CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	208341
Drug Name:	Sofosbuvir 400 mg / Velpatasvir 100 mg fixed dose combination
Indication(s):	Treatment of chronic Hepatitis C virus infection, including patients with compensated and decompensated cirrhosis
Applicant:	Gilead Sciences, Inc.
Date(s):	Received October 28, 2015
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Review Priority:	Priority
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Keywords: Clinical trials, Clopper –Pearson method, non-inferiority, closed testing procedure, Cochran-Mantel-Haenszel test, HCV, compensated cirrhosis, decompensated cirrhosis, Sofosbuvir, Velpatasvir

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1. EXECUTIVE SUMMARY

Gilead submitted a New Drug Application (NDA) 208341 including interim clinical study reports of four Phase 3 studies (i.e., ASTRAL-1 to 4) to seek the approval of fixed dose combination (FDC) of Sofosbuvir (SOF) 400 mg and Velpatasvir (VEL) 100 mg for the treatment of patients with HCV infection. Both SOF and VEL are direct-acting antiviral (DAA) agents. The proposed treatment regimens are SOF/VEL FDC for 12 weeks in subjects with and without compensated cirrhosis and SOF/VEL FDC in combination of ribavirin (RBV) for 12 weeks in subjects with decompensated cirrhosis.

The submission is based on four Phase 3 randomized and multicenter trials. These studies had the same primary efficacy endpoint of sustained virologic response (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. ASTRAL-1 randomized HCV genotype (GT) 1, 2, 4, and 6 subjects with and without compensated cirrhosis to receive either 12 weeks of SOF/VEL or placebo. Subjects infected with HCV GT5 were assigned 12 weeks of SOF/VEL. The placebo arm was for the purpose of comparative safety only since none of the placebo subjects were expected to achieve SVR12. ASTRAL-2 was an active-controlled trial conducted in HCV GT2 subjects with and without compensated cirrhosis to compare 12 weeks of SOF/VEL with the standard of care of SOF plus RBV for 12 weeks. ASTRAL-3 was an active-controlled trial conducted in HCV GT3 subjects with and without compensated cirrhosis. The study compared 12 weeks of SOF/VEL against an approved regimen of 24 weeks of SOF plus RBV. ASTRAL-4 investigated three SOF/VEL-containing regimens in HCV GT1 to 6 subjects with decompensated cirrhosis. The three regimens in the study included 12 weeks of SOF/VEL, 12 weeks of SOF/VEL plus RBV, and 24 weeks of SOF/VEL. The active-controlled design was not feasible for subjects with decompensated cirrhosis because no interferon (IFN)-free DAA-based regimens were approved for the patient population.

Above 95% SVR12 rates for 12 weeks of SOF/VEL were observed in all three trials, ASTRAL-1 to 3, and the SVR12 rates were significantly higher than the pre-specified threshold or the rate for the active control. In ASTRAL-1, the SVR12 rate for 12 weeks of SOF/VEL was as high as 99% in subjects infected with HCV GT1, 2, 4, 5 and 6 which was significantly superior to the pre-specified threshold of 85% (Table 6). In ASTRAL-2, 12 weeks of SOF/VEL resulted in a significantly higher SVR12 rate than 12 weeks of SOF + RBV in subjects with HCV GT2 infection (99% vs. 94%), (Table 12). The results in ASTRAL-3 demonstrated that the 12-week SOF/VEL treatment was significantly superior to the 24-week SOF + RBV treatment in SVR12 rate among subjects infected with HCV GT3 (95% vs. 80%), (Table 17). Baseline cirrhotic status and previous HCV treatment history were two randomization factors in ASTRAL-3. The pre-specified subgroup analyses demonstrated that, compared with 24-week SOF + RBV group, the SVR12 rate for 12 weeks of SOF/VEL was approximately 25% higher (95% CI: [12%, 37%]) in HCV GT3 subjects with cirrhosis and 27% higher (95% CI: [12%, 40%]) among HCV GT3 treatment-experienced (TE) subjects (Table 34). Results from ASTRAL-1 to 3 provided sufficient evidence that SOF/VEL for 12 weeks was effective in treatment of HCV infection without decompensated cirrhosis regardless of genotypes.

Findings from ASTRAL-4 showed that the regimen of SOF/VEL + RBV for 12 weeks had the highest SVR12 rate (94%) compared with SOF/VEL for 12 weeks (83%) and SOF/VEL for 24 weeks (86%). The SVR12 rates of all three treatment groups were clearly superior to the assumed spontaneous rate of 1%. Pairwise comparisons of SVR12 rates among the three treatment groups were not pre-specified. However, the reviewer's exploratory analyses showed that 12-week SOF/VEL + RBV had a nominally significantly higher SVR12 rate than 12-week SOF/VEL (p=0.031 based on Fisher's exact test) and no significant difference in SVR 12 rate for 24-week SOF/VEL (p=0.056 based on Fisher's exact test). Further subgroup analyses suggested that the highest SVR12 rate observed in the 12-week SOF/VEL group was driven by the subjects with HCV GT1 and GT3 infections since the majority of the subjects in the study had GT1 (78%) and GT3 (15%) infections (Table 37). There were limited data for subjects with HCV GT2 and GT4 infections. The study included only 12 GT2 subjects and eight GT4 subjects. Therefore the differences in SVR12 rates across the three groups were not apparent in these two genotypes to draw any meaningful conclusions. In addition, the study did not provide any evidence of efficacy for GT5 and 6 infections since there were no GT5 subjects and only one GT6 subject. There is also similar concern that there was limited number of subjects with Child-Pugh-Turcotte (CPT) classes A and C cirrhosis and therefore the higher SVR12 rate for SOF/VEL for 12 weeks versus the other two regimens was primarily driven by the subjects with CPT class B cirrhosis in the study (Table 37). Specifically, approximately 90% of subjects had CPT class B cirrhosis at baseline. There were only 16 subjects with CPT class A cirrhosis and 11 subjects with CPT class C cirrhosis in total in the study. The sample sizes for subjects with CPT class A and C cirrhosis were limited to make any reliable conclusion of the optimal regimens for the two classes.

2. INTRODUCTION

2.1 Overview

The HCV infection is one of major causes of cirrhosis and other liver diseases. According to the World Health Organization (WHO), 130 to 150 million people are infected with HCV worldwide and 500,000 die from hepatitis C related liver disease every year. There are six major HCV genotypes (1-6) and several subtypes (a, b, c, etc.). The most prevalent genotype is HCV GT1 (46%), followed by HCV GT3 (30%), GT2 (9%), GT4 (8%), GT5 (<1%). In most countries, GT1 is the most common genotype. Meanwhile, GT2 dominates in West African, GT3 in South Asian and parts of Scandinavia, GT4 in central and North Africa, GT5 in South Africa, and GT6 in Southeast Asian (Messina JP, Hematology 2014).

Cirrhosis is divided into two stages: compensated and decompensated. Patients with compensated cirrhosis experience few or no symptoms, whereas patients with decompensated cirrhosis experience many serious and life-threatening symptoms and complications. Patients with decompensated cirrhosis should be considered for liver transplantation.

Treatment of HCV has been changing rapidly in recent years. Treatment contained interferon (IFN) and RBV before 2013. Since then, several IFN-free DAA-based regimens have been approved (Table 1) for HCV infected subjects with and without compensated cirrhosis. Compared with the IFN-containing treatments, the DAA therapies resulted in much higher

SVR12 rates and fewer adverse events (AEs). However, treatment durations of the DAA-based regimens vary not only across different HCV genotypes but also depending on patient baseline disease characteristics within a genotype. Additionally, some DAA-based regimens include RBV. RBV has hematologic, dermatologic and neuropsychiatric side effects although it is much less toxic than IFN. Therefore, the applicant intended to develop a once-daily, single-tablet regimen of a fixed duration for treatment of all HCV genotypes. They presumed that the simplicity of such a regimen would support adherence and allow task shifting of treatment to healthcare providers with less therapeutic expertise. The applicant's findings based on Phase 2 studies led to the conclusion that the combination of SOF 400 mg and VEL 100 mg for 12 weeks had optimal SVR12 rate in subjects infected with GT1 to 6 HCV, including subjects with prior HCV treatment failure and subjects with compensated cirrhosis. Thus, they conducted three Phase 3 trials (i.e., ASTRAL-1 to 3) to evaluate efficacy and safety of SOF/VEL for 12 weeks in a range of HCV-infected patient populations.

Table 1: Approved Indications for IFN-Free DAA-Based HCV Regimens in US by 2015

Genotype	Approved indications for IFN-free DAA-based HCV regimens
GT1	HARVONI® (i.e., FDC of ledipasvir/SOF) • 12 weeks for GT1 TN subjects with or without cirrhosis and for GT1 TE subjects without compensated cirrhosis • 24 weeks for GT1 TE subjects with compensated cirrhosis
	VIEKIRA PAK® (i.e., FDC of paritaprevir/ombitasvir/ritonavir and dasabuvir) • With RBV for 12 weeks for GT1a subjects without compensated cirrhosis • With RBV for 24 weeks for GT1a subjects with compensated cirrhosis • Without RBV for 12 weeks for GT1b subjects without compensated cirrhosis • With RBV for 12 weeks for GT1b subjects with compensated cirrhosis
GT2	SOVALDI® (i.e., SOF tablet) • With RBV for 12 weeks
GT3	SOVALDI® • With RBV for 24 weeks
	DAKLINZA® (i.e., daclatasvir tablet) • With SOF for 12 weeks
GT4	HARVONI® • 12 weeks
	TECHNIVIE® (i.e., FDC of paritaprevir/ombitasvir/ritonavir) • With RBV for 12 weeks
GT5	HARVONI® • 12 weeks
GT6	HARVONI® • 12 weeks

Note: The reviewer generated this table based on labels for HARVONI®, VIEKIRA PAK®, SOVALDI® and TECHNIVIE®.

In addition, no IFN-free DAAs-based regimens were approved for HCV-infected subjects who had decompensated cirrhosis at the time when SOF/VEL was being developed. Therefore, the applicant also carried out a Phase 3 trial (i.e., ASTRAL-4) to evaluate SOF/VEL in combination with RBV for 12 weeks in the subjects with decompensated cirrhosis.

The statistical reviewer evaluated the efficacy of the four pivotal trials. The summaries of the key elements of the study designs are displayed in Table 2.

Table 2: List of Phase 3 Studies Included in Review

Study	Design	Study Population	Treatment Arms and Number of Randomized Subjects per Arm	Primary Efficacy Hypothesis
ASTRAL-1 (GS-US-342-1138)	multicenter (international), randomized, double-blind, placebo-controlled	HCV GT1, 2, 4, 5 and 6 infection with and without compensated cirrhosis	Arm 1: 12-week SOF/VEL, N=625 (including GT5 subjects who were not randomized but were enrolled into this arm) Arm 2: placebo, N=116	The SVR12 rate of the 12-week SOF/VEL regimen was superior to 85%.
ASTRAL-2 (GS-US-342-1139)	multicenter (US only), randomized, open-label, active-controlled, non-inferiority	HCV GT2 infection with and without compensated cirrhosis	Arm 1: 12-week SOF/VEL, N=135 Arm 2: 12-week SOF+RBV, N=134	The SVR12 rate of the 12-week SOF/VEL regimen was non-inferior to the rate of the 12-week SOF+RBV treatment by 10%.
ASTRAL-3 (GS-US-342-1140)	multicenter (international), randomized, open-label, active-controlled, non-inferiority	HCV GT3 infection with and without compensated cirrhosis	Arm 1: 12-week SOF/VEL, N=278 Arm 2: 24-week SOF+RBV, N=280	The SVR12 rate of the 12-week SOF/VEL regimen was non-inferior to the rate of the 24-week SOF+RBV treatment by 10%.
ASTRAL-4 (GS-US-342-1137)	multicenter (US only), randomized, open-label	HCV infection with decompensated cirrhosis (mainly CPT Class B cirrhosis)	Arm 1: 12-week SOF/VEL, N=90 Arm 2: 12-week SOF/VEL+RBV, N=88 Arm 3: 24-week SOF/VEL, N=90	The SVR12 rate of each regimen was superior to the assumed spontaneous rate of 1%.

Note: The reviewer generated this table.

2.2 Data Sources

The data were submitted electronically and are located in \\CDSESUB1\evsprod\NDA208341\0001 .

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data in this NDA is good, and the reviewer did not have any concerns.

3.2 Evaluation of Efficacy

The common efficacy endpoints and statistical methodologies in the four studies are summarized in Section 3.2.1. Then, the review will evaluate the efficacy of each of the four studies separately in Section 3.2.2 to 3.3.5.

3.2.1 Efficacy Endpoints and Statistical Methods Common to All Studies Reviewed

3.2.1.1 Efficacy Endpoints

For the four studies reviewed, the primary efficacy endpoint was the proportion of subjects that achieved SVR12 defined as HCV RNA < LLOQ 12 weeks after cessation of study treatment. In addition to the primary efficacy endpoint, the common secondary efficacy endpoints were:

1) percentage of subjects with sustained virologic response at 4 weeks and 24 weeks after discontinuation of treatment (SVR4 and SVR24)

2) proportion of subjects with HCV RNA < LLOQ while on study by study visit

3) HCV RNA ($\log_{10}$ IU/mL) and change from baseline in HCV RNA through end of treatment

4) percentage of subjects with virologic virologic failure as the following:

- 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 (ie, 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 the end of treatment, confirmed with consecutive values or last available post-treatment measurement

5) characterization of HCV drug resistance substitutions at baseline, during, and after therapy

Of note, ASTRAL-4 was composed of subjects with decompensated cirrhosis, and therefore the study included the additional efficacy endpoints of change from baseline in CPT and Model for End-Stage Liver Disease (MELD) scores. The resistance related endpoint will be evaluated by the virological reviewer, Dr. Lisa Naeger. Also, the applicant did not include SVR24 data in the interim clinical study reports (CSRs) for any of the studies and plans to submit it in the final CSRs.

3.2.1.2 Statistical Methods

This section summarizes the similar statistical methods used in the four studies. The different statistical approaches for a specific study are included in the review of each study in later sections.

A. Efficacy Population and Subgroup Analyses

In all studies, the efficacy analysis population included subjects who received at least one dose of study drugs. The applicant referred to the analysis set as the full analysis set, while the reviewer referred to the analysis population as all treated. Also, subgroup analyses to assess the relationship between different subgroups defined by patient demographics and baseline characteristics were performed in all studies.

