with [TRADENAME] and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin doses used in the [TRADENAME] + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence), HCV genotype (2 vs. 3) and baseline HCV RNA level (< 6 $\log_{10}$IU/mL vs. ≥ 6 $\log_{10}$IU/mL). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio. Treated subjects (N=499) had a median age of 50 years (range: 19 to 77); 66% of the subjects were male; 87% were White, 3% were Black; 14% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 17 to 52 kg/m^2); 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 20% had cirrhosis; 72% had HCV genotype 3. Table 11 presents the response rates for the treatment groups of [TRADENAME] + ribavirin and peginterferon alfa + ribavirin.

Table 11 Response Rates in Study FISSION

	[TRADENAME] + RBV 12 weeks	**Peg-IFN alfa + RBV 24 weeks**
	N=253[a] (b) (4)	N=243[a]
Overall SVR	67%	67% (162/243)
Genotype 2	(b) (4)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for subjects without SVR		
On-treatment virologic failure	<1% (b) (4)	7% (18/243)
Relapse[b]	30% (b) (4)	21% (46/217)
Other[c]	3% (b) (4)	7% (17/243)

(b) (4)

b. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

(b) (4)

Response rates for subjects with cirrhosis at baseline are presented in Table 12 by genotype.

Table 12 SVR Rates by Cirrhosis and Genotype in Study FISSION

	Genotype 2		Genotype 3	
	[TRADENAME] + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks	[TRADENAME] + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N= (b) (4)	N=67	N=183	N=176
Cirrhosis				
No	(b) (4)	81% (44/54)	61% (89/145)	71% (99/139)
Yes		62% (8/13)	34% (13/38)	30% (11/37)

Interferon Intolerant, Ineligible or Unwilling Adults – POSITRON (Study 107)

POSITRON was a randomized, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with [TRADENAME] and ribavirin (N=207) compared to placebo (N=71) in subjects who are interferon intolerant, ineligible or unwilling. Subjects were randomized in 3:1 ratio and stratified by cirrhosis (presence vs. absence).

Treated subjects (N=278) had a median age of 54 years (range: 21 to 75); 54% of the subjects were male; 91% were White, 5% were Black; 11% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 53 kg/m^2); 70% had baseline HCV RNA levels greater than 6 log_{10} IU per mL; 16% had cirrhosis; 49% had HCV genotype 3. The proportions of subjects who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most subjects had no prior HCV treatment (81.3%). Table 13 presents the response rates for the treatment groups of [TRADENAME] + ribavirin and placebo.

Table 13 Response Rates in Study POSITRON

	[TRADENAME] + RBV 12 weeks	**Placebo 12 weeks**
	N=207	N=71
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
Outcome for subjects without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse[a]	20% (42/205)	0/0
Other[b]	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

(b) (4)

Table 14 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 14 SVR Rates for Selected Subgroups by Genotype in POSITRON

	[TRADENAME] + RBV 12 weeks	
	Genotype 2	**Genotype 3**
	N=109	N=98
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon Classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously Treated Adults – FUSION (Study 108)

FUSION was a randomized, double-blinded trial that evaluated 12 or 16 weeks of treatment with [TRADENAME] and ribavirin in subjects who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Subjects were randomized in a 1:1 ratio and stratified by cirrhosis (presence vs. absence) and HCV genotype (2 vs. 3).

Treated subjects (N=201) had a median age of 56 years (range: 24 to 70); 70% of the subjects were male; 87% were White; 3% were Black; 9% were Hispanic or Latino; mean body mass index was 29 kg/m^2 (range: 19 to 44 kg/m^2); 73% had baseline HCV RNA levels greater than $6log_{10}$ IU per mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. Table 15 presents the response rates for the treatment groups of [TRADENAME] + ribavirin for 12 weeks and 16 weeks.

Table 15 Response Rates in Study FUSION

	[TRADENAME] + RBV 12 weeks	[TRADENAME] + RBV 16 weeks
	N= (b) (4)	N= (b) (4)
Overall SVR	50% (b) (4)	(b) (4)
Genotype 2	(b) (4)	(b) (4)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for subjects without SVR		
On-treatment virologic failure	(b) (4)	
Relapse[b]		
Other[c]		

(b) (4)

b. The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

The reviewer has the following comments regarding the label.

1) The efficacy results for Studies 1231 (Fission) and 108 (Fusion) presented in the label were based on the applicant's FAS where the subjects whose HCV genotype was misclassified by LiPA were excluded. The reviewer suggested using the results based on the intent-to-treat population, i.e., All Treated set.

2) (b) (4)

3) (b) (4)

4) The relapse rates at post-treatment Week 12 by the HCV genotypes 2 and 3 in Studies 1231, 107 and 108 should be presented in the label because the rates differed greatly between the two genotypes.

6 APPENDICES

6.1 Study 1231

Table 35: Study Procedures for Study 1231

Assessment	Screening Day –42 to –1	Baseline Day 1	Weeks 1, 2, 3[e]	Weeks 4, 8[e] (SOF+RBV)	Weeks 4, 8, 12, 16, 20[e] (PEG+RBV)	EOT[e]	Posttreatment Week 4[e]	Posttreatment Weeks 8, 12, 16, 20, 24[e]
Informed Consent [a]	X							
Medical History	X							
Physical Examination	X					X		
FibroSure/APRI/liver biopsy/transient elastograph[b]	X							
Blood sample for optional genetic testing[g]		X						
Quality of life questionnaire[h]		X			X[h]	X[h]		X[h]
Height/weight/BMI[c]	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
ECG	X	X				X		
Clinical laboratory assessments	X	X	X	X	X	X	X	X
Pregnancy test (females only)		X		X	X	X	X	X
Pharmacodynamic testing (HCV RNA)	X	X	X	X	X	X	X	X
HCV phenotyping and HCV RNA sequencing		X	X	X	X	X	X	X
Blood sampling for PK analysis[d]			X	X	X	X		

to be continued

Table 35: Study Procedures for Study 1231 (Continued)

Assessment	Screening Day –42 to –1	Baseline Day 1	Weeks 1, 2, 3[e]	Weeks 4, 8[e] (SOF+RBV)	Weeks 4, 8, 12, 16, 20[e] (PEG+RBV)	EOT[e]	Posttreatment Week 4[e]	Posttreatment Weeks 8, 12, 16, 20, 24[e]
Concomitant medication monitoring	X	X	X	X	X	X	X	
Review of inclusion/exclusion criteria	X	X						
Adverse events monitoring	X[f]	X	X	X	X	X	X	X[f]
Study drug(s) dispensation		X	X[i]	X	X			
Study drug(s)			X	X	X	X		

a Informed consent was obtained prior to performance of any study procedures.

b Results from 1 or more of these tests may have been used to establish the presence or absence of cirrhosis.

c Height was measured at screening only.

d Blood samples for PK analysis were collected at Weeks 1, 4, 8, and 12/EOT.

e A 2-day window applied to visits at Weeks 1, 2, and 3. A 5-day window applied to visits after Week 3.

f Only SAEs were collected prior to Day 1. For subjects in the SOF+RBV group, AEs were captured at the posttreatment Week 8, posttreatment Week 12, and posttreatment Week 16 visits so that the duration of AE monitoring was the same for each treatment group. Serious adverse events that occurred after posttreatment Week 16 were captured only if they were assessed as possibly or probably related to study drug(s).

g If separate, specific consent was obtained for optional genetic testing, a blood sample should have been drawn at the Day 1 visit. Samples not obtained at Day 1 may have been obtained at any time during the study once consent was provided.

h All subjects who attended the Day 1 visit subsequent to IRB/IEC approval of protocol Amendment 3 completed the SF-36 Health Survey at the following time points: Day 1, Week 12/EOT, posttreatment Week 12, and posttreatment Week 24 (SOF+RBV group) and Day 1, Weeks 12 and 24/EOT, and posttreatment Week 12 (PEG+RBV group).

i Study drugs were not dispensed at these visits; rather, they were 'redispensed.'

Source: Table 7-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 36: On-Treatment Visit Windows for Study 1231

Visit ID	On-Treatment Visit Windows for HCV RNA (GS-7977+RBV)	On-Treatment Visit Windows for HCV RNA (PEG+RBV)	Visit Windows for Vital Signs and Safety Labs
Baseline	Study Day ≤ 1	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 17	12 ≤ Study Day ≤ 17	12 ≤ Study Day ≤ 17
Week 3	18 ≤ Study Day ≤ 24	18 ≤ Study Day ≤ 24	18 ≤ Study Day ≤ 24
Week 4	25 ≤ Study Day ≤ 42	25 ≤ Study Day ≤ 42	25 ≤ Study Day ≤ 42
Week 8	43 ≤ Study Day ≤ 70	43 ≤ Study Day ≤ 70	43 ≤ Study Day ≤ 70
Week 12	71 ≤ Study Day ≤ 98	71 ≤ Study Day ≤ 98	71 ≤ Study Day ≤ 98
Week 16	N/A	99 ≤ Study Day ≤ 126	99 ≤ Study Day ≤ 126
Week 20	N/A	127 ≤ Study Day ≤ 154	127 ≤ Study Day ≤ 154
Week 24	N/A	155 ≤ Study Day ≤ 182	155 ≤ Study Day ≤ 182

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 37: Post-Treatment Visit Windows for Selected Tests for Study 1231