B. Visit Windows

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

C. Handling Missing Data

The applicant's approaches to handle missing viral load data in the statistical analysis plans in the four studies are summarized as follows:

For analyses of categorical HCV RNA data, missing post-treatment HCV RNA data would be imputed. Missing on-treatment HCV RNA data would be imputed up to the time of the last dose for on-treatment displays. If the study day associated with the last dosing date of any study drug was greater than or equal to the lower bound of a visit window, and the value at the visit was missing, then the value would be imputed. If the study day associated with the last dosing date was less than the lower bound of a visit window then the on-treatment value at that visit would remain missing. Furthermore, the rules to impute the missing HCV RNA measurement at a visit using the preceding and following visits are as follows:

- If an HCV RNA data point was missing and was preceded and followed in time by values that were "< LLOQ target not detected (TND)," then the missing data point would be set to "< LLOQ TND."

- If an HCV RNA data point was missing and was 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

would be set to "< LLOQ detected." In these situations the data point would be termed a bracketed success; otherwise, the data point would be termed a bracketed failure (i.e., ≥ LLOQ detected).

- If a data point was missing and was not bracketed, the missing data point would also be termed a failure (i.e., ≥ LLOQ detected) except for SVR24, which would be imputed according to SVR12 status. A subject categorized as success for SVR12 who had no further HCV RNA measurements collected would be counted as a success for SVR24 due to the high correlation between these 2 endpoints.

3.2.2 ASTRAL-1 (Non-GT3 including compensated cirrhosis)

3.2.2.1 Study Design

ASTRAL -1 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study conducted in 81 sites in the United States, Canada, Europe and Asia. The primary objective was to evaluate efficacy, safety and tolerability of SOF/VEL for 12 weeks for the treatment of HCV non-GT3 infection. Subjects with HCV GT1, 2, 4 or 6 were randomized in a 5:1 ratio into one of the following two treatment groups:

Group 1: SOF/VEL FDC (400/100 mg) tablet once daily (QD) for 12 weeks
Group 2: SOF/VEL placebo tablet QD for 12 weeks

The randomization was stratified by HCV genotype (1, 2, 4, or 6) and cirrhotic status at screening (presence vs. absence). Subjects with GT5 HCV infection were not randomized but were enrolled into the SOF/VEL 12 week arm. Subjects in the placebo group who completed treatment were eligible for treatment with SOF/VEL for 12 weeks in a deferred treatment study (Study GS-US-342-1446). All subjects were to complete the post-treatment Week 4 and 12 visits regardless of their treatment duration. Subjects with HCV RNA < LLOQ at the post-treatment Week 12 visit were also to complete the post-treatment Week 24 visit unless a confirmed viral relapse occurred. The HCV RNA measurements were assessed at Weeks 1, 2, 4, 8, 10, 12 and at post-treatment Weeks 4, 12 and 24 (if applicable).

3.2.2.2 Statistical Methods

Inclusion of placebo in the study was only for safety evaluation because none of subjects in the placebo arm were expected to achieve SVR12 based on historical data. The primary efficacy hypothesis was that the SVR12 rate for 12-week SOF/VEL was superior to the pre-specified threshold of 85%. According to the applicant, the basis for this benchmark included the overall trend toward increasing SVR12 rates in recent years. At the time of review of the study protocol, the review team recommended a randomized controlled trial comparing SOF/VEL against an active comparator, Harvoni, in GT1 population. The active-controlled study design is more interpretable as it can provide more reliable risk/benefit assessment than a single-arm design

comparing the SVR12 versus a historical benchmark. However, the applicant did not incorporate the review team's recommendation.

In the primary analysis, a 2-sided 95% exact confidence interval (CI) based on the Clopper-Pearson method was calculated for the SVR12 rate for 12 weeks of SOF/VEL to assess whether it was superior to 85%.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 3 shows the patient disposition. Six hundred and twenty-five subjects were randomized to receive 12 weeks of SOF/VEL and 116 to receive placebo. All randomized subjects except for one in the 12-week SOF/VEL group took at least one dose of assigned medications. Also, among the randomized and treated subjects, the majority of them completed the study treatment. Two treated subjects in the 12-week SOF/VEL group discontinued the study treatment: one was due to adverse event (AE) and another was due to lost to follow-up. Three placebo subjects withdrew the study drugs prematurely: two were due to AE of increased ALT or/and AST and one based on investigator's discretion.

Table 3: Patient Disposition in ASTRAL-1

	SOF/VEL 12 weeks	Placebo
Randomized	625	116
Treated	624 (100%)	116 (100%)
Completed study treatment	622 (99.7%)	113 (97.4%)
Not completed study treatment	2 (0.3%)	3 (2.6%)
Adverse event	1 (0.2%)	2 (1.7%)
Lost to follow-up	1 (0.2%)	0
Investigator's discretion	0	1 (0.9%)

Source: Table 8-2 in ASTRAL-1 Interim Clinical Study Report

Among 740 randomized and treated subjects, 393 subjects (53.1%) had GT1 infection, 125 subjects (16.9%) had GT2 infection, 138 subjects (18.6%) had GT4 infection, 35 subjects (4.7%) had GT5 infection, and 49 (6.6%) had GT6 infection. The prevalence of HCV genotypes varies across different regions of world. Also, HCV genotype is generally regarded as one of the strongest predictors of treatment response. Therefore, patient demographics and baseline disease characteristics by HCV genotype in addition to overall and by treatment group are summarized and presented in Table 4 and Table 5.

Among all randomized and treated subjects, the average age (standard deviation [SD]) was 54 (10.8) years. The majority of the subjects were male (59.7%) and white (78.8%). Some differences in demographics across HCV genotypes in the 12-week SOF/VEL group were observed. In comparison to other genotypes, there was a higher proportion of subjects enrolled aged 65 years or older in GT5 group (45.7%). Subjects infected with HCV GT6 were predominately Asian (97.6%) and had a lower baseline BMI (97.6% of subjects with BMI < 30 kg/m^2).

Among subjects receiving 12-week SOF/VEL treatment, 19.4% of them had cirrhosis at baseline and 32.2% were treatment-experienced (TE). Similar to patient demographics, there were some

differences in baseline disease characteristics across different HCV genotypes. There was a smaller proportion of cirrhotic subjects (9.6%) than other genotypes. There was also a higher proportion of subjects with IL28B CC (68.3%) and a higher proportion of TN subjects (92.7%) among the subjects infected with HCV GT6.

Table 4: Patient Demographics and Selected Baseline Characteristics in ASTRAL-1 (All Treated)

	Overall (N=740)	Placebo (N=116)	SOF/VEL 12 weeks					
			All (N=624)	GT1 (N=328)	GT2 (N=104)	GT4 (N=116)	GT5 (N=35)	GT6 (N=41)
Age								
Mean (SD)	54 (10.8)	53 (10.4)	54 (10.9)	54 (10.4)	56 (11.9)	52 (10.7)	59 (12.1)	51 (9.7)
Median	56	55	56	56	57	54	63	52
Q1, Q3	48, 61	49, 61	48, 61	49, 61	50, 64	47, 59	54, 69	45, 58
Min, Max	18, 82	25, 74	18, 82	19, 81	21, 82	18, 75	30, 77	24, 64
< 65 years	640 (86.5%)	104 (89.7%)	536 (85.9%)	292 (89.0%)	79 (76.0%)	105 (90.5%)	19 (54.3%)	41 (100%)
≥ 65 years	100 (13.5%)	12 (10.3%)	88 (14.1%)	36 (11.0%)	25 (24.0%)	11 (9.5%)	16 (45.7%)	0
Gender								
Male	442 (59.7%)	68 (58.6%)	374 (59.9%)	197 (60.1%)	57 (54.8%)	86 (74.1%)	14 (40.0%)	20 (48.8%)
Female	298 (40.3%)	48 (41.4%)	250 (40.1%)	131 (39.9%)	47 (45.2%)	30 (25.9%)	21 (60%)	21 (51.2%)
Race								
Black/African American	63 (8.5%)	11 (9.5%)	52 (8.3%)	25 (7.6%)	13 (12.5%)	14 (12.1%)	0	0
White	583 (78.8%)	90 (77.6%)	493 (79.0%)	279 (85.1%)	82 (78.8%)	96 (82.8%)	35 (100%)	1 (2.4%)
Asian	73 (9.9%)	11 (9.5%)	62 (9.9%)	14 (4.3%)	5 (4.8%)	3 (2.6%)	0	40 (97.6%)
Other[1]	18 (2.4%)	4 (3.4%)	14 (2.4%)	8 (2.4%)	3 (2.9%)	3 (2.6%)	0	0
Not disclosed	3 (0.4%)	0	3 (0.5%)	2 (0.6%)	1 (1.0%)	0	0	0
Ethnicity								
Hispanic/Latino								
Yes	36 (4.9%)	5 (4.3%)	31 (5.0%)	20 (6.1%)	7 (6.7%)	4 (3.4%)	0	0
No	700 (94.6%)	111 (95.7%)	589 (94.4%)	306 (93.3%)	96 (92.3%)	112 (96.6%)	35 (100%)	40 (97.6%)
Not disclosed	4 (0.5%)	0	4 (0.6%)	2 (0.6%)	1 (1.0%)	0	0	1 (2.4%)
Region								
US	279 (37.7%)	45 (38.8%)	234 (37.5%)	152 (46.3%)	14 (13.5%)	43 (37.1%)	1 (2.9%)	24 (58.5%)
Non-US								
Canada	62 (8.4%)	7 (6.0%)	55 (8.8%)	24 (7.3%)	16 (15.4%)	8 (6.9%)	5 (14.3%)	2 (4.9%)
China	23 (3.1%)	4 (3.5%)	19 (3.0%)	7 (2.1%)	1 (1%)	0	0	11 (26.8%)
Europe	376 (50.8%)	60 (51.7%)	316 (50.6%)	145 (44.2%)	73 (70.2%)	65 (56.0%)	29 (82.9%)	4 (9.8%)
BMI[2] (kg/m²)								
Mean (SD)	26.6 (4.9)	25.9 (4.2)	26.7 (5.0)	26.6 (5.1)	26.4 (5.1)	28.0 (5.1)	26.8 (4.9)	23.8 (2.4)
Median	25.9	25.6	26.1	26.0	26.1	27.7	26.2	24.0
Q1, Q3	23.2, 29.1	22.8, 28.7	23.3, 29.3	23.3, 29.3	22.5, 28.9	24.6, 30.8	23.2, 29.3	21.9, 25.0
Min, Max	16.9, 56.9	17.9, 40.2	16.9, 56.9	16.9, 56.9	17.3, 44.2	18.2, 45.0	19.9, 38.7	19.3, 30.7
< 30 kg/m²	582 (78.6%)	93 (80.2%)	489 (78.4%)	258 (78.7%)	84 (80.8%)	80 (69.0%)	27 (77.1%)	40 (97.6%)
≥ 30 kg/m²	158 (21.4%)	23 (19.8%)	135 (21.6%)	70 (21.3%)	20 (19.2%)	36 (31.0%)	8 (22.9%)	1 (2.4%)

Source: Tables 8-5 and 8-6 in ASTRAL-1 Interim Clinical Study Report
[1]including American Indian/Alaska Native, Hawaiian or Pacific Islander and other
[2]body mass index

Table 5: Selected Baseline Disease Characteristics in ASTRAL-1 (All Treated)

	Overall (N=740)	Placebo (N=116)	SOF/VEL 12 weeks					
			All (N=624)	GT1 (N=328)	GT2 (N=104)	GT4 (N=116)	GT5 (N=35)	GT6 (N=41)
Cirrhosis								
Yes	142 (19.2%)	21 (18.1%)	121 (19.4%)	73 (22.3%)	10 (9.6%)	27 (23.3%)	5 (14.3%)	6 (14.6%)
No	596 (80.5%)	95 (81.9%)	501 (80.3%)	255 (77.7%)	93 (89.4%)	89 (76.7%)	29 (82.9%)	35 (85.4%)
Missing	2 (0.3%)	0	2 (0.3%)	0	1 (1.0%)	0	1 (2.9%)	0
IL28B								
CC	222 (30.0%)	36 (31.0%)	186 (29.8%)	90 (27.4%)	30 (28.8%)	27 (23.3%)	11 (31.4%)	28 (68.3%)
CT	392 (53.0%)	53 (45.7%)	339 (54.3%)	184 (56.1%)	56 (53.8%)	68 (58.6%)	21 (60.0%)	10 (24.4%)
TT	120 (16.2%)	26 (22.4%)	94 (15.1%)	51 (15.5%)	18 (17.3%)	21 (18.1%)	3 (8.6%)	1 (2.4%)
Missing	6 (0.8%)	1 (0.9%)	5 (0.8%)	3 (0.9%)	0	0	0	2 (4.9%)
Baseline HCV RNA (log_{10}IU/mL)								
Mean (SD)	6.3 (0.65)	6.3 (0.58)	6.3 (0.66)	6.3 (0.59)	6.3 (0.72)	6.1 (0.71)	6.2 (0.68)	6.4 (0.82)
Median	6.4	6.4	6.4	6.4	6.5	6.2	6.4	6.6
Q1, Q3	5.9, 6.7	5.9, 6.8	5.9, 6.7	6.0, 6.7	5.7, 6.8	5.7, 6.5	5.9, 6.7	5.9, 7.0
Min, Max	1.1, 7.8	4.7, 7.5	1.1, 7.8	4.2, 7.5	3.7, 7.4	1.1, 7.1	4.4, 7.4	4.0, 7.8
< 800,000 IU/mL	192 (25.9%)	29 (25.0%)	163 (26.1%)	73 (22.3%)	29 (27.9%)	42 (36.2%)	9 (25.7%)	10 (24.4%)
≥ 800,000 IU/mL	548 (74.1%)	87 (75.0%)	461 (73.9%)	255 (77.7%)	75 (72.1%)	74 (63.8%)	26 (74.3%)	31 (75.6%)
Baseline ALT								
≤ 1.5 x ULN	407 (55.0%)	62 (53.4%)	345 (55.3%)	176 (53.7%)	69 (66.3%)	64 (55.2%)	20 (57.1%)	16 (39.0%)
> 1.5 x ULN	333 (45.0%)	54 (46.6%)	279 (44.7%)	152 (46.3%)	35 (33.7%)	52 (44.8%)	15 (42.9%)	25 (61.0%)
Prior HCV trt history								
TN[1]	506 (68.4%)	83 (71.6%)	423 (67.8%)	218 (66.5%)	79 (76.0%)	64 (55.2%)	24 (68.6%)	38 (92.7%)
TE[2]	234 (31.6%)	33 (28.4%)	201 (32.2%)	110 (33.5%)	25 (24.0%)	52 (44.8%)	11 (31.4%)	3 (7.3%)
Prior HCV treatment (for TE subjects only)	n=234	n=33	n=201	n=110	n=25	n=52	n=11	n=3
DAA+PegIFN+RBV	62 (26.5%)	6 (18.2%)	56 (27.9%)	48 (43.6%)	0	6 (11.5%)	2 (18.2%)	0
DAA	1 (0.4%)	0	1 (0.5%)	1 (0.9%)	0	0	0	0
DAA+RBV	2 (0.9%)	1 (3.0%)	1 (0.5%)	1 (0.9%)	0	0	0	0
PegIFN+RBV	146 (62.4%)	24 (72.7%)	122 (60.7%)	51 (46.4%)	22 (88.0%)	39 (75.0%)	7 (63.6%)	3 (100%)
IFN	8 (3.4%)	0	8 (4.0%)	4 (3.6%)	2 (8.0%)	2 (3.9%)	0	0
IFN+RBV	13 (5.6%)	2 (6.1%)	11 (5.5%)	3 (2.7%)	1 (4.0%)	5 (9.6%)	2 (18.2%)	0
PegIFN	2 (0.9%)	0	2 (1.0%)	2 (1.8%)	0	0	0	0

Source: Tables 8-7 and 8-8 in ASTRAL-1 Interim Clinical Study Report

[1]TN: treatment-naïve; TE: treatment-experienced

3.2.2.4 Results and Conclusions

As shown in Table 6, the applicant's analysis demonstrated that treatment with SOF/VEL for 12 weeks resulted in a 99% SVR12 rate with 95% CI of (97.9%, 99.6%). The reviewer agrees with the applicant's results. This high SVR12 rate was statistically significant in comparison to the 85% threshold ($p < 0.001$, based on the two-sided exact one-sample binomial test for the superiority over 85%). Two subjects in the 12-week SOF/VEL group experienced relapse which was determined at the post-treatment Week 4 visit. Both subjects completed the study treatment. Also, of the four subjects who did not achieve SVR12 due to other reasons in the 12-week SOF/VEL group, two discontinued the study treatment early; one subject completed the study medication, had achieved SVR4, but did not return for the post-treatment Week 12 visit and therefore did not have SVR12 data; and one subject completed study treatment and died in his sleep of unknown causes on post-treatment Day 8. Meanwhile, none of the placebo subjects had SVR12 as expected. The SVR12 rate by different genotypes will be presented in Section 4 of this review.

Table 6: Virologic Outcomes at Post-Treatment Week 12 in ASTRAL-1 (All Treated)

	SOF/VEL 12 Weeks (N=624)	**Placebo[2] (N=116)**
SVR12 rate [95% CI][1]	99.0% (618/624) [97.9%, 99.6%]	0% (0/116) n/a
Not achieving SVR12		
On-treatment virologic failure	0% (0/624)	99.1% (115/116)
Relapse	0.3% (2/623)	n/a (0/0)
Other	0.6% (4/624)	0.9% (1/116)

Sources: Tables 9-1 and 9-2 in ASTRAL-1 Interim Clinical Study Report
[1]based on Clopper-Pearson method
[2]The results for the placebo group were generated by the reviewer.

The secondary efficacy endpoint of SVR4 rate was the same as the SVR12 rate with the exception of one subject. This subject achieved SVR4 but had missing SVR12 data, and therefore was considered to not have achieved SVR12. The applicant presented the observed proportion of subjects with HCV RNA below LLOQ at each on-treatment visit. Their analysis excluded subjects who did not have HCV RNA measurements. In the study, the reason for missing data was discontinuation of study treatment. One sensitivity analysis regards subjects who did not complete study treatment as failures (NC=F). However, the observed response rates should be close to the rates calculated from this sensitivity analysis because only a few subjects discontinued study drug. Table 7 displays the applicant's results. More than 90% of subjects achieved HCV RNA viral suppression 4 weeks after receiving SOF/VEL, and the high response rate was maintained through the end of treatment.

Table 7: Observed Proportion of Subjects with HCV RNA < LLOQ While on Active Treatment by Visit in ASTRAL-1 (All Treated)

Visit	SOF/VEL 12 Weeks (N=624)
Week 1	18.8% (117/624)
Week 2	56.9% (355/624)
Week 4	90.5% (564/623)
Week 6	98.9% (616/623)
Week 8	99.7% (620/622)
Week 10	100% (622/622)
Week 12	100% (622/622)

Source: Tables 9-10 and 15.9.2.4 in Study GS-US-337-0115 Interim Clinical Study Report

3.2.3 ASTRAL-2 (GT2 including compensated cirrhosis)

3.2.3.1 Study Design and Endpoints

ASTRAL-2 was a phase 3, randomized, open-label, multicenter study conducted in 51 sites in the US including Puerto Rico. The primary efficacy objective was to compare the efficacy of treatment with SOF/VEL for 12 weeks against the regimen of SOF + RBV for 12 weeks in subjects infected with GT2 HCV. The 12-week SOF + RBV treatment was the only approved IFN-sparing regimen for GT2 infection at the time of protocol review. Subjects were randomized in a 1:1 ratio into one of the following two groups, stratified by cirrhotic status at screening (present vs. absent) and prior HCV treatment history (TN vs. TE).

Group 1: SOF/VEL FDC tablet QD for 12 weeks
Group 2: SOF QD table + RBV (1000 or 1200 mg/day BID) tables for 12 weeks

All subjects were scheduled to complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 6, 8, 10, and 12 and the post-treatment Week 4 and 12 visits. Subjects with HCV RNA < LLOQ at the post treatment Week 12 visit would complete a post-treatment Week 24 visit unless confirmed viral relapse occurs. The HCV RNA was assessed at each visit.

3.2.3.2 Statistical Methods

The primary efficacy hypothesis was that the SVR12 rate for the treatment of SOF/VEL for 12 weeks was non-inferior to the rate for the regimen of SOF + RBV for 12 weeks in GT2 subjects. The non-inferiority (NI) margin was 10%. The determination of the NI margin was discussed during the time of the protocol review. The statistical margin (M1) can be calculated directly based on the differences in the SVR12 rates between the 12-week SOF+RBV and 12-week SOF alone regimens in GT2 subjects. The applicant used a Bayesian approach to justify M1 because there is limited data for the 12-week SOF alone regimen in GT2 subjects. Their approach borrowed information from the other genotypes and regimens and was also based on assumptions. The four assumptions and their basis and background evidence are displayed in Table 8 below.

Table 8: Assumptions for Noninferiority Margin Justification in ASTRAL-2

	Assumption	Basis of Assumption	Background Evidence for Assumption
Assumption # 1	Assume that SOF+RBV for 12 weeks is better than PEG+RBV for 24 weeks in GT-2 patients	This assumption is based on the results of FISSION in which GT-2 patients receiving SOF+RBV performed 19% points better than patients receiving PEG+RBV	FISSION
Assumption # 2	Within a genotype we assume that SOF Alone will do worse than SOF+RBV.	RBV has been shown to improve outcomes in HCV across a range of regimens including SOF based regimens used in GT-2 and GT-3 patients. It is reasonable to assume, for modeling purposes, that those patients receiving no RBV will have lower SVRs when compared to patients receiving RBV.	Benefit of RBV can be seen in McHutchison et al. (1999) (PEG±RBV); Electron-2 Cohort 2 (Groups 3 and 4; GT 3 subjects receiving SOF/LDV±RBV);
Assumption # 3	But for 1 exception, for any given treatment regimen, we assume that GT-2 patients will have a higher SVR12 rate than GT-3 patients and GT-3 patients will have a higher SVR12 rate than GT-1 patients. The one exception is that we do not assume that GT-1 SOF alone patients will have a better SVR12 rate than SOF alone GT-3 patients.*	A host of data has shown that for a given regimen GT-2 patients have the highest SVR rates, followed by GT-3 patients, followed by GT-1 patients.	ELECTRON; FISSION; POSITRON; FISSION; VALENCE; Shiffman 2007; Lagging 2008; Poynard 2009. In addition, various cross study comparisons have shown this ordering of genotype SVR rates.
Assumption # 4	Within a genotype we assume that SOF alone for 12 weeks will do worse than PEG+RBV.	This assumption is based on the results from FISSION and the assumption # 2 above.	FISSION

* Note that if we ignore this exception (i.e., assume GT-1 patients do worse than GT-3 patients) the credible set (i.e., the Bayesian analog to the confidence interval) for GT-2 patients slightly tightens (i.e., becomes less wide) in our constrained modeling results.

Source: IND118605 / SN28

The reviewer agrees that the applicant's justification for the NI margin could be considered acceptable if the four assumptions are clinically appropriate and the limited data for 12-week SOF in GT2 subjects is reliable in providing prior information.

The primary endpoint was tested using NI and superiority hypotheses. To control for the Type 1 error rate in the analysis of the primary efficacy endpoint of SVR12 rate, a closed testing procedure was employed whereby the NI of SOF/VEL for 12 weeks to SOF + RBV for 12 weeks was first assessed. If the NI null hypothesis was rejected, then the p-value associated with the test of superiority was calculated. To test the NI, the two-sided 95% CI on the difference in SVR12 rates between the two treatment groups (12 weeks of SOF/VEL minus 12 weeks of SOF + RBV) was constructed based on stratum-adjusted Mantel-Haenszel (MH) proportion (Koch GG et al, Statistical Methodology in the Pharmaceutical Sciences, 1989). The strata were defined by randomization stratification factors (i.e., cirrhosis status and prior treatment experience). NI was demonstrated if the lower bound of the 95% CI on the difference was greater than -10%. A Cochran-Mantel-Haenszel (CMH) test was employed to test for the

superiority of SOF/VEL for 12 weeks over SOF + RBV for 12 weeks. Superiority was established if the two-sided p-value was less than 0.05.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

Among the 269 randomized subjects, 266 received at least one dose of study drug. All subjects with exception of two subjects, one in each group, discontinued study drug prematurely. One subject in the SOF/VEL 12 weeks group discontinued on Day 1 due to AE, and another one in the SOF + RBV 12 weeks arm completed the Week 10 study visit but was lost to follow-up thereafter.

Table 9: Patient Disposition in ASTRAL-2

	SOF/VEL 12 weeks	SOF + RBV 12 weeks
Randomized	135	134
Treated	134 (100%)	132 (100%)
Completed study treatment	133 (99.3%)	131 (99.2%)
Not completed study treatment		
Adverse event	1 (0.7%)	0
Lost to follow-up	0	1 (0.8%)

Source: Table 8-2 in ASTRAL-2 Interim Clinical Study Report

As shown in Table 10 and Table 11, patient demographics and baseline characteristics were generally balanced between the two treatment arms. Among the randomized and treated subjects, the mean age (SD) was 57 (10.6) years. The majority of subjects were male (59.4%), white (88.3%), infected with HCV GT2b (77.8%), and had the non-CC IL28B allele (62.0%). Approximately 14.2% of the subjects had cirrhosis at baseline, and 14.7% of subjects were TE.

Table 10: Patient Demographics and Baseline Characteristics in ASTRAL-2 (All Treated)

	SOF/VEL 12 weeks (N=134)	SOF + RBV 12 weeks (N=132)	Total (N=266)
Age at baseline (years)			
Mean (SD)	57 (10.6)	57 (19.3)	57 (10.0)
Median	58	59	58
Q1, Q3	53, 64	53, 63	53, 63
Min, Max	26, 81	23, 76	23, 81
Sex at birth			
Male	86 (64.2%)	72 (54.5%)	158 (59.4%)
Female	48 (35.8%)	60 (45.5%)	108 (40.6%)
Race			
Black or African American	6 (4.5%)	12 (9.1%)	18 (6.8%)
White	124 (92.5%)	111 (84.1%)	235 (88.3%)
Asian	1 (0.7%)	5 (3.8%)	6 (2.3%)
Native Hawaiian or Pacific Islander	0	1 (0.8%)	1 (0.4%)
Other	1 (0.7%)	2 (1.5%)	3 (1.1%)
Not disclosed	2 (1.5%)	1 (0.8%)	3 (1.1%)

(to be continued)

Table 10: Patient Demographics and Baseline Disease Characteristics in ASTRAL-2 (All Treated) (Continued)

	SOF/VEL 12 weeks (N=134)	SOF + RBV 12 weeks (N=132)	Total (N=266)
Ethnicity			
Hispanic or Latino	26 (19.4%)	23 (17.4%)	49 (18.4%)
Not Hispanic or Latino	104 (77.6%)	107 (81.1%)	211 (79.3%)
Not disclosed	4 (3.0%)	2 (1.5%)	6 (2.3%)
Body mass index (kg/m^2) at baseline			
Mean (SD)	28.0 (4.98)	29.3 (6.99)	28.6 (6.08)
Median	27.3	27.5	27.5
Q1, Q3	24.6, 30.5	24.9, 31.5	24.7, 31.2
Min, Max	17.4, 44.6	19.0, 61.0	17.4, 61.0
< 30 kg/m^2	95 (70.9%)	84 (63.6%)	179 (67.3%)
≥ 30 kg/m^2	39 (29.1%)	48 (36.4%)	87 (32.7%)

Source: Table 8-4 in ASTRAL-2 Interim Clinical Study Report

Table 11: Selected Baseline Disease Characteristics in ASTRAL-2 (All Treated)

	SOF/VEL 12 weeks (N=134)	SOF + RBV 12 weeks (N=132)	Total (N=266)
HCV genotype			
GT2 (no confirmed subtype)	13 (9.7%)	12 (9.1%)	25 (9.4%)
GT2a	2 (1.5%)	4 (3.0%)	6 (2.3%)
GT2a/2c	16 (11.9%)	12 (9.1%)	28 (10.5%)
GT2b	103 (76.9%)	104 (78.8%)	207 (77.8%)
Cirrhosis			
No	19 (14.2%)	19 (14.4%)	38 (14.3%)
Yes	115 (85.8%)	112 (84.8%)	227 (85.3%)
Missing	0	1 (0.8%)	1 (0.4%)
IL28B			
CC	55 (41.0%)	46 (34.8%)	101 (38.0%)
Non-CC	79 (59.0%)	86 (65.2%)	165 (62.0%)
CT	61 (45.5%)	64 (48.5%)	125 (47.0%)
TT	18 (13.4%)	22 (16.7%)	40 (15.0%)
HCV RNA at baseline (log_{10} IU/mL)			
Mean (SD)	6.5 (0.78)	6.4 (0.74)	6.4 (0.76)
Median	6.7	6.6	6.7
Q1, Q3	6.2, 7.0	6.0, 6.9	6.1, 7.0
Min, Max	3.9, 7.4	3.8, 7.5	3.8, 7.5
< 800,000 IU/mL	23 (17.2%)	31 (23.5%)	54 (20.3%)
≥ 800,000 IU/mL	111 (82.8%)	101 (76.5%)	212 (79.7%)

(to be continued)

Table 11: Selected Baseline Disease Characteristics in ASTRAL-2 (All Treated) (Continued)

	SOF/VEL 12 weeks (N=134)	SOF + RBV 12 weeks (N=132)	Total (N=266)
ALT at baseline (U/L)			
Mean (SD)	69 (63.1)	69 (60.6)	69 (61.8)
Median	47	45	46
Q1, Q3	29, 86	29, 85	29, 85
Min, Max	12, 448	13, 294	12, 448
≤ 1.5 x ULN	80 (59.7%)	82 (62.1%)	162 (60.9%)
> 1.5 x ULN	54 (40.3%)	50 (37.9%)	104 (39.1%)
Prior HCV treatment history			
Treatment-naïve	115/134 (85.8%)	112/132 (84.8%)	227/266 (85.3%)
Treatment-experienced	19/134 (14.2%)	20/132 (15.2%)	39/266 (14.7%)
Prior HCV treatment			
Pegylated Interferon (Peg-IFN) + RBV	16/19 (84.2%)	15/20 (75.0%)	31/39 (79.5%)
Peg-IFN[1]	0	1/20 (5.0%)	1/39 (2.6%)
IFN + RBV[1]	1/19 (5.3%)	4/20 (20.0%)	5/39 (12.8%)
IFN[1]	2/19 (10.5%)	0	2/39 (5.1%)
Prior HCV treatment response			
Nonresponder	3/19 (15.8%)	3/20 (15.0%)	6/39 (15.4%)
Relapse/Breakthrough	16/19 (84.2%)	17/20 (85.0%)	33/39 (84.6%)

Source: Table 8-5 in ASTRAL-2 Interim Clinical Study Report
[1]The applicant grouped these three categories as "other".