Post-Trt FU Visit ID	Post-Treatment Visit Windows for HCV RNA [a] (Days from Last Study Drug Dose)	Vital Signs and Other Safety Labs[b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 41	3 ≤ FU Day ≤ 30
FU-8	42 ≤ FU Day ≤ 69	N/A
FU-12	70 ≤ FU Day ≤ 97	N/A
FU-16	98 ≤ FU Day ≤ 125	N/A
FU-20	126 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7 (SVR4), 14 (SVR8, SVR12, SVR16, and SVR20), and 21 days (SVR24) of target, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow up visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 38: Patient Demographics and Baseline Characteristics for Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	Total (N=499)
Age (years)			
Mean (SD)	48 (11)	48 (11)	48 (11)
Median (Q1, Q3)	50 (41, 56)	50 (40, 56)	50 (40, 56)
Sex			
Male	171 (67%)	156 (64%)	327 (66%)
Female	85 (33%)	87 (36%)	172 (35%)
Race			
Black	12 (5%)	5 (2%)	17 (3%)
White	223 (87%)	212 (87%)	435 (87%)
Asian	14 (6%)	15 (6%)	29 (6%)
Others	7 (3%)	11 (5%)	18 (4%)
Ethnicity			
Hispanic	41 (16%)	31 (13%)	72 (14%)
Non-Hispanic	215 (84%)	212 (87%)	427 (86%)
Region[2]			
North America	180 (70%)	175 (72%)	355 (71%)
Canada	15 (6%)	24 (10%)	39 (8%)
USA	165 (65%)	151 (62%)	316 (63%)
Australia/New Zealand	61 (24%)	59 (24%)	120 (24%)
Australia	32 (13%)	29 (12%)	61 (12%)
New Zealand	29 (11%)	30 (12%)	59 (12%)
Europe	15 (6%)	9 (4%)	24 (5%)
Italy	8 (3%)	4 (2%)	12 (2%)
Netherland	3 (1%)	1 (<1%)	4 (1%)
Sweden	4 (2%)	4 (2%)	8 (2%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (5)	28 (6)	28 (6)
Median (Q1, Q3)	27 (24, 31)	27 (24, 31)	27 (24, 31)
$< 30\ kg/m^2$	179 (70%)	172 (71%)	351 (70%)
$\geq 30\ kg/m^2$	77 (30%)	71 (29%)	148 (30%)

Source: Table 8-4 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA
[1]All Treated population included all randomized subjects who had received at least one dose of study medication
[2]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 39: Baseline Disease Characteristics for Study 1231 (All Treated)

	12-Week SOF+RBV (N=256)	24-Week PEG+RBV (N=243)	Total (N=499)
HCV genotype			
Genotype 1[1]	3 (1%)	0	0
Genotype 2	70 (27%)	67 (28%)	137 (28%)
Genotype 3	183 (72%)	176 (72%)	359 (72%)
Cirrhosis[2]			
No	205 (80%)	189 (78%)	394 (80%)
Yes	50 (20%)	50 (21%)	100 (20%)
Missing	1 (<1%)	4 (2%)	5 (2%)
IL28 B[2]			
CC	108 (42%)	106 (44%)	214 (43%)
CT	121 (47%)	98 (40%)	219 (44%)
TT	25 (10%)	38 (16%)	63 (13%)
Missing	2 (1%)	1 (<1%)	3 (%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6 (0.8)	6 (0.8)	6 (0.8)
Median (Q1, Q3)	6 (5.5, 6.7)	6 (5.5, 6.7)	6 (5.5, 6.7)
< 6 log_{10} IU/mL	108 (42%)	106 (44%)	214 (43%)
≥ 6 log_{10} IU/mL	148 (58%)	137 (56%)	285 (57%)
Baseline ALT[3]			
$<$ 1 x ULN	54 (21%)	47 (19%)	101 (20%)
$\geq$ 1 x ULN	202 (79%)	196 (81%)	398 (80%)
$\leq$ 1.5 x ULN	118 (46%)	97 (40%)	215 (43%)
$>$ 1.5 x ULN	138 (54%)	146 (60%)	284 (57%)

Source: Table 8-5 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

[1]There were three subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by population sequencing.

[2]The applicant did not count the subjects with missing data when calculating the percentage of subjects in each category. The statistical reviewer re-calculated the percentage of subjects in each category including all subjects, i.e., the denominator was the randomized and treated subjects in each treatment group.

[3]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 40: Patient Demographics and Baseline Disease Characteristics by Genotype in Study 1231 (All Treated)

	Genotype 2		Genotype 3	
	12-Week SOF+RBV (N=73)	24-Week PEG+RBV (N=67)	12-Week SOF+RBV (N=183)	24-Week PEG+RBV (N=176)
Age (years)				
< 50 years old	23 (32%)	18 (27%)	104 (57%)	100 (57%)
≥ 50 years old	50 (68%)	49 (73%)	79 (43%)	76 (43%)
Sex				
Male	46 (63%)	39 (58%)	125 (68%)	117 (66%)
Female	27 (37%)	28 (42%)	58 (32%)	59 (34%)
Race				
Black	4 (5%)	2 (3%)	8 (4%)	3 (2%)
White	65 (89%)	62 (93%)	158 (86%)	150 (85%)
Asian	1 (1%)	1 (1%)	13 (7%)	14 (8%)
Others	3 (4%)	2 (3%)	4 (2%)	9 (5%)
Region				
North America	71 (97%)	66 (99%)	109 (60%)	109 (62%)
Canada	0	0	15 (8%)	24 (14%)
USA	71 (97%)	66 (99%)	94 (51%)	85 (48%)
Australia/New Zealand	2 (3%)	1 (1%)	59 (32%)	58 (33%)
Australia	0	0	32 (17%)	29 (16%)
New Zealand	2 (3%)	1 (1%)	27 (15%)	29 (16%)
Europe	0	0	15 (8%)	9 (5%)
Italy	0	0	8 (4%)	4 (2%)
Netherland	0	0	3 (2%)	1 (1%)
Sweden	0	0	4 (2%)	4 (2%)
Ethnicity				
Hispanic	17 (23%)	9 (13%)	24 (13%)	22 (13%)
Non-Hispanic	56 (77%)	58 (87%)	159 (87%)	154 (88%)
Baseline body mass index				
< 30 kg/m^2	53 (73%)	45 (67%)	126 (69%)	127 (72%)
≥ 30 kg/m^2	20 (27%)	22 (33%)	57 (31%)	49 (28%)
Cirrhosis				
No	61 (84%)	54 (81%)	145 (79%)	139 (79%)
Yes	12 (16%)	13 (19%)	38 (21%)	37 (21%)
IL28 B				
CC	33 (45%)	34 (51%)	75 (41%)	72 (41%)
CT or TT	40 (55%)	33 (49%)	108 (59%)	104 (59%)
Baseline HCV RNA				
< 6 log_{10} IU/mL	25 (34%)	23 (34%)	83 (45%)	83 (47%)
≥ 6 log_{10} IU/mL	48 (66%)	44 (66%)	100 (55%)	93 (53%)
Baseline ALT				
≤ 1.5 x ULN	37 (51%)	35 (52%)	81 (44%)	62 (35%)
> 1.5 x ULN	36 (49%)	32 (48%)	102 (56%)	114 (65%)

Table 41: Reviewer's Results for Subgroup Analysis in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	63% (80/127)	73% (86/118)	-10% (-22%, 2%)
≥ 50 years old	71% (91/129)	61% (76/125)	10% (-2%, 21%)
Sex			
Male	61% (104/171)	62% (96/156)	-0.1% (-11%, 10%)
Female	79% (67/85)	76% (66/87)	3% (-10%, 15%)
Race			
Black	75% (9/12)	40% (2/5)	35% (-14%, 84%)
Other	66% (162/244)	67% (160/238)	-0.1% (-9%, 8%)
Region			
US	75% (123/165)	69% (104/151)	6% (-4%, 16%)
Non-US	53% (48/91)	63% (58/92)	-10% (-25%, 4%)
Ethnicity			
Hispanic	71% (29/41)	65% (20/31)	6% (-16%, 28%)
Non-Hispanic	66% (142/215)	67% (142/212)	-1% (-10%, 8%)
Baseline body mass index			
< 30 kg/m^2	68% (121/179)	68% (117/172)	-0.4% (-10%, 9%)
≥ 30 kg/m^2	65% (50/77)	63% (45/71)	2% (-14%, 17%)
Cirrhosis			
No	72% (148/206)	74% (143/193)	-2% (-11%, 6%)
Yes	46% (23/50)	38% (19/50)	8% (-11%, 27%)
IL28 B			
CC	69% (75/108)	77% (82/106)	-8% (-20%, 4%)
CT or TT	65% (96/148)	58% (80/137)	6% (-5%, 18%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	75% (81/108)	67% (71/106)	8% (-4%, 20%)
≥ 6 $\log_{10}$ IU/mL	61% (90/148)	66% (91/137)	-6% (-17%, 6%)
Baseline ALT			
≤ 1.5 x ULN	70% (83/118)	72% (70/97)	-1% (-14%, 10%)
> 1.5 x ULN	63% (92/146)	64% (88/138)	-1% (-12%, 10%)

[1]based on the Wald asymptotic confidence limits

Table 42: Reviewer's Results for Subgroup Analysis among Genotype 2 Subjects in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	96% (22/23)	78% (14/18)	18% (-3%, 39%)
≥ 50 years old	94% (47/50)	78% (38/49)	16% (3%, 30%)
Sex			
Male	93% (43/46)	69% (27/39)	24% (8%, 40%)
Female	96% (26/27)	89% (25/28)	7% (-6%, 21%)
Race			
Black	75% (3/4)	50% (1/2)	25% (-56%, 100%)
Non Black	96% (66/69)	78% (51/65)	17% (6%, 28%)
Region			
US	94% (67/71)	77% (51/66)	17% (6%, 29%)
Non-US	100% (2/2)	100% (1/1)	n/a
Ethnicity			
Hispanic	88% (15/17)	67% (6/9)	22% (-13%, 56%)
Non-Hispanic	96% (54/56)	79% (46/58)	17% (6%, 29%)
Baseline body mass index			
< 30 kg/m^2	96% (51/53)	78% (35/45)	18.5% (5%, 32%)
≥ 30 kg/m^2	90% (18/20)	77% (17/22)	13% (-9%, 35%)
Cirrhosis			
No	97% (59/61)	81% (44/54)	15% (4%, 27%)
Yes	83% (10/12)	62% (8/13)	22% (-12%, 56%)
IL28 B			
CC	97% (32/33)	82% (28/34)	15% (0.5%, 29%)
CT or TT	93% (37/40)	73% (24/33)	20% (2.5%, 37%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	100% (25/25)	74% (17/23)	26% (8%, 44%)
≥ 6 $\log_{10}$ IU/mL	92% (44/48)	80% (35/44)	12% (-2%, 26%)
Baseline ALT			
≤ 1.5 x ULN	95% (35/37)	80% (28/35)	15% (-0.5%, 30%)
> 1.5 x ULN	94% (34/36)	75% (24/32)	19% (3%, 36%)

[1]based on the Wald asymptotic confidence limits

Table 43: Reviewer's Results for Subgroup Analysis among Genotype 3 Subjects in Study 1231 (All Treated)