3.2.3.4 Results and Conclusions

The applicant's analysis demonstrated that subjects treated with SOF/VEL for 12 weeks resulted in a 99.3% SVR12 rate which was statistically significantly higher than the 93.9% SVR12 rate using SOF + RBV for 12 weeks (Table 12). The reviewer agrees with applicant's results. In the 12-week SOF/VEL group, no subjects relapsed and one subject did not achieve SVR12 due to discontinuation of study drug at Day 1. In the 12-week SOF + RBV group, six subjects experienced relapse determined at post-treatment Week 4 (n=4) or Week 12 (n=2) visit; and two subjects completed the study drug but did not have SVR12 data.

Table 12: Virologic Outcomes at Post-Treatment Week 12 in ASTRAL-2 (All Treated)

	SOF/VEL 12 Weeks (N=134)	SOF+ RBV 12 Weeks (N=132)	Difference in SVR12 rate	
			Prop Diff (95% CI)[2]	p-value[3]
SVR12 rate (number of responders/N) [95% CI][1]	99.3% (133/134) [95.9%, 100.0%]	93.9% (124/132) [88.4%, 97.3%]	5.2% (0.2%, 10.3%)	0.018
Not achieving SVR12			n/a	
On-trt virologic failure	0% (0/134)	0% (0/132)		
Relapse	0% (0/133)	4.5% (6/132)		
Other	0.7% (1/134)	1.5% (2/132)		

Sources: Tables 9-1 and 9-2 in ASTRAL-2 Interim Clinical Study Report
[1]based on Clopper-Pearson method
[2]95% CI stratified by cirrhosis status (present vs. absent) and prior treatment experience (TN vs. TE)
[3]CMH test stratified by cirrhosis status and prior treatment experience (TN vs. TE)

The secondary efficacy endpoint of SVR4 rate was identical to SVR12 rate in the 12-week SOF/VEL arm. In the 12-week SOF+RBV group, one subject was lost to follow-up and two subjects relapsed between post-treatment Week 4 and 12 visits. Therefore, the SVR4 rate was slightly higher (i.e., 96.2% [127/132]) than SVR12 rate.

Similar to the ASTRAL-1 study, only two subjects with one in each group missed HCV RNA measurement at some visits due to early discontinuation of study drug. Therefore, the observed proportions of subjects with HCV RNA below LLOQ during on-treatment visits should be almost identical to the rate calculated based on NC=F approach. The applicant's observed rates are shown in Table 13 below. Above 90% of the subjects in both arms achieved HCV RNA < LLOQ four weeks after taking study medicine. The response rates were above 95% in both arms by Week 6 and the high response rates were maintained thereafter up to the end of the 12-week treatment course.

Table 13: Observed Proportion of Subjects with HCV RNA < LLOQ While on Active Treatment by Visit in ASTRAL-2 (All Treated)

Visit	SOF/VEL 12 Weeks (N=134)	SOF+RBV 12 Weeks (N=132)
Week 1	12.8% (17/133)	22.7% (30/132)
Week 2	57.1% (76/133)	59.8% (79/132)
Week 4	90.2% (120/133)	90.2% (119/132)
Week 6	97.7% (130/133)	99.2% (131/132)
Week 8	100% (133/133)	100% (132/132)
Week 10	100% (133/133)	100% (132/132)
Week 12	100% (133/133)	100% (131/131)

Source: Tables 9-10 and 15.9.2.4 in Study GS-US-337-1139 Interim Clinical Study Report

3.2.4 ASTRAL-3 (GT3 including compensated cirrhosis)

3.2.4.1 Study Design

ASTRAL-3 was a phase 3, randomized, multicenter study conducted in 76 sites in the United States, Canada, Europe and Austria/New Zealand. The primary objective was to evaluate efficacy, safety and tolerability of the regimen of SOF/VEL for 12 weeks in comparison to SOF+RBV for 24 weeks in GT3 subjects. The regimen of 24-week SOF+RBV was the only approved regimen to treat GT3 subjects during the protocol development. Eligible subjects were randomized in 1:1 ratio into one of the following two treatment groups:

Group 1: SOF/VEL FDC (400/100 mg) tablet once daily (QD) for 12 weeks
Group 2: SOF QD table + RBV (1000 or 1200 mg/day BID) tables for 24 weeks

Randomization was stratified by cirrhotic status at screening (present vs. absent) and prior HCV treatment history (TN vs. TE).

All subjects were to complete the following study visits: Screening, Baseline/Day 1, on-treatment visits at the end of Weeks 1, 2, 4, 6, 8, 10, and 12. Subjects in Group 2 would have additional on-treatment visits at the end of Weeks 16, 20 and 24. All subjects would complete the post-treatment Week 4 and 12 visits. Subjects with HCV RNA < LLOQ at the post-treatment Week12 visit would complete a post-treatment Week 24 visit unless confirmed viral relapse occurred. HCV RNA was measured at each visit.

3.2.4.2 Statistical Methods

The primary efficacy hypothesis was that the SVR12 rate for 12-week SOF/VEL regimen was non-inferior to the rate for 24-week SOF + RBV by 10%. Similar to ASTRAL-2, the NI margin was discussed during the protocol review. The margin was determined directly based on the difference in SVR12 rates between the 24-week SOF + RBV and 12-week SOF alone regimens in GT3 subjects. Due to limited data on the SVR12 rate in GT3 subjects using SOF alone, the applicant conservatively included data from various 12-week SOF + RBV regimens (including both low dose RBV and standard weight-based RBV) to approximate the efficacy of SOF alone given for 12 weeks. The conservative SVR12 rate for 12-week SOF alone based on a pooled meta-analysis from these studies was 54.3% (245/251). On the other hand, based on the VALENCE study which was a Phase 3 trial conducted in Europe to evaluate different durations of SOF + RBV in GT2 and GT3 subjects, the SVR12 rate for 24-week SOF + RBV treatment in GT3 subject was 85.2% (213/250). The difference between the two regimens was approximately 31% with 95% CI (24.5%, 37.2%). If the lower bound of the 95% CI was regarded as the control treatment effect (M1=24.5%) and the NI margin (M2) was estimated based on preserving 50% of the control treatment effect (i.e., approximately 12%), the 10% NI margin was deemed acceptable.

The statistical approaches to analyze the primary efficacy endpoint were similar to ASTRAL-2. In order to control the Type 1 error due to multiple testing of NI and superiority, the closed testing procedure was used to first test NI between the two treatment and then superiority of SOF/VEL for 12 weeks over SOF + RBV for 24 weeks. The 95% CI based on stratum-adjusted MH proportion was calculated to assess the NI and the CMH test was conducted to test for the superiority. The strata were defined by the two randomization stratification factors of cirrhosis status and prior HCV treatment history in both analyses.

3.2.4.3 Patient Disposition, Demographics and Baseline Characteristics

Table 14 shows the patient disposition. All except for six randomized subjects received at least one dose of study drug and were included in the analysis set used for the efficacy analysis. Among 277 randomized subjects who received at least one dose of study drug in the SOF/VEL 12 weeks group, less than 1%, (i.e., two subjects) did not complete the study regimen. On the other hand, approximately 8% out of the 275 randomized and treated subjects in the SOF + RBV 24 weeks group did not complete treatment with the study drug. The most common reason for discontinuation of the study drug in that group was adverse event. Treatment containing RBV and longer duration could be attributable to more AEs compared to the 12-week SOF/VEL arm. Please refer to the review of Drs. Prabha Viswanathan and Sarah Connelly for more on the safety

findings.

Table 14: Patient Disposition in ASTRAL-3

	SOF/VEL 12 weeks	SOF + RBV 24 weeks
Randomized	278	280
Treated	277 (100%)	275 (100%)
Completed study treatment	275 (99.3%)	254 (92.4%)
Not completed study treatment		
Lack of efficacy	1 (0.4%)	1 (0.4%)
Adverse event	0	9 (3.3%)
Death	0	2 (0.7%)
Noncompliance with study drug	1 (0.4%)	2 (0.7%)
Lost to follow-up	0	4 (1.5%)
Withdrew consent	0	3 (1.1%)

Source: Table 8-2 in ASTRAL-3 Interim Clinical Study Report

Table 16 show that patient demographics and selected baseline disease characteristics were well balanced between the two treatment groups. Among 552 randomized and treated subjects, the mean age (SD) was 50 (10.2) years. The majority of the subjects were male (61.4%) and white (88.6%). Approximately 22% of subjects were enrolled and treated in US sites. Also, most of subjects had GT3a infection (93.3%) and non-CC IL28B allele (60.9%). Approximately 29.5% of subjects had cirrhosis at baseline, and 25.7% were TE. With the exception of one TE subject, none of the subjects had previously received DAA treatment for HCV infection.

Table 15: Patient Demographics and Baseline Characteristics in ASTRAL-3 (All Treated)

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
Age at baseline (years)			
Mean (SD)	49 (10.4)	50 (10.0)	50 (10.2)
Median	52	52	52
Q1, Q3	44, 57	45, 57	44, 57
Min, Max	21, 76	19, 74	19, 76
Sex at birth			
Male	170 (61.4%)	174 (63.3%)	344 (62.3%)
Female	107 (38.6%)	101 (36.7%)	208 (37.7%)
Race			
Black or African American	3 (1.1%)	1 (0.4%)	4 (0.7%)
White	250 (90.3%)	239 (86.9%)	489 (88.6%)
Asian	23 (8.3%)	29 (10.5%)	52 (9.4%)
American Indian or Alaska Native	1 (0.4%)	3 (1.1%)	4 (0.7%)
Native Hawaiian or Pacific Islander	0	2 (0.7%)	2 (0.4%)
Not disclosed	0	1 (0.4%)	1 (0.2%)
Ethnicity			
Hispanic or Latino	11 (4.0%)	11 (4.0%)	22 (4.0%)
Not Hispanic or Latino	266 (96.05)	263 (95.6%)	592 (95.8%)
Not disclosed	0	1 (0.4%)	1 (0.2%)

(to be continued)

Table 15: Patient Demographics and Baseline Disease Characteristics in ASTRAL-3 (All Treated) (Continued)

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
Region			
US	60 (21.7%)	60 (21.8%)	120 (21.7%)
Non-US			
Canada	15 (5.4%)	18 (6.6%)	33 (6.0%)
Europe	144 (52.0%)	145 (52.7%)	289 (52.4%)
Austria/New Zealand	58 (20.9%)	52 (18.9%)	110 (19.9%)
Baseline BMI (kg/m^2)			
Mean (SD)	26.4 (5.1)	26.6 (5.3)	26.5 (5.2)
Median	25.8	26.0	25.9
Q1, Q3	23.1, 28.4	23.1, 29.2	23.1, 28.8
Min, Max	16.6, 48.2	16.9, 56.2	16.6, 56.2
< 30 kg/m^2	226 (81.6%)	214 (77.8%)	440 (79.7%)
≥ 30 kg/m^2	51 (18.4%)	61 (22.2%)	112 (20.3%)

Source: Table 8-4 in ASTRAL-3 Interim Clinical Study Report

Table 16: Selected Baseline Disease Characteristics in ASTRAL-3 (All Randomized)

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
HCV genotype			
GT3 (no confirmed subtype)	9 (3.2%)	18 (6.5%)	27 (4.9%)
GT3a	265 (95.7%)	250 (90.9%)	515 (93.3%)
GT3b	2 (0.7%)	5 (1.8%)	7 (1.3%)
GT3h	0	2 (0.7%)	2 (0.4%)
GT3k	1 (0.4%)	0	1 (0.2%)
Cirrhosis			
No	80 (28.9%)	83 (30.2%)	163 (29.5%)
Yes	197 (71.1%)	187 (68.0%)	384 (69.6%)
Missing	0	5 (1.8%)	5 (0.9%)
IL28B			
CC	105 (37.9%)	111 (40.4%)	216 (39.1%)
Non-CC	172 (62.1%)	164 (59.6%)	336 (60.9%)
CT	148 (53.4%)	133 (48.4%)	281 (50.9%)
TT	24 (8.7%)	31 (11.3%)	55 (10.0%)
HCV RNA at baseline (log_{10} IU/mL)			
Mean (SD)	6.2 (0.72)	6.3 (0.71)	6.3 (0.72)
Median	6.3	6.4	6.4
Q1, Q3	5.8, 6.8	5.8, 6.8	5.8, 6.8
Min, Max	3.7, 7.5	3.6, 7.5	3.6, 7.5
< 800,000 IU/mL	86 (31.0%)	81 (29.5%)	167 (30.3%)
≥ 800,000 IU/mL	191 (69.0%)	194 (70.5%)	385 (69.7%)

(to be continued)

Table 16: Selected Baseline Disease Characteristics in ASTRAL-3 (All Treated) (Continued)

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
ALT at baseline (U/L)			
Mean (SD)	109 (80.1)	96 (65.1)	103 (73.3)
Median	88	80	83
Q1, Q3	49, 147	53, 122	51, 131
Min, Max	18, 457	16, 516	16, 516
≤ 1.5 x ULN	95 (34.3%)	87 (31.6%)	182 (33.0%)
> 1.5 x ULN	182 (65.7%)	188 (68.4%)	370 (67.0%)
Prior HCV treatment history			
Treatment-naïve	206/277 (74.4%)	204/275 (74.2%)	410/552 (74.3%)
Treatment-experienced	71/277 (25.6%)	71/275 (25.8%)	142/552 (25.7%)
Prior HCV treatment			
DAA + Peg-IFN + RBV	1/71 (1.4%)	0/71 (0%)	1/142 (0.7%)
Peg-IFN + RBV	64/71 (90.1%)	65/71 (91.5%)	129/142 (90.8%)
IFN + RBV	4/71 (5.6%)	3/71 (4.2%)	7/142 (4.9%)
PegIFN	0/71 (0%)	1/71 (1.4%)	1/142 (0.7%)
IFN	2/71 (2.8%)	2/71 (2.8%)	4/142 (2.8%)
Prior HCV treatment response			
Nonresponder	20/71 (28.2%)	24/71 (33.8%)	44/142 (31.0%)
Relapse/Breakthrough	51/71 (71.8%)	47/71 (66.2%)	98/142 (69.0%)

Source: Table 8-5 in ASTRAL-3 Interim Clinical Study Report

3.2.4.4 Results and Conclusions

The applicant's analysis demonstrated that the 12-week SOF/VEL treatment resulted in a 95.3% SVR12 rate which was statistically significantly higher than the 80.4% SVR12 rate seen in the 24-week SOF + RBV group (Table 17). The 12-week SOF/VEL group had a lower relapse rate than the 24-week SOF + RBV group (4.0% vs. 14.2%). The reviewer agrees with the applicant's results.

Table 17: Virologic Outcomes at Post-Treatment Week 12 in ASTRAL-3 (All Treated)

	SOF/VEL 12 Weeks (N=277)	SOF + RBV 24 Weeks (N=275)	Diff in SVR12 rate	
			Rate Diff (95% CI)[2]	P-value[3]
SVR12 rate	95.3% (264/277)	80.4% (221/275)	14.8% (9.6%, 20.0%)	<0.001
[95% CI][1]	[92.1%, 97.5%]	[75.2%, 84.9%]		
Not achieving SVR12			n/a	
On-treatment virologic failure	0% (0/277)	0.4% (1/275)		
Relapse	4.0% (11/276)	14.2% (38/272)		
Other	0.7% (2/277)	5% (15/275)		

Sources: Tables 9-1 and 9-2 in ASTRAL-3 Interim Clinical Study Report
[1]based on Clopper-Pearson method
[2]95% CI stratified by cirrhosis status (present vs. absent) and prior treatment experience (TN vs. TE)
[3]CMH test stratified by cirrhosis status and prior treatment experience (TN vs. TE)

Table 18 shows SVR4 rates which are similar to SVR12 rates shown in Table 17above. This is because most relapses occurred by post-treatment Week 4 visit. Eight out of 11 relapses in the 12-week SOF/VEL group, and 34 of 38 relapses in the 24-week SOF + RBV group occurred by post-treatment Week 4.

Table 18: SVR4 in ASTRAL-3 (All Treated)

	SOF/VEL 12 Weeks (N=277)	**SOF + RBV 24 Weeks (N=275)**
SVR4 rate [95% CI][1]	96.8% (268/277) [93.9%, 98.5%]	81.8% (225/275) [76.7%, 86.2%]

Sources: Table 9-3 in ASTRAL-3 Interim Clinical Study Report
[1]based on Clopper-Pearson method

Table 19 displays the applicant's results of the observed proportion of subjects with HCV RNA below LLOQ during on-treatment visits, and Table 20 summarizes the reviewer's results based on NC=F. Only two subjects in the 12-week SOF/VEL missed HCV RNA at some visits due to lost to follow-up. Therefore, the observed rates were similar to the rates calculated based on NC=F in this group. However, in the 24-week SOF + RBV group, more subjects discontinued study drug prematurely. Six subjects withdrew from study drug by Week 6, and twenty-one subjects discontinued by Week 24. Thus, there were 2% to 7% differences between the observed response rates and the rates based on NC=F in this group since Week 6. Nevertheless, the results from both analyses indicated that approximately 90% subjects in both groups achieved HCV RNA below LLOQ by four weeks after treatment, and the high response rates were maintained through the end of treatment.

Table 19: Applicant's Results for Observed Proportion of Subjects with HCV RNA < LLOQ While on Active Treatment by Visit in ASTRAL-3 (All Treated)

Visit	**SOF/VEL 12 Weeks (N=277)**	**SOF+RBV 24 Weeks (N=275)**
Week 1	18.4% (51/277)	17.5 % (48/275)
Week 2	62.0% (171/276)	50.0% (137/274)
Week 4	91.7% (253/276)	88.2% (240/272)
Week 6	96.7% (267/276)	98.9% (266/269)
Week 8	99.6% (275/276)	99.3% (267/269)
Week 10	100% (276/276)	99.3% (266/268)
Week 12	100% (275/275)	99.6% (264/265)
Week 16	n/a	98.9% (259/262)
Week 20	n/a	99.6% (259/260)
Week 24	n/a	100% (255/255)

Source: Tables 9-10 and 15.9.2.4 in ASTRAL-3 Interim Clinical Study Report

Table 20: Reviewer's Results for Proportion of Subjects with HCV RNA < LLOQ While on Active Treatment by Visit in ASTRAL-3 (NC=F) (All Treated)

Visit	SOF/VEL 12 Weeks (N=277)	SOF+RBV 24 Weeks (N=275)
Week 1	18.4% (51/277)	17.5 % (48/275)
Week 2	61.7% (171/277)	49.8% (137/275)
Week 4	91.3% (253/277)	87.3% (240/275)
Week 6	96.4% (267/277)	96.7% (266/275)
Week 8	99.3% (275/277)	97.1% (267/275)
Week 10	99.6% (276/277)	96.7% (266/275)
Week 12	99.3% (275/277)	96.0% (264/275)
Week 16	n/a	94.2% (259/275)
Week 20	n/a	94.2% (259/275)
Week 24	n/a	92.7% (255/275)

3.2.5 ASTRAL-4 (Decompensated cirrhosis)

3.2.5.1 Study Design

ASTRAL-4 was a phase 3, randomized, multicenter study conducted in 47 sites in the United States. The primary objective was to evaluate efficacy, safety and tolerability of SOF/VEL FDC with and without RBV for 12 weeks and SOF/VEL FDC for 24 weeks in HCV subjects with CPT class B cirrhosis. Eligible subjects were randomized in 1:1:1 ratio into one of the following three treatment groups stratified by HCV genotype (1, 2, 3, 4, 5, 6, and indeterminate).

Group 1: SOF/VEL FDC (400/100 mg QD) for 12 weeks
Group 2: SOF/VEL FDC (400/100 mg QD) + RBV (1000 or 1200 mg/day BID) for 12 weeks
Group 3: SOF/VEL FDC (400/100 mg QD) for 24 weeks

On treatment study visits would occur on Day 1 and at weeks 1, 2, 4, 6, 8, and 12 and for subjects in group 3 weeks 16, 20 and 24. Post-treatment visits were timed from the last day of study drug administration and would occur at post-treatment Week 4 and 12. Subjects with HCV RNA < LLOQ at post-treatment Week 12 would complete a post-treatment Week 24 visit. Subjects with a confirmed HCV RNA > LLOQ at Week 12 would be withdrawn from the study. HCV RNA was measured at each visit.

3.2.5.2 Statistical Methods

The primary efficacy hypothesis was that the SVR12 rate in each treatment group was higher than the assumed spontaneous rate of 1%. There were no IFN-free approved regimens for this patient population during the protocol development. Thus, an active-controlled design was not feasible. In addition, subjects are not expected to achieve SVR12 if no treatment is received. The placebo-controlled design was essentially the same as a single-arm in evaluation of efficacy. Furthermore, subjects with decompensated cirrhosis are generally considered the most difficult to treat successfully. Therefore, the proposed single arm to compare with a performance goal of a spontaneous rate of 1% was deemed acceptable.

In the primary efficacy analysis, the SVR12 rate in each of the three treatment groups was compared to the assumed spontaneous rate of 1%. To control the overall Type I error, each comparison was tested at the significance level of 0.0167 using a Bonferroni adjustment. Also, similar to ASTRAL-1, a 2-sided 95% exact CI based on Clopper-Pearson was calculated for SVR12 rate for each treatment.

3.2.5.3 Patient Disposition, Demographics and Baseline Characteristics

Table 21 displays the patient disposition. Two hundred and sixty-eight subjects were randomized into the three treatment groups. All except for one subject in the 12-week SOF/VEL + RBV group received at least one dose of study drug. Few subjects prematurely discontinued study treatment with more discontinuing in the 12-week SOF/VEL + RBV and 24-week SOF/VEL arms. The most common reason for discontinuation was AE.

Table 21: Patient Disposition in ASTRAL-4

	SOF/VEL 12 Weeks	**SOF/VEL + RBV 12 Weeks**	**SOF/VEL 24 Weeks**
Randomized	90	88	90
Treated	90 (100%)	87 (100%)	90 (100%)
Completed study treatment	89 (98.9%)	82 (94.3%)	84 (93.3%)
Discontinued study treatment	1 (1.1%)	5 (5.7%)	6 (6.7%)
AE	1 (1.1%)	4 (4.6%)	4 (4.4%)
Lack of efficacy	0	1 (1.1%)	1 (1.1%)
Noncompliance with study drug	0	0	1 (1.1%)

Source: Table 8-2 in ASTRAL-4 Interim Clinical Study Report

Patient demographics and baseline disease characteristics were well balanced across the three treatment groups (Table 22 and Table 23). Overall the mean age (SD) of the randomized subjects was 58 (6.3) years old. Among the 267 randomized subjects, approximately 69.7% were males and 89.5% were white. The majority of the randomized subjects had GT1 infection (77.5%), and the next most common genotype was GT3 (14.6%). There were very small proportions of GT2 (4.5%), GT4 (3.0%) and GT6 (0.4%) subjects, and no GT5 subjects. More than half of the subjects were TE, and most of the TE subjects previously received Peg-IFN + RBV. Approximately 90% of the subjects had CPT Class B cirrhosis at baseline. This was consistent with the original plan to only enroll subjects with CPT Class B cirrhosis. It was noticed that almost all subjects who were CPT Class A or C at baseline were CPT Class B at screening because of dynamic changes in CPT parameters over time. Slightly above 95% of the subjects had MELD score of ≤ 15 at baseline

Table 22: Patient Demographics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks (N=90)	SOF/VEL + RBV 12 Weeks (N=87)	SOF/VEL 24 Weeks (N=90)	Total (N=267)
Age				
Mean (SD)	58 (6.3)	58 (6.9)	58 (5.8)	58 (6.3)
Median	59	59	58	59
Q1, Q3	54, 62	54, 62	54, 62	54, 62
Min, Max	42, 73	40, 71	46, 72	40, 73
< 65 years	81 (90.0%)	74 (85.1%)	79 (87.8%)	234 (87.6%)
≥ 65 years	9 (10.0%)	13 (14.9%)	11 (12.2%)	33 (12.4%)
Gender				
Male	57 (63.3%)	66 (75.9%)	63 (70.0%)	186 (69.7%)
Female	33 (36.7%)	21 (24.1%)	27 (30.0%)	81 (30.3%)
Race				
Black/African American	6 (6.7%)	5 (5.7%)	6 (6.7%)	17 (6.4%)
White	79 (87.8%)	79 (90.8%)	81 (90.0%)	239 (89.5%)
Other[1]	5 (5.6%)	3 (3.4%)	2 (2.2%)	10 (3.7%)
Not disclosed	0	0	1 (1.1%)	1 (0.4%)
Ethnicity				
Hispanic or Latino	13 (14.4%)	13 (14.9%)	13 (14.4%)	39 (14.6%)
Not Hispanic or Latino	77 (85.6%)	74 (85.1%)	77 (85.6%)	228 (85.4%)
Baseline BMI[2] (kg/m^2)				
Mean (SD)	31.2 (7.4)	29.5 (5.8)	30.4 (6.8)	30.4 (6.7)
Median	29.7	28.8	29.0	29.2
Q1, Q3	26.2, 34.4	25.2, 32.8	25.5, 34.4	25.3, 34.0
Min, Max	16.7, 55.6	19.5, 54.9	18.4, 49.8	16.7, 55.6
< 30 kg/m^2	48 (53.3%)	54 (62.1%)	52 (57.8%)	154 (57.7%)
≥ 30 kg/m^2	42 (46.7%)	33 (37.9%)	38 (42.2%)	113 (42.3%)

Source: Table 8-4 in ASTRAL-4 Interim Clinical Study Report
[1]including Asian, American Indian/Alaska Native, Hawaiian or Pacific Islander, and other
[2]BMI = body mass index

Table 23: Selected Baseline Disease Characteristics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks (N=90)	SOF/VEL + RBV 12 Weeks (N=87)	SOF/VEL 24 Weeks (N=90)	Total (N=267)
HCV genotype				
GT1	68 (75.6%)	68 (78.2%)	71 (78.9%)	207 (77.5%)
GT2	4 (4.4%)	4 (4.6%)	4 (4.4%)	12 (4.5%)
GT3	14 (15.6%)	13 (14.9%)	12 (13.3%)	39 (14.6%)
GT4	4 (4.4%)	2 (2.3%)	2 (2.2%)	8 (3.0%)
GT5	0	0	0	0
GT6	0	0	1 (1.1%)	1 (0.4%)

(to be continued)

Table 23: Selected Baseline Disease Characteristics in ASTRAL-4 (All Treated) (Continued)