	12-Week SOF+RBV	24-Week PEG+RBV	12-Week SOF+RBV vs. 24-Week PEG+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	56% (58/104)	72% (72/100)	-16% (-29%, -3%)
≥ 50 years old	56% (44/79)	50% (38/76)	6% (-10%, 21%)
Sex			
Male	49% (61/125)	59% (69/117)	-10% (-23%, 2 %)
Female	71% (41/58)	69% (41/59)	1% (-15%, 18%)
Race			
Black	75% (6/8)	33% (1/3)	42% (-20%, 100%)
Non Black	55% (96/175)	63% (109/173)	-8% (-18%, 2%)
Region			
US	60% (56/94)	62% (53/85)	-3% (-17%, 12%)
Non-US	52% (46/89)	63% (57/91)	-11% (-25%, 3%)
Ethnicity			
Hispanic	58% (14/24)	64% (14/22)	-5% (-33%, 23%)
Non-Hispanic	55% (88/159)	62% (96/154)	-7% (-18%, 4%)
Baseline body mass index			
< 30 kg/m^2	56% (70/126)	65% (82/127)	-9% (-21%, 3%)
≥ 30 kg/m^2	56% (32/57)	57% (28/49)	-1% (-20%, 18%)
Cirrhosis			
No	61% (89/145)	71% (99/139)	-10% (-21%, 1%)
Yes	34% (13/38)	30% (11/37)	4% (-17%, 26%)
IL28 B			
CC	57% (43/75)	75% (54/72)	-18% (-33%, -3%)
CT or TT	55% (59/108)	54% (56/104)	1% (-13%, 14%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	67% (56/83)	65% (54/83)	2% (-12%, 17%)
≥ 6 $\log_{10}$ IU/mL	46% (46/100)	60% (56/93)	-14% (-28%, -0.3%)
Baseline ALT			
≤ 1.5 x ULN	59% (48/81)	68% (42/62)	-8% (-24%, 7%)
> 1.5 x ULN	53% (54/102)	60% (68/114)	-7% (-20%, 7%)

[1]based on the Wald asymptotic confidence limits

6.2 Study 107

Table 44: On-Treatment Study Procedures in Study 107

	Screening	Baseline/Day 1[c]	Visit Identified by On-Treatment Study Week							Early Termination
			1	2	4	6	8	10	12	
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination	X	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X									
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Health-Related Quality of Life Survey (SF-36)[f]		X							X	
Review of Study Drugs Compliance			X	X	X	X	X	X	X	
Study Drug Dispensing[b]		X			X		X			
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X

to be continued

Table 44: On-Treatment Study Procedures in Study 107 (Continued)

	Screening	Baseline/Day 1[c]	Visit Identified by On-Treatment Study Week							Early Termination
			1	2	4	6	8	10	12	
Coagulation Tests	X	X							X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[d]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA_{1c}, FibroTest	X									
Thyroid-Stimulating Hormone	X									
Pharmacogenomics, GGT		X[e]								

EGC = electrocardiogram; GGT = gamma-glutamyl transpeptidase; HbA_{1c} = hemoglobin A_{1c}; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = interactive web response system; PK = pharmacokinetic(s); RNA = ribonucleic acid

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b The IWRS provided information regarding each subject's study drug dispensing.

c Day 1 (baseline) assessments were performed prior to dosing.

d Plasma samples were collected and stored for potential HCV sequencing and other virology studies

e Pharmacogenomic testing was only for subjects who consented to this testing. If consent was not obtained at baseline, the sample could be drawn at any time during the study.

f SF-36 Health Survey collected if a site was approved to use the survey.

Source: Table 7-2 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 45: Post-Treatment Study Procedures in Study 107

	4 Weeks Posttreatment	12 Weeks Posttreatment	24 Weeks Posttreatment
Clinical Assessments			
Vital Signs[a]	X	X	X
Weight		X	X
Adverse Events	X		
Concomitant Medications	X		
Health-Related Quality of Life Survey (SF-36)[b]	X		
Laboratory Assessments			
Hematology, Chemistry	X		
HCV RNA	X	X	X
Viral Sequencing (archive)[c]	X	X	X
Urine Pregnancy Test	X	X	X
Pregnancy Prevention Counseling	X	X	X

HCV = hepatitis C virus; RNA = ribonucleic acid

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b SF-36 Health Survey collected if a site was approved to use the survey.

c Plasma samples were collected and stored for potential HCV sequencing and other virology studies

Source: Table 7-3 in Study P7977-1231 Interim Clinical Study Report submitted in this NDA

Table 46: On-Treatment Visit Windows in Study 107

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital Signs and Other Safety Labs
Baseline	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Table 47: Post-Treatment Visit Windows in Study 107

Off-Treatment FU Visit ID	Post-Treatment Visit Windows for HCV RNA [a] (Days from Last Study Drug Dose)	Vital Signs and Other Safety Labs [b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow up visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

Table 48: Patient Demographics and Baseline Characteristics in Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	Total (N=278)
Age (years)			
Mean (SD)	52 (10)	52 (8)	52
Median (Q1, Q3)	53 (47, 58)	54 (49, 57)	54 (47, 58)
Sex			
Male	117 (57%)	34 (48%)	151 (54%)
Female	90 (44%)	37 (52%)	127 (46%)
Race			
Black	9 (4%)	4 (6%)	13 (5%)
White	188 (91%)	66 (93%)	254 (91%)
Asian	7 (3%)	1 (1%)	8 (3%)
Others	3 (2%)	0	3 (2%)
Ethnicity			
Hispanic	19 (9%)	11 (16%)	30 (11%)
Non-Hispanic	188 (91%)	60 (85%)	248 (89%)
Region[1]			
North America	183 (88%)	68 (96%)	251 (90%)
Canada	15 (7%)	8 (11%)	23 (8%)
USA	168 (81%)	60 (85%)	228 (82%)
Australia/New Zealand	24 (12%)	3 (4%)	27 (10%)
Australia	18 (9%)	3 (4%)	21 (8%)
New Zealand	6 (3%)	0	6 (3%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (6)	28 (6)	28 (6)
Median (Q1, Q3)	28 (24, 31)	27 (23, 32)	28 (24, 31)

Source: Table 8-4 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA
[1]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 49: Baseline Disease Characteristics for Study 107 (All Treated)

	12-Week SOF+RBV (N=207)	Placebo (N=71)	Total (N=278)
HCV genotype			
Genotype 2	109 (53%)	34 (48%)	143 (51%)
Genotype 3	98 (47%)	37 (52%)	135 (49%)
Interferon classification			
Ineligible	88 (43%)	33 (47%)	121 (44%)
Intolerant	17 (8%)	8 (11%)	25 (9%)
Unwilling	102 (49%)	30 (42%)	132 (47%)
Duration on prior HCV treatment			
No	170 (82%)	56 (79%)	226 (81%)
≤ 12 weeks	21 (10%)	8 (11%)	29 (10%)
> 12 weeks	16 (8%)	7 (10%)	23 (8%)
Cirrhosis			
No	176 (85%)	58 (82%)	234 (84%)
Yes	31 (15%)	13 (18%)	44 (16%)
IL28 B			
CC	97 (47%)	29 (41%)	126 (45%)
CT	84 (41%)	36 (51%)	120 (43%)
TT	26 (13%)	6 (9%)	32 (12%)
Baseline HCV RNA (log_{10} IU/mL)	6.3 (0.8)	6.3 (0.8)	6.3 (0.8)
Mean (SD)	6.4 (5.8, 6.8)	6.5 (6.1, 6.8)	6.4 (5.9, 6.8)
Median (Q1, Q3)			
	67 (32%)	17 (24%)	84 (30%)
< 6 log_{10} IU/mL	140 (68%)	54 (76%)	194 (70%)
≥ 6 log_{10} IU/mL			
Baseline ALT[1]			
≤ 1 x ULN	52 (25%)	15 (21%)	67 (24%)
> 1 x ULN	155 (75%)	56 (79%)	211 (76%)
≤ 1.5 x ULN	90 (44%)	29 (41%)	119 (43%)
> 1.5 x ULN	117 (57%)	42 (59%)	159 (57%)

Source: Table 8-5 in Study GS-US-334-0107 Interim Clinical Study Report submitted in this NDA

[1]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 50: Reviewer's Results for Patient Demographics and Baseline Disease Characteristics for Subjects Receiving 12 Weeks of SOF+RBV by HCV Genotype in Study 1231 and Study 107

	Genotype 2		Genotype 3	
	Study 1231 (N=73)	**Study 107 (N=93)**	**Study 1231 (N=183)**	**Study 107 (N=77)**
Age (years)				
Mean (SD)	52 (10)	54 (10)	46 (11)	48 (10)
Median (Q1, Q3)	54 (46, 58)	56 (49, 60)	48 (39, 54)	50 (41, 55)
< 50 years old	23 (32%)	25 (27%)	104 (57%)	38 (49%)
≥ 50 years old	50 (68%)	68 (73%)	79 (43%)	39 (51%)
Sex				
Male	46 (63%)	54 (58%)	58 (32%)	37 (48%)
Female	27 (37%)	39 (42%)	125 (68%)	40 (52%)
Race				
Black	4 (5%)	9 (10%)	8 (4%)	0
White	65(89%)	81 (87%)	158 (86%)	70 (91%)
Others	4 (5%)	3 (3%)	17 (9%)	7 (9%)
Region				
North America	71 (97%)	89 (96%)	109 (59%)	59 (78%)
USA	71 (97%)	81 (87%)	94 (51%)	53 (69%)
Canada	0	8 (9%)	15 (8%)	6 (8%)
Australia/New Zealand	2 (3%)	4 (4%)	59 (32%)	18 (23%)
Australia	0	3 (3%)	32 (17%)	14 (18%)
New Zealand	2 (3%)	1 (1%)	27 (15%)	4 (5%)
Europe	0	0	15 (8%)	0
Italy	0	0	8 (4%)	0
Netherland	0	0	3 (2%)	0
Sweden	0	0	4 (2%)	0
Ethnicity				
Hispanic	17 (23%)	9 (10%)	24 (13%)	7 (9%)
Non-Hispanic	56 (77%)	84 (90%)	159 (87%)	70 (91%)
Baseline body mass index				
< 30 kg/m^2	53 (73%)	56 (60%)	126 (69%)	55 (71%)
≥ 30 kg/m^2	20 (27%)	37 (40%)	57 (31%)	22 (29%)
Cirrhosis				
No	61 (84%)	79 (85%)	144 (79%)	73 (95%)
Yes	12 (16%)	14 (15%)	38 (21%)	4 (5%)
Missing	0	0	1(1%)	0
IL28 B				
CC	33 (45%)	38 (41%)	75 (41%)	40 (52%)
CT or TT	40 (55%)	55 (59%)	108 (59%)	37 (48%)
Baseline HCV RNA (log_{10} IU/mL)				
Mean (SD)	6.2 (0.9)	6.3 (0.8)	6.0 (0.8)	6.1 (0.8)
Median (Q1, Q3)	6.4 (5.6, 6.7)	6.5 (5.9, 6.9)	6.1 (5.4, 6.3)	6.3 (5.8, 6.7)
< 6 log_{10} IU/mL	25 (34%)	27 (29%)	83 (45%)	31 (40%)
≥ 6 log_{10} IU/mL	48 (66%)	66 (71%)	100 (55%)	46 (60%)
Baseline ALT				
≤ 1.5 x ULN	37 (51%)	49 (53%)	81 (44%)	29 (38%)
> 1.5 x ULN	36 (49%)	44 (47%)	102 (56%)	48 (62%)