	SOF/VEL 12 Weeks (N=90)	SOF/VEL + RBV 12 Weeks (N=87)	SOF/VEL 24 Weeks (N=90)	Total (N=267)
IL28B				
CC	20 (22.2%)	22 (25.3%)	20 (22.2%)	62 (23.2%)
CT	51 (56.7%)	46 (52.9%)	49 (54.4%)	146 (54.7%)
TT	19 (21.1%)	19 (21.8%)	19 (21.1%)	57 (21.3%)
Missing	0	0	2 (2.2%)	2 (0.7%)
Baseline HCV RNA (log_{10}IU/mL)				
Mean (SD)	6.0 (0.54)	5.8 (0.61)	5.9 (0.63)	5.9 (0.60)
Median	6.0	5.9	5.9	6.0
Q1, Q3	5.7, 6.3	5.5, 6.2	5.6, 6.3	5.6, 6.3
Min, Max	3.7, 7.2	3.9, 7.1	3.5, 7.2	3.5, 7.2
< 800,000 IU/mL	31 (34.4%)	42 (48.3%)	45 (50.0%)	118 (44.2%)
≥ 800,000 IU/mL	59 (65.6%)	45 (51.7%)	45 (50.0%)	149 (55.8%)
Baseline ALT				
≤ 1.5 x ULN	45 (50.0%)	46 (52.9%)	47 (52.2%)	138 (51.7%)
> 1.5 x ULN	45 (50.0%)	41 (47.1%)	43 (47.8%)	129 (48.3%)
Prior HCV treatment history				
TN	32 (35.6%)	40 (46.0%)	48 (53.3%)	120 (44.9%)
TE	58 (64.4%)	47 (54.0%)	42 (46.7%)	147 (55.1%)
Prior HCV treatment (for TE subjects only)[1]	n=58	n=47	n=42	n=147
DAA + PegIFN + RBV	9 (15.5%)	12 (25.5%)	7 (16.7%)	28 (19.0%)
DAA	1 (1.7%)	0	0	1 (0.7%)
PegIFN + RBV	30 (51.7%)	27 (57.4%)	28 (66.7%)	85 (57.8%)
IFN + RBV	15 (25.9%)	5	5 (11.9%)	25 (17.0%)
IFN	2 (3.4%)	3	2 (4.8%)	7 (4.8%)
Missing	1 (1.7%)	0	0	1 (0.7%)
Baseline CPT score				
CPT A (5-6)	3 (3.3%)	6 (6.9%)	7 (7.8%)	16 (6.0%)
CPT B (7-9)	86 (95.6%)	77 (88.5%)	77 (85.6%)	240 (89.9%)
CPT C (10-12)	1 (1.1%)	4 (4.6%)	6 (6.7%)	11 (4.1%)
Baseline MELD score				
< 10	36 (40.0%)	29 (33.3%)	26 (28.9%)	91 (34.1%)
10 – 15	50 (55.6%)	54 (62.1%)	59 (65.6%)	163 (61.0%)
16 – 20	3 (3.3%)	4 (4.6%)	5 (5.6%)	12 (4.5%)
21 – 25	1 (1.1%)	0	0	1 (0.4%)
Baseline Ascites				
None	16 (17.8%)	22 (25.3%)	15 (16.7%)	53 (19.9%)
Mild/Moderate	72 (80.0%)	61 (70.1%)	74 (82.2%)	207 (77.5%)
Severe	2 (2.2%)	4 (4.6%)	1 (1.1%)	7 (2.6%)
Baseline Encephalopathy				
None	38 (42.2%)	33 (37.9%)	31 (34.4%)	102 (38.2%)
Grade 1 – 2	52 (57.8%)	54 (62.1%)	59 (65.6%)	165 (61.8%)
Grade 3 – 4	0	0	0	0

Source: Table 8-5 in ASTRAL-4 Interim Clinical Study Report

[1]Category of other in original table was expanded to DAA, IFN+RBV, IFN by the reviewer.

3.2.5.4 Efficacy Results

Table 24 summarizes the applicant's results for SVR12. The reviewer agrees with the applicant's results. The SVR12 rates of all three treatment groups were clearly superior to 1%. Among the three groups, SOF/VEL + RBV 12 weeks had the highest SVR12 rate and lowest relapse rate. Pair-wise comparisons among the three treatment groups were not pre-specified. However, the reviewer's exploratory analyses showed that 12-week SOF/VEL + RBV had a nominally significantly higher SVR12 rate than 12-week SOF/VEL (p=0.031 based on Fisher's exact test) and not a significant finding compared to 24-week SOF/VEL (p=0.056 based on Fisher's exact test). On the other hand, the differences in SVR12 and relapse rates between 12-week and 24-week SOF/VEL were not obvious. The relapse rate for 24-week SOF/VEL group was lower than 12-week SOF/VEL group. The subgroup analyses of SVR12 rate by different HCV genotypes and CPT are discussed and presented in Section 4.

Table 24: Virologic Outcomes at Post-Treatment Week 12 in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks (N=90)	**SOF/VEL + RBV 12 Weeks (N=87)**	**SOF/VEL 24 Weeks (N=90)**
SVR12 rate [95% CI][1]	83.3% (75/90) [74.0%, 90.4%]	94.3% (82/87) [87.1%, 98.1%]	85.6% (77/90) [76.6%, 92.1%]
Not achieving SVR12			
On-treatment virologic failure	0% (0/90)	1.1% (1/87)	1.1% (1/90)
Relapse	12.2% (11/90)	2.4% (2/85)	8.0% (7/88)
Other	4.4% (4/90)	2.3% (2/87)	5.6% (5/90)

Sources: Tables 9-1 and 9-2 in ASTRAL-4 Interim Clinical Study Report
[1]based on Clopper-Pearson method

Table 25 summarizes the applicant's SVR4 rate. The largest difference between SVR4 and SVR12 rates was observed in the 12-week SOF/VEL group since there were more relapses between post-treatment Weeks 4 and 12 in the group. Specifically, five of 11 relapses occurred between post-treatment Weeks 4 and 12. In the 12-week SOF/VEL + RBV group, the SVR4 rate was very similar to SVR12 rate because one out of two relapses occurred between post-treatment Weeks 4 and 12. In the 24-week SOF/VEL group, two out of seven relapses were observed between post-treatment Weeks 4 and 12.

Table 25: SVR4 in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks (N=90)	**SOF/VEL + RBV 12 Weeks (N=87)**	**SOF/VEL 24 Weeks (N=90)**
SVR4 rate [95% CI][1]	92.2% (83/90) [84.6%, 96.8%]	95.4% (83/87) [88.6%, 98.7%]	90.0% (81/90) [81.9%, 95.3%]

Sources: Table 9-3 in ASTRAL-4 Interim Clinical Study Report
[1]based on Clopper-Pearson method

Table 26 summarizes the applicant's results of observed proportion of subjects with HCV RNA below LLOQ at treatment visits. Similar to ASTRAL-1 and -2 studies, the observed rates should be similar to the rates based on NC=F since few subjects missed HCV RNA at some visits due to

discontinuation of study treatment. Above 97% of the subjects achieved HCV RNA below LLOQ six weeks after treatment.

Table 26: Applicant's Results for Observed Proportion of Subjects with HCV RNA < LLOQ While on Active Treatment by Visit in ASTRAL-4 (All Treated)

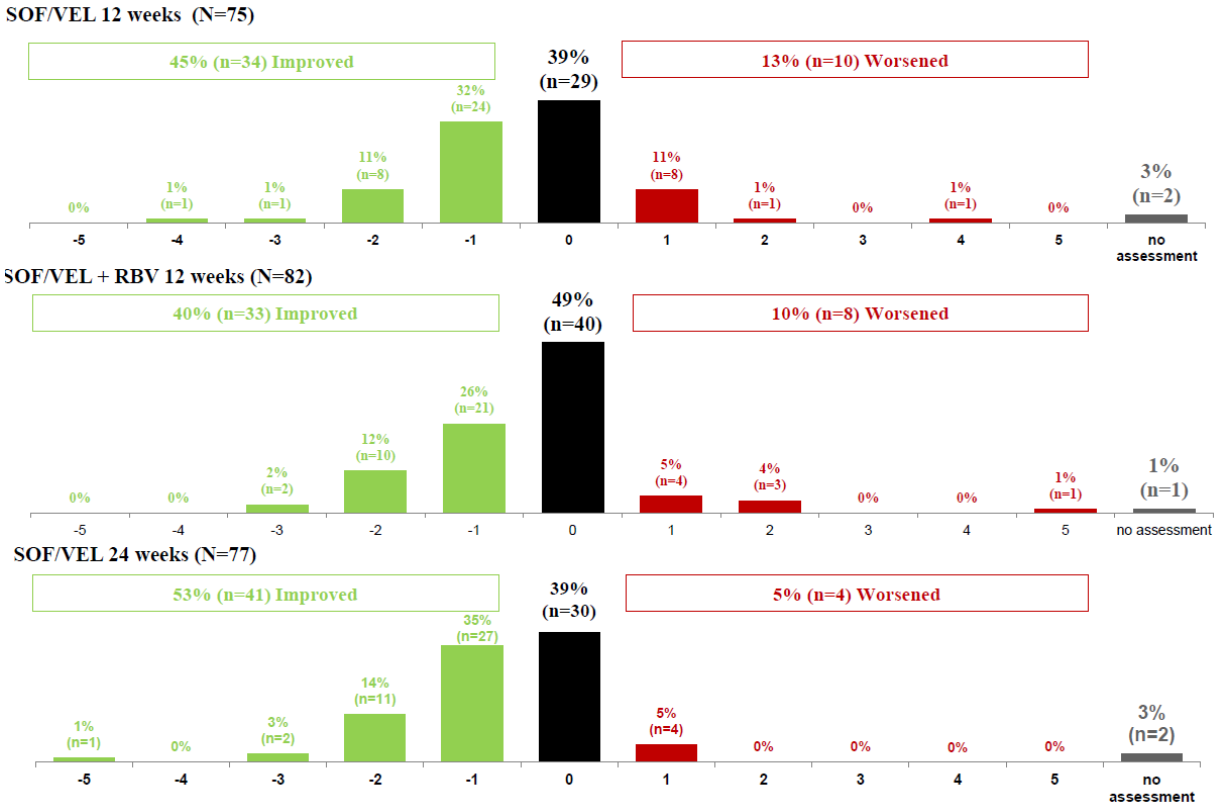
Visit	SOF/VEL 12 Weeks (N=90)	SOF/VEL + RBV 12 Weeks (N=87)	SOF+RBV 24 Weeks (N=90)
Week 1	2.2% (2/90)	14.9% (13/87)	11.1% (10/90)
Week 2	34.4% (31/90)	49.4% (43/87)	39.3% (35/89)
Week 4	81.1% (73/90)	80.5% (70/87)	91.0% (81/89)
Week 6	98.9% (88/89)	97.6% (83/85)	98.9% (87/88)
Week 8	98.9% (88/89)	98.8% (83/84)	100% (87/87)
Week 10	100% (89/89)	98.8% (83/84)	100% (87/87)
Week 12	100% (89/89)	98.8% (83/84)	97.7% (85/87)
Week 16	n/a	n/a	97.7% (84/86)
Week 20	n/a	n/a	100% (84/84)
Week 24	n/a	n/a	100% (84/84)

Source: Tables 9-10 and 15.9.2.4 in ASTRAL-4 Interim Clinical Study Report

Since the ASTRAL-4 study consisted of HCV subjects with decompensated cirrhosis, the secondary efficacy endpoints included changes from baseline in CPT and MELD scores at post-treatment Week 12. It is hypothesized that a subject's CPT and MELD scores will improve after their HCV viral load is suppressed. However, changes in CPT and MELD scores at a longer follow-up time than 12 weeks are considered more clinically relevant. Nevertheless, the results of changes at post-treatment Week 12 in subjects who achieved SVR12 are presented in the following paragraphs.

The applicant presented the results of change from baseline in CPT score at post-treatment Week 12 for all subjects who achieved SVR12 regardless of treatment groups. In contrast, the reviewer summarized the results separately for each of the treatment groups as shown in Figure 1. The patterns are similar among the three groups. Across the three treatment arms, 40% to 53% of subjects with SVR12 had improvement in CPT score, 39% to 49% of subjects had no change, and 5% to13% of subjects experienced worsening. It is noticed that, among the subjects who had improved score, the majority of them had a one-point improvement.

Figure 1: Reviewer's Results of Changes in CPT Scores from Baseline to Post-Treatment Week 12 in Subjects Achieving SVR12 in ASTRAL-4 (ALL Treated)



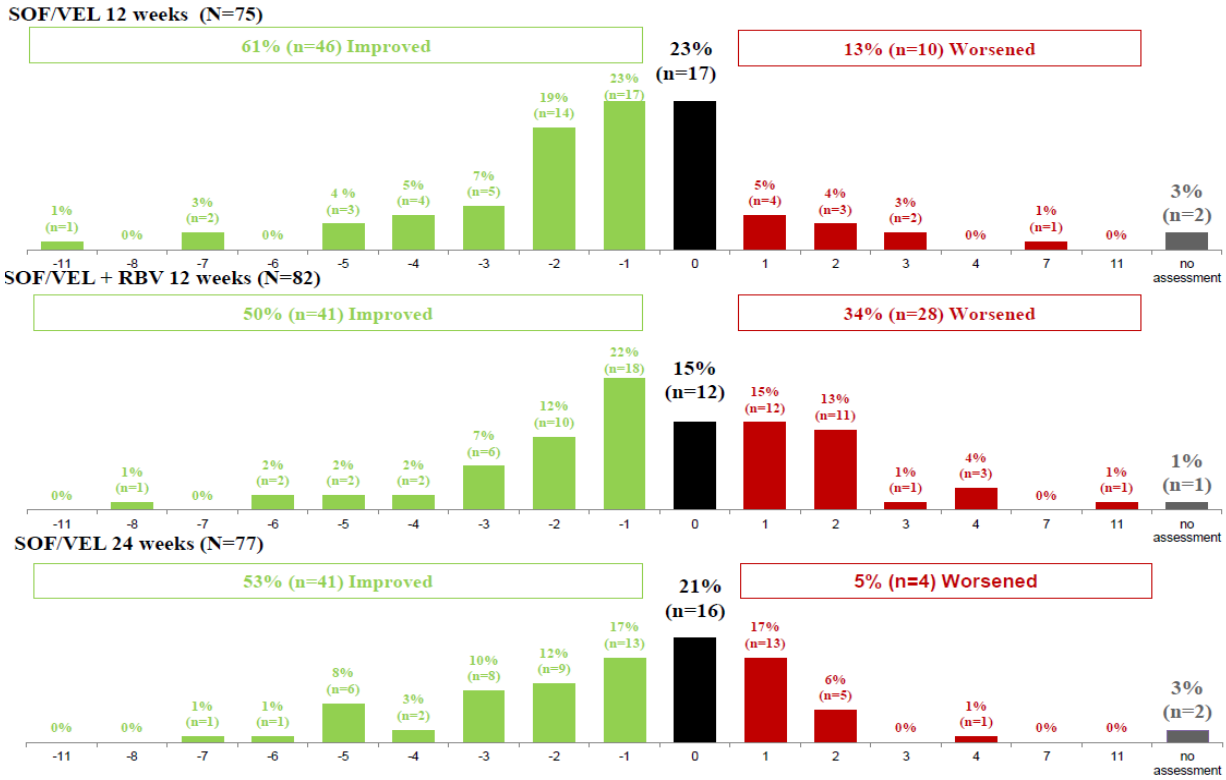
Both the applicant and the reviewer generated shift tables of CPT class from baseline to post-treatment Week 12 in subjects achieving SVR12. The slight difference was that the applicant excluded subjects with no assessment at post-treatment Week 12 when calculating the percentage in each row. Table 27 displays the reviewer's results. Among CPT class B subjects in all groups, the majority of subjects remained in the same CPT class at post-treatment Week 12 as that they were in at baseline. There were not enough subjects in CPT class A and C to make any meaningful conclusions.