Table 51: Reviewer's Results for Subgroup Comparison between Study 1231 and Study 107 in HCV Genotype 3 Treat-Naïve Subjects

	12-Week SOF+RBV		
	Study 1231	**Study 107**	**Study 1231 vs. Study 107 Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	56% (58/104)	66% (25/38)	-10% (-28%, 8%)
≥ 50 years old	56% (44/79)	74% (28/28)	-19% (-36%, -1%)
Sex			
Male	49% (61/125)	58% (23/40)	-9% (-26%, 9%)
Female	71% (41/58)	84% (31/37)	-13% (-30%, 4%)
Race			
White	54% (85/158)	67% (47/70)	-13% (-27%, 0.1%)
Other	68% (17/25)	100% (7/7)	-32% (-50%, -14%)
Region			
US	60% (56/94)	66% (35/53)	-6% (-23%, 10%)
Non-US	52% (46/89)	79% (19/24)	-27% (-47%, -8%)
Ethnicity			
Hispanic	58% (14/24)	71% (5/7)	-13% (-52%, 26%)
Non-Hispanic	55% (88/159)	70% (49/70)	-15% (-28%, -1%)
Baseline body mass index			
< 30 kg/m^2	56% (70/126)	69% (38/55)	-14% (-29%, 1%)
≥ 30 kg/m^2	56% (32/57)	73% (16/22)	-17% (-39%, 6%)
Cirrhosis			
No	61% (89/145)	71% (52/73)	-10% (-23%, 3%)
Yes	34% (13/38)	50% (2/4)	-16% (-67%, 35.5%)
IL28 B			
CC	57% (43/75)	78% (31/40)	-20% (-37%, -3%)
CT or TT	55% (59/108)	62% (23/37)	-8% (-26%, 11%)
Baseline HCV RNA			
<6 log_{10} IU/mL	67% (56/83)	68% (21/31)	-0.3% (-20%, 19%)
≥ 6 log_{10} IU/mL	46% (46/100)	72% (33/46)	-26% (-42%, -10%)
Baseline ALT			
≤ 1.5 x ULN	59% (48/81)	55% (16/29)	4% (-17%, 25%)
> 1.5 x ULN	53% (54/102)	79% (38/48)	-26% (-41%, -11%)

[1]based on the Wald asymptotic confidence limits

Table 52: Reviewer's Results for Subgroup Analysis in Study 107 (All Treated)

	12-Week SOF+RBV	Placebo	12-Week SOF+RBV vs. Placebo Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	74% (53/72)	0% (0/20)	74% (63%, 84%)
≥ 50 years old	80% (108/135)	0% (0/51)	80% (73%, 87%)
Sex			
Male	73% (85/117)	0% (0/34)	73% (65%, 81%)
Female	84% (76/90)	0% (0/37)	84% (77%, 92%)
Race			
Black	89% (8/9)	0% (0/4)	89% (68%, 100%)
Other	77% (153/198)	0% (0/67)	77% (71%, 83%)
Region			
US	77% (130/168)	0% (0/60)	77% (71%, 84%)
Non-US	79% (31/39)	0% (0/11)	79.5% (67%, 92%)
Ethnicity			
Hispanic	74% (14/19)	0% (0/11)	74% (54%, 93%)
Non-Hispanic	78% (147/188)	0% (0/60)	78% (72%, 84%)
Baseline body mass index			
< 30 kg/m^2	76% (103/136)	0% (0/49)	76% (69%, 83%)
≥ 30 kg/m^2	82% (58/71)	0% (0/22)	82% (73%, 91%)
HCV Genotype			
Genotype 2	93% (101/109)	0% (0/34)	93% (88%, 98%)
Genotype 3	61% (60/98)	0% (0/37)	61% (52%, 71%)
Interferon Classification			
Ineligible	78% (69/88)	0% (0/33)	78% (70%, 87%)
Intolerant	76% (13/17)	0% (0/8)	77% (56%, 97%)
Unwilling	77% (79/102)	0% (0/30)	78% (69%, 86%)
Duration of prior HCV treatment			
No	82% (140/170)	0% (0/56)	82% (77%, 88%)
≤ 12 weeks	71% (15/21)	0% (0/8)	71% (52%, 91%)
> 12 weeks	38% (6/16)	0% (0/7)	37.5% (14%, 61%)
Cirrhosis			
No	81% (142/176)	0% (0/58)	81% (75%, 87%)
Yes	61% (19/31)	0% (0/13)	61% (44%, 78%)
IL28B			
CC	76% (74/97)	0% (0/29)	76% (68%, 85%)
CT or TT	79% (87/110)	0% (0/42)	79% (71%, 87%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	76% (51/67)	0% (0/17)	76% (66%, 86%)
≥ 6 $\log_{10}$ IU/mL	79% (110/140)	0% (0/54)	79% (72%, 85%)
Baseline ALT			
≤ 1.5 x ULN	79% (71/90)	0% (0/29)	79% (71%, 87%)
> 1.5 x ULN	77% (90/117)	0% (0/42)	77% (69%, 85%)

[1]based on the Wald asymptotic confidence limits

Table 53: Reviewer's Results for SVR12 Rates by Genotype and Subgroup in 12-Week SOF+RBV Group in Study 107 (All Treated)

	12-Week SOF+RBV		
	Genotype 2	**Genotype 3**	**Genotype 2 vs. Genotype 3 Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	93% (27/29)	60% (26/43)	33% (15%, 50%)
≥ 50 years old	93% (74/80)	62% (34/55)	31% (17%, 45%)
Sex			
Male	92% (59/64)	49% (26/53)	43% (28%, 58%)
Female	93% (42/45)	76% (34/45)	18% (3%, 32%)
Race			
Black	89% (8/9)	0/0	n/a
Other	93% (93/100)	61% (60/98)	32% (21%, 43%)
Region			
US	94% (89/95)	56% (41/73)	38% (25%, 50%)
Non-US	86% (12/14)	76% (19/25)	10% (-15%, 35%)
Ethnicity			
Hispanic	82% (9/11)	63% (5/8)	19% (-21%, 60%)
Non-Hispanic	94% (92/98)	61% (55/90)	33% (22%, 44%)
Baseline body mass index			
< 30 kg/m^2	92% (61/66)	60% (42/70)	32% (19%, 45%)
≥ 30 kg/m^2	93% (40/43)	64% (18/28)	29% (9%, 48%)
Interferon Classification			
Ineligible	88% (36/41)	70% (33/47)	18% (1%, 34%)
Intolerant	100% (9/9)	50% (4/8)	50% (15%, 85%)
Unwilling	95% (56/59)	53% (23/43)	41% (26%, 57%)
Duration of prior HCV treatment			
No	92% (86/93)	70% (54/77)	22% (11%, 34%)
≤ 12 weeks	100% (11/11)	40% (4/10)	60% (30%, 90%)
> 12 weeks	80% (4/5)	18% (2/11)	62% (20%, 100%)
Cirrhosis			
No	92% (85/92)	68% (57/84)	25% (13%, 36%)
Yes	94% (16/17)	21% (3/14)	73% (48%, 97%)
IL28B			
CC	89% (40/45)	65% (34/52)	24% (8%, 39%)
CT or TT	95% (61/64)	57% (26/46)	39% (24%, 54%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	88% (29/33)	65% (22/34)	23% (4%, 43%)
≥ 6 $\log_{10}$ IU/mL	95% (72/76)	59% (38/64)	35% (22%, 48%)
Baseline ALT			
≤ 1.5 x ULN	91% (53/58)	56% (18/32)	35% (16%, 54%)
> 1.5 x ULN	94% (48/51)	64% (42/66)	30% (17%, 44%)

[1]based on the Wald asymptotic confidence limits

6.3 Study 108

Table 54: On-Treatment Study Procedures in Study 108

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week								Early Termination
			1	2	4	6	8	10	12	16	
Clinical Assessments											
Informed Consent	X										
Determine Eligibility	X	X									
Medical History	X										
Physical Examination	X	X							X	X	X
Height	X										
Weight	X	X							X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X										
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X		X
Quality of Life Surveys[c]		X			X				X	X	X
Review of Study Drug Compliance			X	X	X	X	X	X	X	X	
Study Drug Dispensing[d]		X			X		X		X		

to be continued

Table 54: On-Treatment Study Procedures in Study 108 (Continued)

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week								Early Termination
			1	2	4	6	8	10	12	16	
Laboratory Tests											
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[e]		X	X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X	X
Urinalysis	X										
Urine Drug Screen	X										
HCV Genotyping, IL28B	X										
HCV, HIV, HBV Serology	X										
HbA_{1c}	X										
Thyroid-Stimulating Hormone	X										
Pharmacogenomics		X[f]									

a Day 1 (baseline) assessments were performed prior to dosing.

b Vital signs included blood pressure, pulse, respiratory rate, and temperature.

c Quality of life surveys were completed by subjects at Day 1, and at the Week 4, 12, and 16 visits if a site was approved to use the survey.

d The IWRS provided information regarding each subject's study drug dispensing.

e Plasma samples were collected and stored for potential HCV sequencing and other virology studies.

f Pharmacogenomic testing was only for subjects who consented to this testing. If the blood sample was not obtained at baseline, the sample could have been drawn at any time during the study.