Table 27: Reviewer's Shift Table of CPT Class from Baseline to Post-treatment Week 12 in Subjects Achieving SVR12 in ASTRAL-4 (All Treated)

Baseline CPT class	Post-treatment Week 12 CPT class			
	CPT A	CPT B	CPT C	No assessment
SOF/VEL 12 Weeks (n=75)				
CPT A (n=3)	66.7% (2)	33.3% (1)	0% (0)	0% (0)
CPT B (n=71)	22.5% (16)	71.8% (51)	2.8% (2)	2.8% (2)
CPT C (n=1)	0% (0)	100% (1)	0% (0)	0% (0)
SOF/VEL + RBV 12 Weeks (n=82)				
CPT A (n=6)	50.0% (3)	33.3% (2)	0% (0)	16.7% (1)
CPT B (n=72)	11.1% (8)	87.5% (63)	1.4% (1)	0% (0)
CPT C (n=4)	0% (0)	25.0% (1)	75.0% (3)	0% (0)
SOF/VEL 24 Weeks (n=77)				
CPT A (n=6)	83.3% (5)	16.7% (1)	0% (0)	0% (0)
CPT B (n=66)	15.2% (10)	80.3% (53)	1.5% (1)	3.0% (2)
CPT C (n=5)	20.0% (1)	60.0% (3)	20.0% (1)	0% (0)

Similar to the CPT score, the applicant presented change from baseline in MELD score at post-treatment Week 12 for all subjects who achieved SVR12. The reviewer summarized the endpoint for each of the treatment group (Figure 2). Across the three groups, above 50% of subjects achieving SVR12 had improvement on MELD score at post-treatment Week 12. However, the majority of improvement was within three points.

Figure 2: Reviewer's Results of Changes in MELD Scores from Baseline to Post-Treatment Week 12 in Subjects Achieving SVR12 in ASTRAL-4 (ALL Treated)



Both the applicant and the reviewer generated shift tables of MELD score (< 15 or ≥ 15) from baseline to post-treatment Week 12 in subjects achieving SVR12. Like the shift table for CPT class, the reviewer included the missing data in calculation of percentage in each row (Table 28). In all three groups, the majority of subjects had MELD score < 15 at baseline and above 94% of them remained < 15 at post-treatment Week 12. On the other hand, few subjects had baseline MELD score ≥ 15. Among the subjects with MELD score ≥ 15, most of them remained the same in the 12-week SOF/VEL and 12-week SOF/VEL + RBV groups, but most of them improved to MELD score < 15 in the 24-week SOF/VEL group.

Table 28: Reviewer's Shift Tables of MELD Class (< or ≥ 15) from Baseline to Post-treatment Week 12in Subjects Achieving SVR12 in ASTRAL-4 (All Treated)

Baseline MELD score	Post-treatment Week 12 MELD score		
	< 15	≥ 15	No assessment
SOF/VEL 12 weeks (n=75)			
< 15 (n=69)	94.2% (65)	2.9% (2)	2.9% (2)
≥ 15 (n=6)	83.3% (5)	1.7% (1)	0% (0)
SOF/VEL + RBV 12 weeks (n=82)			
< 15 (n=72)	94.4% (68)	4.2% (3)	1.4% (1)
≥ 15 (n=10)	40.0% (4)	60.0% (6)	0% (0)
SOF/VEL 24 weeks (n=77)			
< 15 (n=67)	95.5% (64)	1.5% (1)	3.0% (2)
≥ 15 (n=10)	70.0% (7)	30.0% (3)	0% (0)

3.3 Evaluation of Safety

Please refer to the clinical review by Drs. Prabha Viswanathan and Sarah Connelly for more details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the subgroup analyses for the SVR12 rate in each study. All 95% CIs were calculated based on the Clopper-Pearson method. These subgroup analyses are exploratory, and the results should be interpreted with caution because of multiple comparisons with no adjustments applied, small sample sizes in some of the subgroups, and the lack of an active control as in ASTRAL-1 and -4 studies.

4.1 ASTRAL-1 (Non-GT3 including compensated cirrhosis)

In ASTRAL-1, the SVR12 rate was 99.0% (618/624) in the 12-week SOF/VEL group. The SVR12 rates were high for all subgroups by patient demographics and baseline disease characteristics (Table 29 and Table 30). Of note, the SVR12 rate was 98.6% (72/73) for GT1 cirrhotic subjects and 99.1% (109/110) for GT1 TE subjects in the 12-week SOF/VEL group.

Table 29: SVR12 Rates by Demographics in ASTRAL-1 (All Treated)

	SOF/VEL 12 Weeks (N=624)	95% CI
Age		
< 65 years	98.9% (530/536)	(97.6%, 99.6%)
≥ 65 years	100% (88/88)	(95.9%, 100%)
Gender		
Male	98.7% (369/374)	(96.9%, 99.6%)
Female	99.6% (249/250)	(97.8%, 100%)
Race		
White	99.0% (488/493)	(97.6%, 99.7%)
Black/African American	98.1 % (51/52)	(89.7%, 100%)
Other	100% (76/76)	(95.3%, 100%)
Ethnicity		
Hispanic or Latino	100% (31/31)	(88.8%, 100%)
Not Hispanic or Latino	99.0% (583/589)	(97.8%, 99.6%)
Region		
US	99.6% (233/234)	(97.6%, 100%)
Non-US	98.7% (385/390)	(97.0%, 99.6%)
Baseline BMI		
< 30 kg/m^2	99.0% (484/489)	(97.6%, 99.7%)
≥ 30 kg/m^2	99.3% (134/135)	(95.9%, 100%)

Source: Table 9-6 in ASTRAL-1 Interim Clinical Study Report

Table 30: SVR12 Rates by Selected Baseline Disease Characteristics in ASTRAL-1 (All Treated)

	SOF/VEL 12 Weeks (N=624)	95% CI
Genotype		
GT1	98.1% (323/328)	(96.5%, 99.5%)
GT1a	98.1% (206/210)	(95.2%, 99.5%)
GT1b	99.2% (117/118)	(95.4%, 100.0%)
GT2	100% (104/104)	(96.5%, 100.0%)
GT4	100% (116/116)	(96.9%, 100.0%)
GT5	97.1% (34/35)	(85.1%, 99.9%)
GT6	100% (41/41)	(91.4%, 100.0%)
Cirrhosis		
No	99.0% (496/501)	(97.7%, 99.7%)
Yes	99.2% (120/121)	(95.5%, 100.0%)
HCV treatment history		
TN	98.8% (418/423)	(97.3%, 99.6%)
TE	99.5% (200/201)	(97.3%, 100.0%)
IL28B		
CC	99.5% (185/186)	(97.0%, 100.0%)
CT	99.1% (336/339)	(97.4%, 99.8%)
TT	97.9% (92/94)	(92.5%, 99.7%)
Baseline HCV RNA		
< 800,000 IU/mL	98.8% (161/163)	(95.6%, 99.9%)
≥ 800,000 IU/mL	99.1% (457/461)	(97.8%, 99.8%)
Baseline ALT		
≤ 1.5 x ULN	99.1% (342/345)	(95.6%, 99.9%)
> 1.5 x ULN	98.9% (276/279)	(96.9%, 99.8%)

Source: Tables 9-2, 9-3 and 9-8 in ASTRAL-1 Interim Clinical Study Report

4.2 ASTRAL-2 (GT2 including compensated cirrhosis)

In ASTRAL-2, the SVR12 rate was 99% (133/134) in the 12-week SOF/VEL group and 94% (124/132) in the 12-week SOF + RBV group. The reviewer agrees with the applicant that the high SVR12 rates in both groups preclude meaningful interpretation of subgroup analyses. Table 31 and Table 32 present the subgroup analyses by demographic and baseline disease characteristics, respectively.

Table 31: SVR12 Rates by Demographics in ASTRAL-2 (All Treated)

	SOF/VEL 12 Weeks (N=134)	SOF + RBV 12 Weeks (N=132)	Diff in SVR12 rate (95% CI)
Age (years)			
< 65	99.1% (105/106)	92.7% (102/110)	6.3% (1.1%, 12.9%)
≥ 65	100% (28/28)	100% (22/22)	0.0% (-12.4%, 15.5%)
Gender			
Male	98.8% (85/86)	90.3% (65/72)	8.6% (1.4%, 17.8%)
Female	100% (48/48)	98.3% (59/60)	1.7% (-5.8%, 9.2%)
Race			
White	100% (124/124)	94.6% (105/111)	5.4% (1.7%, 11.4%)
Black/African American	83.3% (5/6)	83.3% (10/12)	0.0% (-47.6%, 37.4%)
Other	100% (2/2)	100% (8/8)	0.0% (-84.2%, 44.0%)
Ethnicity			
Hispanic or Latino	100% (26/26)	87.0% (20/23)	13.0% (-2.1%, 33.6%)
Not Hispanic or Latino	99.0% (103/104)	95.3% (102/107)	3.7% (-1.2%, 9.7%)
Baseline BMI (kg/m^2)			
< 30	98.9% (94/95)	92.9% (78/84)	6.1% (0.1%, 13.7%)
≥ 30	100% (39/39)	95.8% (46/48)	4.2% (-5.0%, 14.3%)

Source: Table 9-4 in ASTRAL-2 Interim Clinical Study Report

Table 32: SVR12 Rates by Selected Baseline Disease Characteristics in ASTRAL-2 (All Treated)

	SOF/VEL 12 Weeks	SOF + RBV 12 Weeks	Diff in SVR12 rate (95% CI)
Cirrhosis			
Yes	100% (19/19)	94.7% (18/19)	5.3% (-13.2%, 26.0%)
No	99.1% (114/115)	93.8% (105/112)	5.4% (0.5%, 11.6%)
Prior HCV trt			
TN	99.1% (114/115)	95.5% (107/112)	3.6% (-0.9%, 9.2%)
TE	100% (19/19)	85.0% (17/20)	15.0% (-4.1%, 37.9%)
IL28B			
CC	100% (55/55)	100% (46/46)	0.0% (-6.8%, 7.9%)
CT	100% (61/61)	92.2% (59/64)	7.8% (1.3%, 17.3%)
TT	94.4% (17/18)	86.4% (19/22)	8.1% (-15.0%, 30.0%)
Baseline HCV RNA			
< 800,000 IU/mL	100% (23/23)	96.8% (30/31)	3.2% (-11.5%, 17.4%)
≥ 800,000 IU/mL	99.1% (110/111)	93.1% (94/101)	6.0% (0.8%, 12.8%)
Baseline ALT			
≤ 1.5 x ULN	98.8 (79/80)	93.9% (77/82)	4.8% (-1.5%, 12.5%)
> 1.5 x ULN	100% (54/54)	94.0% (47/50)	6.0% (-1.0%, 16.5%)
Prior HCV trt history			
TE	99.1% (114/115)	95.5% (107/112)	3.6% (-0.9%, 9.2%)
TE	100% (19/19)	85.0% (17/20)	15.0% (-4.1%, 37.9%)

Source: Table 9-5 in ASTRAL-2 Interim Clinical Study Report

4.3 ASTRAL-3 (GT3 including compensated cirrhosis)

Table 33 and Table 34 display the subgroup analyses by demographic and baseline disease characteristics in ASTRAL-3. No apparent treatment by subgroup interaction was identified. The SVR12 rates in the 12-week SOF/VEL regimen were consistently higher than the rates in the 24-week SOF + RBV treatment across all subgroups except for black/African American and subjects infected with GT3b where sample sizes were too small in these two subgroups to be conclusive. HCV GT3 cirrhotic subjects and TE subjects are generally considered difficult to treat. The subgroup analyses demonstrated that the treatment difference was approximately 25.0% in the cirrhotic subjects and 26.8% in the TE subjects in favor of 12 weeks of SOF/VEL.

Table 33: SVR12 Rates by Demographics in ASTRAL-3 (All Treated)

	SOF/VEL 12 weeks (N=277)	**SOF + RBV 24 weeks (N=275)**	**Diff in SVR12 rate (95% CI)**
Age at baseline (years)			
< 65 years	95.2% (257/270)	80.5% (210/261)	14.7% (9.3%, 20.4%)
≥ 65 years	100% (7/7)	78.6% (11/14)	21.4% (-21.3%, 50.8%)
Sex at birth			
Male	93.5% (257/270)	75.9% (132/174)	17.7% (10.1%, 25.4%)
Female	98.1% (105/107)	88.1% (89/101)	10.0% (3.2%, 18.1%)
Race			
Black or African American	100% (3/3)	100% (1/1)	0.0% (-70.8%, 97.5%)
White	95.2% (238/250)	78.2% (187/239)	17.0% (11.1%, 23.1%)
Other	95.8% (23/24)	94.1% (32/34)	1.7% (-15.7%, 16.0%)
Ethnicity			
Hispanic or Latino	100% (11/11)	81.8% (9/11)	18.2% (-12.2%, 51.8%)
Not Hispanic or Latino	95.1% (253/266)	80.2% (211/263)	14.9% (9.4%, 20.6%)
Region			
US	95.0% (57/60)	76.7% (46/60)	18.3% (5.5%, 31.4%)
Non-US	95.4% (207/217)	81.4% (175/215)	14.0% (8.1%, 20.2%)
Body mass index (kg/m^2) at baseline			
< 30 kg/m^2	94.7% (214/226)	81.3% (174/214)	13.4% (7.4%, 19.7%)
≥ 30 kg/m^2	98.0% (50/51)	77.0% (47/61)	21.0% (8.8%, 33.7%)

Sources: Table 9-4 in ASTRAL-3 Interim Clinical Study Report

Table 34: SVR12 Rates by Selected Baseline Disease Characteristics in ASTRAL-3 (All Treated)

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Diff in SVR12 rate (95% CI)-
HCV genotype			
GT3 (no confirmed subtype)	88.9% (8/9)	83.3% (15/18)	5.6% (-32.0%, 33.7%)
GT3a	95.5% (253/265)	79.6% (199/250)	15.9% (10.2%, 21.7%)
GT3b	100% (2/2)	100% (5/5)	0.0% (-84.2%, 52.5%)
GT3h	n/a	100% (2/2)	n/a
GT3k	100% (1/1)	n/a	n/a
Cirrhosis			
No	97.0% (191/197)	87.2% (163/187)	9.8% (4/2%, 15.7%)
Yes	91.3% (73/80)	66.3% (55/83)	25.0% (11.5%, 37.2%)
Missing	0/0	60% (3/5)	n/a
IL28B			
CC	94.3% (99/105)	80.2% (89/111)	14.1% (4.3%, 23.4%)
Non-CC	95.9% (165/172)	80.5% (132/164)	15.4% (8.6%, 22.6%)
CT	96.6% (143/148)	79.7% (106/133)	16.9% (9.4%, 25.0%)
TT	91.7% (22/24)	83.9% (26/31)	7.8% (-12.6%, 26.6%)
HCV RNA at baseline			
< 800,000 IU/mL	98.8% (85/86)	88.9% (72/81)	9.9% (2.8%, 18.9%)
≥ 800,000 IU/mL	93.7% (179/191)	76.8% (149/194)	16.9% (9.9%, 24.0%)
ALT at baseline (U/L)			
≤ 1.5 x ULN	96.8% (92/95)	83.9% (73/87)	12.9% (3.9%, 22.6%)
> 1.5 x ULN	94.5% (172/182)	78.7% (148/188)	15.8% (8.8%, 22.9%)
Prior HCV treatment history			
Treatment-naïve	97.1% (200/206)	86.3% (176/204)	10.8% (5.3%, 16.5%)
Treatment-experienced	90.1% (64/71)	63.4% (45/71)	26.8% (12.2%, 40.1%)
Prior HCV treatment			
DAA + Peg-IFN + RBV	100% (1/1)	0/0	n/a
Peg-IFN + RBV	89.1% (57/64)	63.1% (41/65)	26.0% (9.8%, 40.3%)
Other	100% (6/6)	66.7% (4/6)	33.3% (-17.4%, 77.7%)
Prior HCV treatment response			
Nonresponder	85.0% (17/20)	58.3% (14/24)	26.7% (-1.2%, 51.8%)
Relapse/Breakthrough	92.2% (47/51)	66.0% (31/47)	26.2% (8.9%, 42.5%)

Sources: Table 9-5 in ASTRAL-3 Interim Clinical Study Report

Baseline cirrhotic status and prior HCV treatment history were the two stratification factors at randomization. Table 35 summarizes SVR12 rates by randomization strata. As expected, the SVR12 rates were lowest for TE subjects with cirrhosis and highest for TN subjects without cirrhosis in both treatment groups. In all strata, 12 weeks of SOF/VEL showed better SVR12 rates than 24 weeks of SOF/VEL. The treatment difference was largest among TE subjects with cirrhosis and smallest among TN subjects without cirrhosis.