Source: Table 7-2 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 55: Post-Treatment Study Procedures in Study 108

	4 Weeks Posttreatment	8 Weeks Posttreatment	12 Weeks Posttreatment	20 Weeks Posttreatment	24 Weeks Posttreatment
Clinical Assessments					
Vital Signs[a]	X	X	X	X	X
Weight			X		X
Adverse Events	X				
Concomitant Medications	X				
Quality of Life Surveys[b]	X	X	X		X
Pregnancy Prevention Counseling	X	X	X	X	X
Laboratory Assessments					
Hematology, Chemistry	X	X	X		
HCV RNA	X	X	X	X	X
Viral Sequencing[c]	X	X	X	X	X
Urine Pregnancy Test	X	X	X	X	X

a Vital signs included blood pressure, pulse, respiratory rate, and temperature.

b Quality of life surveys were completed by all subjects at posttreatment Week 4, 8, 12, and 24 visits if a site was approved to use the survey.

c Plasma samples were collected and stored for potential HCV sequencing and other virology studies.

Source: Table 7-3 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 56: On-Treatment Visit Windows in Study 108

Visit ID	On-Treatment Visit Windows for Group 1	On-Treatment Visit Windows for Group 2
Baseline	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	2 ≤ Study Day ≤ 11
Week 2	12 ≤ Study Day ≤ 21	12 ≤ Study Day ≤ 21
Week 4	22 ≤ Study Day ≤ 35	22 ≤ Study Day ≤ 35
Week 6	36 ≤ Study Day ≤ 49	36 ≤ Study Day ≤ 49
Week 8	50 ≤ Study Day ≤ 63	50 ≤ Study Day ≤ 63
Week 10	64 ≤ Study Day ≤ 77	64 ≤ Study Day ≤ 77
Week 12	78 ≤ Study Day ≤ 98	78 ≤ Study Day ≤ 98
Week 16	99 ≤ Study Day ≤ 126 [a]	99 ≤ Study Day ≤ 126

a Visit Week-16 of Group 1 will be summarized for vital signs and safety labs, but not for HCV RNA.

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 57: Post-Treatment Visit Windows in Study 108

Off-Treatment FU Visit ID	Posttreatment Visit Windows for HCV RNA [a] (Days from Last Dose of Active Treatment)	Vital Signs and Other Safety Labs[c] (Days from Last Dose Date)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A
FU-24	147 ≤ FU Day ≤ 190	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the 4-week follow-up visit (up to 30 days post last dose of study drugs).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

Table 58: Patient Demographics and Baseline Characteristics for Study 108 (All Treated)

	12-week SOF+RBV (N=103)	16-week SOF+RBV (N=98)	Total (N=201)
Age (years)			
Mean (SD)	54 (7.7)	54 (7.8)	54 (7.8)
Median (Q1, Q3)	56 (51, 59)	55 (50, 58)	56 (51, 59)
Sex			
Male	73 (71%)	67 (68%)	140 (70%)
Female	30 (29%)	31 (32%)	61 (30%)
Race			
Black	5 (5%)	1 (1%)	6 (3%)
White	88 (85%)	86 (88%)	174 (87%)
Asian	7 (8%)	5 (5%)	12 (6%)
Others	3 (3%)	6 (6%)	9 (3%)
Ethnicity			
Hispanic	10 (10%)	8 (8%)	18 (9%)
Non-Hispanic	93 (90%)	89 (91%)	182 (91%)
Declined to disclose	0	1 (1%)	1 (1%)
Country[1]			
Canada	26 (25%)	17 (17%)	43 (21%)
USA	74 (72%)	76 (78%)	150 (76%)
New Zealand	3 (3%)	5 (5%)	8 (4%)
Baseline body mass index (kg/m^2)			
Mean (SD)	28 (5)	29 (5)	29 (5)
Median (Q1, Q3)	27 (25, 31)	29 (26, 32)	28 (25, 31)
< 30 kg/m^2	74 (72%)	62 (63%)	136 (68%)
≥ 30 kg/m^2	29 (28%)	36 (37%)	65 (32%)

Source: Table 8-4 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA
[1]The distribution of subjects by country within each treatment arm was obtained by the statistical reviewer.

Table 59: Baseline Disease Characteristics for Study 108 (All Treated)

	12-Week SOF+RBV (N=103)	16-Week SOF+RBV (N=98)	Total (N=201)
HCV genotype			
Genotype 1[1]	3 (3%)	3 (3%)	6 (3%)
Genotype 2	36 (35%)	32 (33%)	68 (34%)
Genotype 3	64 (62%)	63 (64%)	127 (63%)
Cirrhosis			
No	66 (65%)	66 (67%)	132 (66%)
Yes	36 (35%)	32 (33%)	68 (34%)
IL28 B			
CC	31 (30%)	30 (31%)	61 (30%)
CT	53 (52%)	56 (57%)	109 (54%)
TT	19 (18%)	12 (12%)	31 (15%)
Response to prior HCV trt			
Nonresponse	25 (24%)	25 (26%)	50 (25%)
Relapse/Breakthrough	78 (76%)	73 (75%)	151 (75%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.5 (0.7)	6.5 (0.6)	6.5 (0.7)
Median (Q1, Q3)	6.6 (6.0, 7.0)	6.6 (5.9, 7.1)	6.6 (6.0, 7.0)
< 6 log_{10} IU/mL	26 (25%)	29 (30%)	55 (27%)
≥ 6 log_{10} IU/mL	77 (75%)	69 (70%)	146 (73%)
Baseline ALT[2]			
≤ 1 x ULN	23 (22%)	20 (20%)	43 (21%)
> 1 x ULN	80 (78%)	78 (80%)	158 (79%)
≤ 1.5 x ULN	40 (39%)	42 (43%)	82 (41%)
> 1.5 x ULN	63 (61%)	56 (57%)	119 (59%)

Source: Table 8-5 in Study GS-US-334-0108 Interim Clinical Study Report submitted in this NDA

[1]There were six subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis.

[2]The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 60: Reviewer's Results for Subgroup Analysis in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Proportion Diff (95% CI)[1]
Age (years)			
< 50 years old	43% (9/21)	70% (16/23)	-27% (-55%, 2%)
≥ 50 years old	51% (42/82)	72% (54/75)	-21% (-36%, -6%)
Sex			
Male	41% (30/73)	64% (43/67)	-23% (-39%, -7%)
Female	70% (21/30)	87% (27/31)	-17% (-37%, 3%)
Race			
Black	100% (1/1)	100% (5/5)	n/a
Other	71% (69/97)	47% (46/98)	-24% (-38%, -11%)
Region			
US	53% (39/74)	75% (57/76)	-22% (-37%, -7%)
Non-US	41% (12/29)	59% (13/22)	-18% (-45%, 10%)
Ethnicity			
Hispanic	40% (4/10)	63% (5/8)	-23% (-68%, 23%)
Non-Hispanic	51% (47/93)	72% (64/89)	-21% (-35%, -8%)
Baseline body mass index			
< 30 kg/m^2	54% (40/74)	71% (45/63)	-17% (-33%, -1%)
≥ 30 kg/m^2	38% (11/29)	71% (25/35)	-34% (-57%, -10%)
Cirrhosis			
No	60% (40/67)	74% (49/66)	-5% (-30%, 1%)
Yes	31% (11/36)	66% (21/32)	-35% (-6%, -13%)
IL28B			
CC	52% (16/31)	67% (20/30)	-15% (-39%, 9%)
CT or TT	49% (35/72)	74% (50/68)	-25% (-1%, -9%)
Response to prior HCV trt			
Nonresponse	44% (11/25)	64% (16/25)	-20% (-47%, 7%)
Relapse/Breakthrough	51% (40/78)	74% (54/73)	-23% (-38%, -8%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	50% (13/26)	62% (18/29)	-12% (-38%, 14%)
≥ 6 $\log_{10}$ IU/mL	49% (38/77)	75% (52/69)	-26% (-41%, -11%)
Baseline ALT			
≤ 1.5 x ULN	65% (26/40)	76% (32/42)	-11% (-31%, 8%)
> 1.5 x ULN	40% (25/63)	68% (38/56)	-28% (-45%, -11%)

[1]based on the Wald asymptotic confidence limits

Table 61: Reviewer's Results for Subgroup Analysis among Genotype 2 Subjects in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	83% (5/6)	75% (3/4)	8% (-44%, 60%)
≥ 50 years old	82% (27/33)	90% (28/31)	-9% (-25%, 8%)
Sex			
Male	72% (18/25)	84% (21/25)	-12% (-35%, 11%)
Female	100% (14/14)	100% (10/10)	n/a
Race			
Black	0	100% (4/4)	n/a
Other	80% (28/35)	86% (31/35)	-9% (-26%, 8%)
Region			
US	82% (27/33)	91% (29/32)	-9% (-25%, 8%)
Non-US	83% (5/6)	67% (2/3)	17% (-44%, 78%)
Ethnicity			
Hispanic	80% (4/5)	100% (1/1)	-20% (-55%, 15%)
Non-Hispanic	82% (28/34)	88% (30/34)	-6% (-23%, 11%)
Baseline body mass index			
< 30 kg/m^2	86% (24/28)	94% (16/17)	8% (-9%, 26%)
≥ 30 kg/m^2	73% (8/11)	83% (15/18)	-11% (-42%, 21%)
Cirrhosis			
No	90% (26/29)	92% (24/26)	-3% (-18%, 12%)
Yes	60% (6/10)	78% (7/9)	-18% (-59%, 23%)
IL28 B			
CC	88% (7/8)	71% (10/14)	16% (-17%, 49%)
CT or TT	81% (25/31)	100% (21/21)	-19% (-33%, -5%)
Response to prior HCV trt			
Nonresponse	70% (7/10)	88% (7/8)	-18% (-54%, 19%)
Relapse/Breakthrough	86% (25/29)	89% (24/27)	-3% (-20%, 15%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	89% (8/9)	100% (3/3)	-11% (-32%, 9%)
≥ 6 $\log_{10}$ IU/mL	80% (24/30)	88% (28/32)	-8% (-26%, 11%)
Baseline ALT			
≤ 1.5 x ULN	83% (20/24)	91% (20/22)	-8% (-27%, 12%)
> 1.5 x ULN	80% (28/35)	86% (31/35)	-5% (-33%, 24%)

[1]based on the Wald asymptotic confidence limits

Table 62: Reviewer's Results for Subgroup Analysis among Genotype 3 Subjects in Study 108 (All Treated)

	12-Week SOF+RBV	16-Week SOF+RBV	12-Week vs. 16-Week SOF+RBV Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	27% (4/15)	68% (13/19)	-42% (-72%, -11%)
≥ 50 years old	31% (15/49)	59% (26/44)	-28% (-48%, -9%)
Sex			
Male	25% (12/48)	52% (22/42)	-27% (-47%, -8%)
Female	44% (7/16)	81% (17/21)	-37% (-67%, -8%)
Race			
Black	100% (1/1)	100% (1/1)	n/a
Other	29% (18/63)	61% (38/62)	-33% (-49%, -16%)
Region			
US	29% (12/41)	64% (28/44)	-34% (-54%, -14%)
Non-US	30% (7/23)	58% (11/19)	-27% (-57%, 2%)
Ethnicity			
Hispanic	0% (0/5)	57% (4/7)	-57% (-94%, -20%)
Non-Hispanic	32% (19/59)	62% (34/55)	-30% (-47%, -12%)
Baseline body mass index			
< 30 kg/m^2	35% (16/46)	63% (29/46)	-28% (-48%, -9%)
≥ 30 kg/m^2	17% (3/18)	59% (10/17)	-42% (-71%, -13%)
Cirrhosis			
No	37% (14/38)	63% (25/40)	-26% (-47%, -4%)
Yes	19% (5/26)	61% (14/23)	-42% (-67%, -17%)
IL28 B			
CC	39% (9/23)	63% (10/16)	-23% (-54%, 8%)
CT or TT	24% (10/41)	62% (29/47)	-37% (-56%, -18%)
Response to prior HCV trt			
Nonresponse	27% (4/15)	53% (9/17)	-26% (-59%, 6%)
Relapse/Breakthrough	31% (15/49)	65% (30/46)	-35% (-53%, -16%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	29% (5/17)	58% (15/26)	-28% (-57%, 0.5%)
≥ 6 $\log_{10}$ IU/mL	30% (14/47)	65% (24/37)	-35% (-55%, -15%)
Baseline ALT			
≤ 1.5 x ULN	38% (6/16)	60% (12/20)	-23% (-55%, 10%)
> 1.5 x ULN	27% (13/48)	63% (27/43)	-36% (-55%, -17%)

[1]based on the Wald asymptotic confidence limits

6.4 Study 110

Table 63: On-Treatment Study Procedures in Study 110

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week							
			1	2	4	6	8	10	12	Early Termination
Clinical Assessments										
Informed Consent	X									
Determine Eligibility	X	X								
Medical History	X									
Physical Examination[b]	X[b]	X							X	X
Height	X									
Weight	X	X							X	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X							X	X
AEs and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pregnancy Prevention Counseling		X							X	X
Quality of Life Surveys		X							X	X
Review of Study Drug Compliance			X	X	X	X	X	X	X	
Study Drug Dispensing[d]		X			X		X			

to be continued

Table 63: On-Treatment Study Procedures for Study 110 (Continued)

	Screening	Baseline/Day 1[a]	Visit Identified by On-Treatment Study Week							
			1	2	4	6	8	10	12	Early Termination
Laboratory Assessments										
Hematology, Chemistry	X	X	X	X	X	X	X	X	X	X
Coagulation Tests	X	X							X	X
HCV RNA	X	X	X	X	X	X	X	X	X	X
Viral Sequencing (archive)[e]		X	X	X	X	X	X	X	X	X
Single PK		X	X	X	X	X	X	X	X	X
Serum or Urine Pregnancy Testing	X	X			X		X		X	X
Urinalysis	X									
Urine Drug Screen	X									
HCV Genotyping, IL28B	X									
HCV, HIV, HBV Serology	X									
HbA_{1c}	X									
TSH	X								X	X
Pharmacogenomic		X[f]								

a Day 1 assessments were performed prior to dosing

b Retinal examination was performed at screening only

c Vital signs included blood pressure, pulse, respiratory rate, and temperature

d The interactive web response system (IWRS) provided direction on the specifics of each subject's study drug dispensing.

e Plasma samples were collected and stored for potential HCV sequencing and other virology studies

f Only for subjects who consented to this testing. If not obtained at Day 1, the sample was drawn at any time during the study.

Source: Table 7-2 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 64: Post-Treatment Study Procedures for Study 110

	Posttreatment Week 4	Posttreatment Week 12	Posttreatment Week 24
Clinical Assessments			
Vital Signs	X		
Weight	X		
AEs	X		
Concomitant Medications	X		
Laboratory Assessments			
Hematology, Chemistry	X	X	
HCV RNA	X	X	X
Viral Sequencing	X	X	X
Urine Pregnancy Test	X	X	X
Quality of Life Surveys	X	X	X
Pregnancy Prevention Counseling	X	X	X

Source: Table 7-3 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 65: On-Treatment Visit Windows for Study 110

Visit ID	On-Treatment Visit Windows for HCV RNA, Vital signs, Safety Labs	Coagulation Tests
Baseline	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 11	N/A
Week 2	12 ≤ Study Day ≤ 21	N/A
Week 4	22 ≤ Study Day ≤ 35	N/A
Week 6	36 ≤ Study Day ≤ 49	N/A
Week 8	50 ≤ Study Day ≤ 63	N/A
Week 10	64 ≤ Study Day ≤ 77	N/A
Week 12	78 ≤ Study Day ≤ 98	2 ≤ Study Day ≤ 98

Source: Table 1 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 66: Post-Treatment Visit Windows for Selected Tests for Study 110

Post - Treatment FU Visit ID	Post-Treatment Visit Windows for HCV RNA[a] (Days from Last Study Drug Dose)	Vital Signs[b] (Days from Last Study Drug Dose)	Safety Labs[b] (Days from Last Study Drug Dose)
FU-4	21 ≤ FU Day ≤ 69	3 ≤ FU Day ≤ 30	3 ≤ FU Day ≤ 30
FU-12	70 ≤ FU Day ≤ 146	N/A	NA
FU-24	147 ≤ FU Day ≤ 190	N/A	N/A

a SVR follow-up visit window (lower bound) must occur within 7, 14, and 21 days of target for SVR4, SVR12, and SVR24, respectively.

b Vital signs and safety labs will only be summarized for the FU-4 visit (up to 30 days post last dose).

Source: Table 2 in Statistical Analysis Plan in Appendix 16.1.9 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 67: Patient Demographics and Baseline Characteristics for Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)
Age (years)	
Mean (SD)	52 (10)
Median (Q1, Q3)	54 (46, 59)
Sex	
Male	209 (64%)
Female	118 (36%)
Race	
Black	54 (17%)
White	257 (79%)
Asian	7 (2%)
Others	9 (3%)
Ethnicity	
Hispanic	46 (14%)
Non-Hispanic	281 (86%)
Baseline body mass index (kg/m^2)	
Mean (SD)	29 (7)
Median (Q1, Q3)	28 (25, 32)

Source: Table 8-4 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 68: Baseline Disease Characteristics for Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)
HCV genotype	
Genotype 1a/1b	1 (<1%)
Genotype 1a	225 (69%)
Genotype 1b	66 (20%)
Genotype 4	28 (9%)
Genotype 5	1 (<1%)
Genotype 6	6 (2%)
Cirrhosis	
No	270 (83%)
Yes	54 (17%)
Missing	3 (1%)
IL28 B	
CC	95 (29%)
CT	181 (55%)
TT	51 (16%)
Baseline HCV RNA (log_{10} IU/mL)	
Mean (SD)	6.4 (0.67)
Median (Q1, Q3)	6.6 (6.1, 6.9)
< 6 log_{10} IU/mL	71 (22%)
≥ 6 log_{10} IU/mL	256 (78%)
Baseline ALT[2]	
≤ 1 x ULN	68 (21%)
> 1 x ULN	259 (79%)
≤ 1.5 x ULN	161 (49%)
> 1.5 x ULN	51% (166)

Source: Table 8-5 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

[1]There were six subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis.

[2] The distribution of subjects with baseline ALT < 1xULN or ≥ 1xULN within each treatment group was calculated by the statistical reviewer.

Table 69: Patient Demographics and Baseline Characteristics by HCV Genotype in Study 110 (All Treated)

	12-Week SOF+PEG+RBV (N=327)	
	Genotype 1a (n=225)	**Genotype 1b (n=66)**
Age (years)		
Mean (SD)	51 (11)	56 (8)
Median (Q1, Q3)	53 (46, 58)	58 (53, 62)
< 50 years old	81 (36%)	12 (18%)
≥ 50 years old	144 (64%)	54 (82%)
Sex		
Male	143 (64%)	45 (68%)
Female	82 (36%)	21 (32%)
Race		
Black	33 (15%)	17 (26%)
White	185 (82%)	48 (73%)
Others	7 (3%)	1 (2%)
Ethnicity		
Hispanic	36 (16%)	6 (9%)
Non-Hispanic	189 (84%)	60 (91%)
Baseline body mass index		
< 30 kg/m^2	134 (60%)	91 (59%)
≥ 30 kg/m^2	91 (40%)	27 (41%)
Cirrhosis		
No	180 (80%)	56 (85%)
Yes	43 (19%)	9 (14%)
Missing	2 (1%)	1 (2%)
IL28 B		
CC	72 (32%)	13 (20%)
CT or TT	153 (68%)	53 (80%)
Baseline HCV RNA (log_{10} IU/mL)		
Mean (SD)	6.5 (0.7)	6.5 (0.6)
Median (Q1, Q3)	6.6 (6.2, 7.0)	6.7 (6.2, 6.9)
< 6 log_{10} IU/mL	46 (20%)	9 (14%)
≥ 6 log_{10} IU/mL	179 (80%)	57 (86%)
Baseline ALT[2]		
≤ 1.5 x ULN	98 (44%)	38 (58%)
> 1.5 x ULN	127 (56%)	28 (42%)

Source: Table 3.2 in Section 15.1 of Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA

Table 70: Applicant's Results for Subgroup Analysis in Study 110 (All Treated)

	SVR12 Rate	95% CI[1]
Age (years)		
< 50 years old	95% (104/110)	(89%, 98%)
≥ 50 years old	88% (191/217)	(83%, 92%)
Sex		
Male	88% (184/209)	(83%, 92%)
Female	94% (111/118)	(88%, 98%)
Race		
Black	87% (47/54)	(75%, 95%)
Non-black	91% (248/273)	(87%, 94%)
Ethnicity		
Hispanic	91% (42/46)	(79%, 98%)
Non-Hispanic	90% (253/281)	(86%, 93%)
Baseline body mass index		
< 30 kg/m^2	93% (184/198)	(88%, 96%)
≥ 30 kg/m^2	86% (111/129)	(79%, 91.5%)
HCV Genotype		
Genotype 1a	92% (206/225)	(87%, 95%)
Genotype 1b	82% (54/66)	(70%, 90%)
Genotype 4	96% (27/28)	(82%, 100%)[3]
Genotype 5	100% (1/1)	n/a
Genotype 6	100% (6/6)	n/a
Cirrhosis		
No[2]	92% (252/273)	(87%, 95%)
Yes	80% (43/54)	(66%, 89%)
IL28 B		
CC	98% (93/95)	(93%, 100%)
CT or TT	87% (202/232)	(82%, 91%)
Baseline HCV RNA		
< 6 $\log_{10}$ IU/mL	96% (68/71)	(88%, 99%)
≥ 6 $\log_{10}$ IU/mL	89% (227/256)	(84%, 92%)
Baseline ALT		
≤ 1.5 x ULN	90% (145/161)	(84%, 94%)
> 1.5 x ULN	90% (150/166)	(85%, 94%)

Source: Table 9-4 in Study GS-US-334-0110 Interim Clinical Study Report submitted in this NDA
[1]Clopper-Pearson exact 95% CI
[2]CIRRHOSIS = NO for subjects with missing cirrhosis status
[3]calculated by reviewer using Clopper-Pearson exact 95% CI

Table 71: Reviewer's Results for Subgroup Comparisons between HCV Genotype 1a and Genotype 1b in Study 110 (All Treated)

	12-Week SOF+PEG+RBV		
	Genotype 1a (n=225)	**Genotype 1b (n=66)**	**Genotype 1a vs. Genotype 1b Prop Diff (95% CI)[1]**
Age (years)			
< 50 years old	94% (76/81)	92% (11/12)	2% (-14%, 19%)
≥ 50 years old	90% (130/144)	80% (43/54)	11% (-1%, 22%)
Sex			
Male	90% (128/143)	78% (35/45)	12% (-1%, 25%)
Female	95% (78/82)	91% (19/21)	5% (-9%, 18%)
Race			
Black	91% (30/33)	77% (13/17)	14% (-8%, 37%)
Non-black	92% (176/192)	84% (41/49)	8% (-3%, 19%)
Ethnicity			
Hispanic	92% (33/36)	83.3% (5/6)	8% (-23%, 39%)
Non-Hispanic	92% (173/189)	82% (49/60)	10% (-1%, 20%)
Baseline body mass index			
< 30 kg/m^2	95% (127/134)	85% (33/39)	10% (-2%, 22%)
≥ 30 kg/m^2	87% (79/91)	78% (21/27)	9% (-8%, 26%)
Cirrhosis			
No	93% (168/180)	84% (47/56)	9% (-1%, 20%)
Yes	84% (36/43)	67% (6/9)	17% (-16%, 50%)
IL28 B			
CC	99% (71/72)	92% (12/13)	6% (-8%, 21%)
CT or TT	88% (135/153)	79% (42/53)	9% (-3%, 21%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	96% (44/46)	100% (9/9)	-4% (-2%, 10%)
≥ 6 $\log_{10}$ IU/mL	91% (162/179)	79% (45/57)	12% (0.1%, 23%)
Baseline ALT[2]			
≤ 1.5 x ULN	91% (89/98)	82% (31/38)	9% (-4%, 23%)
> 1.5 x ULN	92% (117/127)	82% (23/28)	10% (-5%, 25%)

[1]based on the Wald asymptotic confidence limits

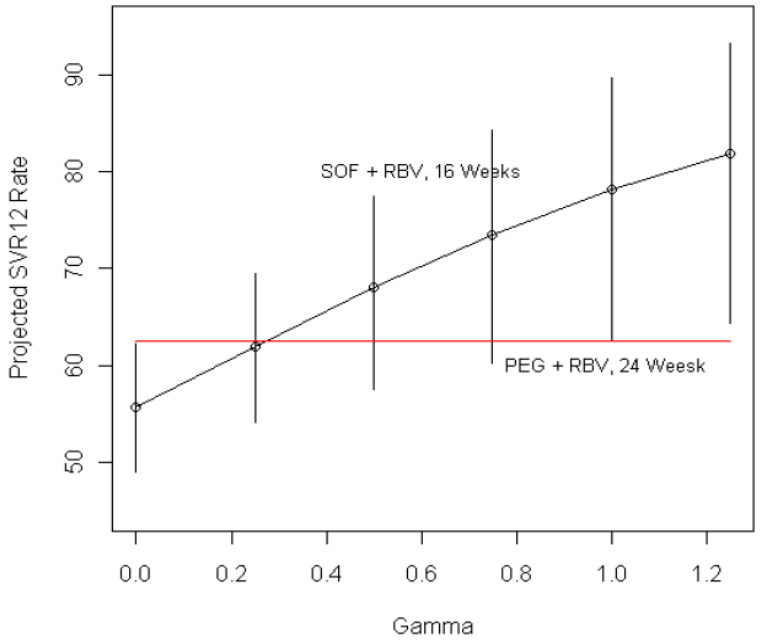
6.5 Bridging Analysis

Table 72: Applicant's Bridging Analyses Results

Study	Treatment	Estimated and Predicted SVR12 Rate (95% Credible Set) from Bayesian Model Based on Data from Studies P7977-1231 and GS-US-334-0108	Actual SVR12 Rate
Noninteraction Model			
P7977-1231	SOF+RBV for 12 weeks (Estimated)	55.7% (49%, 62.7%)	55.7%
GS-US-334-0108	SOF+RBV for 12 weeks (Estimated)	29.7% (19.8%, 40.5%)	29.7%
GS-US-334-0108	SOF+RBV for 16 weeks(Estimated)	61.9% (50.3%, 73.1%)	61.9%
P7977-1231	SOF+RBV for 16 weeks (Projected)	80.7% (66.8%, 90.5%)	NA
Interaction Model			
P7977-1231	SOF+RBV for 12 weeks (Estimated)	55.7% (49.1%, 62.3%)	55.7%
GS-US-334-0108	SOF+RBV for 12 weeks (Estimated)	29.7% (19.4%, 40.8%)	29.7%
GS-US-334-0108	SOF+RBV for 16 weeks(Estimated)	62.0% (50.1%, 73.1%)	61.9%
P7977-1231	SOF+RBV for 16 weeks (Projected)	78.2% (62.5%, 89.6%)	NA

Source: Table 1 in Section 2.7 3 Summary of Clinical Efficacy submitted in this NDA.

Figure 12: Applicant's Sensitivity Analysis for Impact of 16-Week Treatment Duration of SOF+RBV Using Model 2



Source: Figure 3 in Section 2.7.3 Summary of Clinical Efficacy submitted in this NDA.

6.6 Exploratory Analysis to Evaluate Gender Difference in SVR12 Rate for SOF+RBV among HCV Genotype 3 Subjects

Table 73: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 1231 (All Treated)

	Females (N=58)	Males (N=125)	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	71% (22/31)	49% (36/73)	22% (2%, 41%)
≥ 50 years old	70% (19/27)	48% (25/52)	22% (0.4%, 44%)
Race			
White	69% (33/48)	47% (52/110)	21% (5%, 386%)
Other	80% (8/10)	60% (9/15)	20% (-15%, 55%)
Region			
US	67% (20/30)	56% (36/64)	10% (-10%, 31%)
Non-US	75% (21/28)	41% (25/61)	34% (14%, 54%)
Ethnicity			
Hispanic	80% (4/5)	53% (10/19)	27% (-14%, 69%)
Non-Hispanic	70% (37/53)	48% (51/106)	22% (6%, 37%)
Baseline body mass index			
< 30 kg/m^2	69% (27/39)	49% (43/87)	20% (2%, 38%)
≥ 30 kg/m^2	74% (14/19)	47% (18/38)	26% (1%, 52%)
Cirrhosis			
No	43% (3/7)	32% (10/31)	11% (-30%, 51%)
Yes	75% (38/51)	54% (51/94)	20% (5%, 36%)
IL28 B			
CC	70% (14/20)	53% (29/55)	17% (-7%, 41%)
CT or TT	71% (27/38)	46% (32/70)	25% (7%, 44%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	76% (26/34)	61% (30/49)	15% (-4%, 35%)
≥ 6 $\log_{10}$ IU/mL	63% (15/24)	41% (31/76)	22% (-1%, 44%)
Baseline ALT			
≤ 1 x ULN	79% (11/14)	47% (9/19)	31% (0.1%, 62%)
> 1 x ULN	68% (30/44)	49% (52/106)	19% (2%, 36%)

[1]based on the Wald asymptotic confidence limits

Table 74: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 107 (All Treated)

	Females (N=45)	Males (N=53)	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	65% (11/17)	58% (15/26)	7% (-23%, 37%)
≥ 50 years old	82% (23/28)	41% (11/27)	41% (18%, 65%)
Race			
Black	0	0	n/a
Other	76% (34/45)	49% (26/53)	27% (8%, 45%)
Region			
US	71% (25/35)	42% (16/38)	29% (8%, 51%)
Non-US	90% (9/10)	67% (10/15)	23% (-7%, 54%)
Ethnicity			
Hispanic	100% (1/1)	57% (4/7)	43% (6%, 80%)
Non-Hispanic	75% (33/44)	48% (22/46)	27% (8%, 46%)
Baseline body mass index			
< 30 kg/m^2	75% (24/32)	47% (18/38)	28% (6%, 49%)
≥ 30 kg/m^2	77% (10/13)	53% (8/15)	24% (-11%, 58%)
Cirrhosis			
No	77% (33/43)	59% (24/41)	18% (-1%, 38%)
Yes	50% (1/2)	17% (2/12)	33% (-39%, 100%)
IL28 B			
CC	72% (18/25)	59% (16/27)	13% (-13%, 38%)
CT or TT	80% (16/20)	38% (10/26)	42% (16%, 67%)
Duration of Prior HCV Trt			
No	84% (31/37)	58% (23/40)	26% (7%, 46%)
≤ 12 weeks	67% (2/3)	29% (2/7)	38% (-25%, 100%)
> 12 weeks	20% (1/5)	17% (1/6)	3% (-43%, 49%)
Interferon Class			
Ineligible	81% (17/21)	62% (16/26)	19% (-6%, 45%)
Intolerant	100% (2/2)	33% (2/6)	67% (29%, 100%)
Unwilling	68% (15/22)	38% (8/21)	30% (2%, 59%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	94% (15/16)	39% (7/18)	55% (29%, 80%)
≥ 6 $\log_{10}$ IU/mL	66% (19/29)	54% (19/35)	11% (-13%, 35%)
Baseline ALT			
≤ 1.5 x ULN	71% (12/17)	40% (6/15)	31% (-2%, 64%)
> 1.5 x ULN	79% (22/28)	53% (20/38)	26% (4%, 48%)

[1]based on the Wald asymptotic confidence limits

Table 75: Subgroup Comparison between Females and Males in 12-Week SOF+RBV Group in Study 108 (All Treated)

	Females	Males	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	100% (1/1)	21% (3/14)	79% (57%, 100%)
≥ 50 years old	40% (6/15)	26% (9/34)	15% (-15%, 42%)
Race			
White	50% (2/4)	40% (2/5)	10% (-55%, 75%)
Other	42% (5/12)	23% (10/43)	18% (-12%, 49%)
Region			
US	50% (5/10)	23% (7/31)	27% (-7%, 62%)
Non-US	33% (2/6)	29% (5/17)	4% (-40%, 47%)
Ethnicity			
Hispanic	0/0	0% (0/5)	n/a
Non-Hispanic	44% (7/16)	28% (12/43)	16% (-12%, 44%)
Baseline BMI			
< 30 kg/m^2	60% (6/10)	28% (10/36)	32% (-1%, 66%)
≥ 30 kg/m^2	17% (1/6)	17% (2/12)	0% (-37%, 37%)
Cirrhosis			
No	56% (5/9)	31% (9/29)	25% (-12%, 61%)
Yes	29% (2/7)	16% (3/19)	13% (-24%, 50%)
IL28 B			
CC	33% (2/6)	41% (7/17)	-8% (-52%, 37%)
CT or TT	50% (5/10)	16% (5/31)	34% (0.3%, 67%)
Response to prior HCV trt			
Nonresponse	33% (2/6)	22% (2/9)	11% (-35%, 58%)
Relapse/Breakthrough	50% (5/10)	26% (10/39)	24% (-10%, 58%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	40% (2/5)	25% (3/12)	15% (-34%, 64%)
≥ 6 $\log_{10}$ IU/mL	45% (5/11)	25% (9/36)	20% (-12%, 53%)
Baseline ALT			
≤ 1 x ULN	100% (2/2)	40% (2/5)	60% (17%, 100%)
> 1 x ULN	36% (5/14)	23% (10/43)	12% (-16%, 41%)

[1]based on the Wald asymptotic confidence limits

Table 76: Subgroup Comparison between Females and Males in 16-Week SOF+RBV Group in Study 108 (All Treated)

	Females	Males	Females vs. Males Prop Diff (95% CI)[1]
Age (years)			
< 50 years old	86% (6/7)	58% (7/12)	27% (-11%, 65%)
≥ 50 years old	79% (11/14)	50% (15/30)	29% (1%, 57%)
Race			
White	80% (12/15)	53% (20/38)	27% (2%, 53%)
Other	83% (5/6)	50% (2/4)	33% (-24%, 91%)
Region			
US	83% (10/12)	56% (18/32)	27% (-0.1%, 54%)
Non-US	78% (7/9)	40% (4/10)	38% (-3%, 79%)
Ethnicity			
Hispanic	0/0	57% (4/7)	n/a
Non-Hispanic	80% (16/20)	51% (18/35)	29% (4.5%, 53%)
Baseline BMI			
< 30 kg/m^2	86% (12/14)	53% (17/32)	33% (7%, 58%)
≥ 30 kg/m^2	71% (5/7)	50% (5/10)	21% (-24%, 67%)
Cirrhosis			
No	75% (12/16)	54% (13/24)	21% (-8%, 50%)
Yes	100% (5/5)	50% (9/18)	50% (27%, 73%)
IL28 B			
CC	100% (3/3)	54% (7/13)	46% (19%, 73%)
CT or TT	78% (14/18)	52% (15/29)	26% (-0.4%, 53%)
Response to prior HCV trt			
Nonresponse	63% (5/8)	44% (4/9)	18% (-29%, 65%)
Relapse/Breakthrough	92% (12/13)	55% (18/33)	38% (15%, 60%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	75% (6/8)	50% (9/18)	25% (-13%, 63%)
≥ 6 $\log_{10}$ IU/mL	85% (11/13)	54% (13/24)	30% (2%, 58%)
Baseline ALT			
≤ 1 x ULN	50% (1/2)	50% (3/6)	0% (-80%, 80%)
> 1 x ULN	84% (16/19)	53% (19/36)	31% (8%, 55%)

[1]based on the Wald asymptotic confidence limits

6.7 Adverse Events for 12-Week SOF+RBV in Studies 1231, 107 and 108

Table 77: Adverse Events for 12-Week SOF+RBV in Studies 1231, 107 and 108 (All Treated)

	Study 1231 (N=256)	Study 107 (N=207)	Study 108 (N=103)	Total (N=566)
Number (%) of Subjects Experiencing Any				
Adverse Event (AE)	220 (86)	185 (89)	92 (89)	496 (88)
Treatment-Related AE	183 (72)	150 (73)	75 (73)	408 (72)
Serious Adverse Event (SAE)	7 (3)	11 (5)	5 (5)	22 (4)
Treatment-Related SAE	1 (<1)	1 (<1)	0	2 (<1)
Grade 3 & 4 AE	18 (7)	17 (8)	8 (8)	41 (7)
Treatment-Related Grade 3 & 4 AE	8 (3)	3 (1)	4 (4)	15 (3)
AE Leading to Permanent Discontinuation from Study Drugs (Any Study Drug)	3 (1)	5 (2)	1 (1)	9 (2)
AE Leading to Permanent Discontinuation from All Study Drugs	3 (1)	4 (2)	1 (1)	8 (1)
AE Leading to Modification or Interruption of Study Drugs (Any Study Drug)	25 (10)	29 (14)	9 (9)	63 (11)
Death	1 (<1)	0	0	1 (<1)

Source: report from the medical officer, Dr. Poonam Mishra

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/s/

XIAOJING K QI
09/06/2013

WEN ZENG
09/06/2013

DIONNE L PRICE
09/06/2013
concur with overall conclusions

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	**Applicant:**	**Stamp Date:**
204671	Gilead Science, Inc.	April 8, 2013
Drug Name:	**NDA/BLA Type:**	
Sofosbuvir	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.

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**	**Treatment arms/Sample size (Number of randomized and treated)**	**Primary endpoint /Analysis**	**Primary hypothesis**	**Sponsor's findings**
P7977-1231 (Fission)	phase 3, multicenter, randomized, active-controlled, non-inferiority study in treatment-naïve (TN) subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week sofosbuvir and ribavirin (SOF+RBV), N=256 Arm 2: 24-week pegylated interferon and ribavirin (PEG+RBV), N=243	SVR12 rate defined as the proportion of subjects with HCV RNA <LOQ 12 weeks after cessation of therapy	The SVR12 rate in the12-week GS+RBV treatment arm is non-inferior to the 24-week PEG+RBV by 15%.	The SVR12 rate in the 12-week SOF+RBV group was 67%, which was non-inferior to the SVR12 rate of 67% in the 24-week PEG+RBV group. However, there was obvious interaction between treatment and HCV genotype. Among genotype 2 subjects, the SVR12 rates for the SOF+RBV and PEG+RBV arms were 97% and 78%, respectively. On the other hand, the SVR12 rate for genotype 3 subjects was 56% in the SOF+RBV group and 63% in the PEG+RBV group.
GS-US-334-0107 (Positron)	phase 3, multicenter, randomized, double-blind, placebo-controlled study in subjects with chronic genotype 2 or 3 HCV infection who are interferon intolerant, interferon ineligible or unwilling to take interferon	Arm 1: 12-week SOF+RBV, N=207 Arm 2: placebo, N=71	SVR12 rate	The SVR12 rate for the 12-week SOF+RBV is superior to placebo.	The SVR12 rate in the 12-week SOF+RBV group was 78% while no subjects in the placebo group achieved SVR12. The superiority of the12-week SOF+RBV over the placebo appeared to be established. The SVR12 for HCV-2 was 93%, but was 61% for HCV-3 subjects.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Study number	Design	Treatment arms/Sample size (Number of randomized and treated)	Primary endpoint /Analysis	Primary hypothesis	Sponsor's findings
GS-US-334-0108 (Fusion)	phase 3, multicenter, randomized, double-blind, historical control study in treatment-experienced (TE) subjects with chronic genotype 2 or 3 HCV infection	Arm 1: 12-week SOF+RBV, N=103 Arm 2: 16-week SOF+RBV, N=98	SVR12 rate	The SVR12 rate in each of the 2 treatment arms is no worse than 25%.	The SVR12 rate for the 12-week SOF+RBV group was 50% with 95% CI of (40%, 60%), and rate for the 16-week SOF+RBV group was 73% with 95% CI of (63%, 81%). The SVR12 rates in both groups appeared superior to 25%. However, the treatment by genotype interaction was apparent. Among the HCV genotype 2 subjects, the SVR12 rate was 86% in the 12-week SOF+RBV group and 94% in the 16-week SOF+RBV group. Meanwhile, among the HCV genotype 3 subjects, the rate was 30% in the 12-week arm and 62% in the 16-week arm.
GS-US-334-0110 (Neutrino)	phase 3, multicenter, open-label, single-arm, historical control study in TN subjects with genotype 1, 4, 5 or 6 HCV infection	12-week for GS-7977+PEG+RBV, 327 recruited and treated subjects	SVR12 rate	The SVR12 rate in the study arm is greater than 60%.	The overall SVR12 rate was 90% with 95% CI of (87%, 93%), which was superior to 60% in the null hypothesis. Furthermore, the majority of subjects in the study (89%) had genotype1 HCV infection.

Karen Qi 05/03/2013

Reviewing Statistician Date

Wen Zeng 05/06/2013

Supervisor/Acting Team Leader Date

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/s/

XIAOJING K QI
05/10/2013

WEN ZENG
05/10/2013