Table 35: SVR12 Rates by Baseline Cirrhosis and Prior HCV Treatment History in ASTRAL-3 (All Treated)

	SOF/VEL 12 Weeks	SOF + RBV 24 Weeks	Diff in SVR12 rate (95% CI)
Cirrhosis & prior HCV treatment history			
Cirrhotic, TE	89.2% (33/37)	57.9% (22/38)	31.3% (10.8%, 49.8%)
Non-cirrhotic, TE	91.2% (31/34)	71.0% (22/31)	20.2% (0.5%, 40.3%)
Cirrhotic, TN	93.0% (40/43)	73.3% (33/45)	19.7% (3.7%, 35.7%)
Non-cirrhotic, TN	98.2% (160/163)	90.4% (141/156)	7.8% (2.6%, 13.6%)

4.4 ASTRAL-4 (Decompensated cirrhosis)

Table 36 and Table 37 display the subgroup analyses for SVR12 rate by demographics and baseline disease characteristics in all treated subjects in ASTRAL-4. It is of clinical interest to examine the reasons why subjects did not achieve SVR 12 at post-treatment Week 12 by HCV genotype since different HCV genotypes are expected to have different results. Therefore, the virologic outcomes at post-treatment Week 12 by HCV genotype are summarized in Table 38. Finally the subgroup analyses for GT1 and GT3 subjects separately are summarized in Table 39 to Table 42.

Overall the SVR12 rates for 12-week SOF/VEL + RBV were numerically higher than 12-week SOF/VEL or 24-week SOF/VEL across most of subgroups by patient demographics and selected baseline disease characteristics (Table 36 and Table 37). Similar trends were observed for the subgroup analyses for GT1 and GT3 subjects, respectively (Table 39 to Table 42).

As mentioned in 3.2.5.3, 77.5% of the subjects in ASTRAL-4 had GT1 infection. The 12-week SOF/VEL + RBV treatment had the highest SVR12 rate of 95.6% among GT1 subjects as shown in Table 37 and Table 38. A small sample of GT3 subjects was in the study, ranging from 12 to 14 subjects in each group. Similar to GT1 subjects, the 12-week SOF/VEL regimen led to the highest SVR12 rate in GT3 subjects. The SVR12 rate was 84.6% for the 12-week SOF/VEL group compared with 50% in the other two groups. There was very limited data for subjects with GT2, 4, 5 and 6 infections, mainly because GT4, 5 and 6 were not prevalent in the US. Specifically, the study included only 12 GT2 subjects with four in each group, eight GT4 subjects with two to four in each group, no GT5 subjects and one GT6. Furthermore, the differences in SVR12 rates among the three groups were not apparent in GT2 and GT4 infections. Among GT2 subjects, all of the four subjects in each of the 12-week SOF/VEL with and without RBV groups achieved SVR12, and three out of four subjects receiving 24-week SOF/VEL SVR12. All of GT4 subjects in the study achieved SVR12, including four subjects in the 12-week SOF/VEL group, two subjects in the 12-week SOF/VEL + RBV group, and two subjects in the 24-week SOF/VEL group. In conclusion, the study did not provide sufficient evidence to select the optimal regimen for GT2, 4, 5 and 6 subjects with decompensated cirrhosis.

Similarly, approximately 90% of subjects in ASTRAL-4 had CPT class B cirrhosis at baseline. The higher SVR12 rate for SOF/VEL for 12 weeks compared to the other two regimens was driven by the subjects with CPT class B cirrhosis. There were only 16 subjects with CPT class A cirrhosis and 11 subjects with CPT class C cirrhosis in total. Among subjects with CPT class A cirrhosis, all three subjects in the 12-week SOF/VEL group and six subjects in the 12-week SOF/VEL group had SVR12, and six out of seven subjects in the 24-week SOF/VEL group achieved SVR12. Similarly, among subjects with CPT class C cirrhosis, the one subject receiving 12-week SOF/VEL and all four subjects receiving 12-week SOF/VEL + RBV achieved SVR12, while five out of six subjects receiving 24-week SOF/VEL had SVR12. Again, the sample sizes for subjects with CPT class A and C in the study were too small to be conclusive.

Table 36: SVR12 Rates by Demographics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
Age at baseline (years)						
< 65 years	81.5% (66/81)	(71.3%, 89.2%)	95.9% (71/74)	(88.6%, 99.2%)	84.8% (67/79)	(75.0%, 91.9%)
≥ 65 years	100% (9/9)	(66.4%, 100%)	84.6% (11/13)	(54.6%, 98.1%)	90.9% (10/11)	(58.7%, 99.8%)
Sex at birth						
Male	78.9% (45/57)	(66.1%, 88.6%)	92.4% (61/66)	(83.2%, 97.5%)	82.5% (52/63)	(70.9%, 90.9%)
Female	90.9% (30/33)	(75.7%, 98.1%)	100% (21/21)	(83.9%, 100%)	92.6% (25/27)	(75.7%, 99.1%)
Race						
Black or African American	66.7% (4/6)	(22.3%, 95.7%)	100% (5/5)	(47.8%, 100%)	83.3% (5/6)	(35.9%, 99.6%)
White	83.5% (66/79)	(73.5%, 90.9%)	93.7% (74/79)	(85.8%, 97.9%)	85.2% (69/81)	(75.6%, 92.1%)
Other	100% (5/5)	(47.8%, 100%)	100% (3/3)	(29.2%, 100%)	100% (2/2)	(15.8%, 100%)
Ethnicity						
Hispanic or Latino	84.6% (11/13)	(54.6%, 98.1%)	100% (13/13)	(75.3%, 100%)	100% (13/13)	(75.3%, 100%)
Not Hispanic or Latino	83.1% (64/77)	(72.9%, 90.7%)	93.2% (69/74)	(84.9%, 97.8%)	83.1% (64/73)	(72.9%, 90.7%)
BMI at baseline						
< 30 kg/m^2	81.3% (39/48)	(67.4%, 91.1%)	92.6% (50/54)	(82.1%, 97.9%)	90.4% (47/52)	(79.0%, 96.8%)
≥ 30 kg/m^2	85.7% (36/42)	(71.5%, 94.6%)	97.0% (32/33)	(84.2%, 99.9%)	78.9% (30/38)	(62.7%, 90.4%)

Source: Table 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

Table 37: SVR12 Rates by Selected Baseline Disease Characteristics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
Genotype						
GT1	88.2% (60/68)	(78.1%, 94.8%)	95.6% (65/68)	(87.6%, 99.1%)	91.5% (65/71)	(82.5%, 96.8%)
GT1a	88.0% (44/50)	(75.7%, 95.5%)	94.4% (51/54)	(84.4%, 98.8%)	92.7% (51/55)	(82.4%, 98.0%)
GT1b	88.9% (16/18)	(65.3%, 98.6%)	100% (14/14)	(76.8%, 100%)	87.5% (14/16)	(61.7%, 98.4%)
GT2	100% (4/4)	(39.8%, 100%)	100% (4/4)	(39.8%, 100%)	75.0% (3/4)	(19.4%, 99.4%)
GT3	50.0% (7/14)	(23.0%, 77.0%)	84.6% (11/13)	(54.6%, 98.1%)	50.0% (6/12)	(21.1%, 78.9%)
GT4	100% (4/4)	(39.8%, 100%)	100% (2/2)	(15.8%, 100%)	100% (2/2)	(15.8%, 100%)
GT5	0/0	n/a	0/0	n/a	0/0	n/a
GT6	0/0	n/a	0/0	n/a	100% (1/1)	(2.5%, 100%)
IL28B						
CC	80.0% (16/20)	(56.3%, 94.3%)	100% (22/22)	(84.6%, 100%)	85.0% (17/20)	(62.1%, 96.8%)
CT	82.4% (42/51)	(69.1%, 91.6%)	93.5% (43/46)	(82.1%, 98.6%)	85.7% (42/49)	(72.8%, 94.1%)
TT	89.5% (17/19)	(66.9%, 98.7%)	89.5% (17/19)	(66.9%, 98.7%)	89.5% (17/19)	(66.9%, 98.7%)
Baseline HCV RNA (IU/mL)						
< 800,000	87.1% (27/31)	(70.2%, 96.4%)	95.2% (40/42)	(83.8%, 99.4%)	91.1% (41/45)	(78.8%, 97.5%)
≥ 800,000	81.4% (48/59)	(69.1%, 90.3%)	93.3% (42/45)	(81.7%, 98.6%)	80.0% (36/45)	(65.4%, 90.4%)
Baseline ALT						
≤ 1.5 x ULN	77.8% (35/45)	(62.9%, 88.8%)	93.5 % (43/46)	(82.1%, 98.6%)	80.9% (38/47)	(66.7%, 90.9%)
> 1.5 x ULN	88.9% (40/45)	(75.9%, 96.3%)	95.1% (39/41)	(83.5%, 99.4%)	90.7% (39/43)	(77.9%, 97.4%)
Baseline CPT score						
CPT A	100% (3/3)	(29.2%, 100%)	100% (6/6)	(54.1%, 100%)	85.7% (6/7)	(42.1%, 99.6%)
CPT B	82.6% (71/86)	(72.9%, 89.9%)	93.5% (72/77)	(85.5%, 97.9%)	85.7% (66/77)	(75.9%, 92.6%)
CPT C	100% (1/1)	(2.5%, 100%)	100% (4/4)	(39.8%, 100%)	83.3% (5/6)	(35.9%, 99.6%)
Baseline MELD score						
< 10	77.8% (28/36)	(60.8%, 89.9%)	100% (29/29)	(88.1%, 100%)	92.3% (24/26)	(74.9%, 99.1%)
10 – 15	86.0% (43/50)	(73.3%, 94.2%)	90.7% (49/54)	(79.7%, 96.9%)	81.4% (48/59)	(69.1%, 90.3%)
16 – 20	100% (3/3)	(29.2%, 100%)	100% (4/4)	(39.8%, 100%)	100% (5/5)	(47.8%, 100%)
21 – 25	100% (1/1)	(2.5%, 100%)	0/0	n/a	0/0	n/a
Prior HCV treatment history						
TN	84.4% (27/32)	(67.2%, 94.7%)	90.0% (36/40)	(76.3%, 97.2%)	85.4% (41/48)	(72.2%, 93.9%)
TE	82.8% (48/58)	(70.6%, 91.4%)	97.9% (46/47)	(88.7%, 99.9%)	85.7% (36/42)	(71.5%, 94.6%)

Source: Tables 9-1 and 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

Table 38: Virologic Outcomes at Post-Treatment Week 12 by HCV Genotype in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks	SOF/VEL + RBV 12 Weeks	SOF/VEL 24 Weeks
GT1			
SVR12 rate [95% CI][1]	88.2% (60/68) [78.1%, 94.8%]	95.6% (65/68) [87.6%, 99.1%]	91.5% (65/71) [82.5%, 96.8%]
Not achieving SVR12			
On-treatment virologic failure	0% (0/68)	0% (0/68)	0% (0/71)
Relapse	7.4% (5/68)	1.5% (1/67)	4.2% (3/71)
Other	4.4% (3/68)	2.9% (2/68)	4.2% (3/71)
GT2			
SVR12 rate [95% CI][1]	100% (4/4) [39.8%, 100%]	100% (4/4) [39.8%, 100%]	75.0% (3/4) [19.4%. 99.4%]
Not achieving SVR12			
On-treatment virologic failure	n/a	n/a	n/a
Relapse	n/a	n/a	n/a
Other	n/a	n/a	25.0% (1/4)
GT3			
SVR12 rate [95% CI][1]	50.0% (7/14) [23.0%, 77.0%]	84.6% (11/13) [54.6%, 98.1%]	50.0% (6/12) [21.1%, 78.9%]
Not achieving SVR12			
On-treatment virologic failure	0% (0/14)	7.7% (1/13)	8.3% (1/12)
Relapse	42.9% (6/14)	8.3% (1/12)	40.0% (4/10)
Other	7.1% (1/14)	0% (0/13)	8.3% (1/12)
GT4			
SVR12 rate [95% CI][1]	100% (4/4) [39.8%, 100%]	100% (2/2) [15.8%, 100%]	100% (2/2) [15.8%, 100%]
GT6			
SVR12 rate [95% CI][1]	n/a	n/a	100% (1/1) [2.5%, 100%]

Sources: Tables 9-1 and 9-2 in ASTRAL-4 Interim Clinical Study Report
[1]based on Clopper-Pearson method

Table 39: SVR12 Rates by Demographics among GT1 Subjects in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
Age at baseline (years)						
< 65 years	86.4% (51/59)	(75.0%, 94.0%)	98.2% (54/55)	(90.3%, 100%)	90.5% (57/63)	(80.4%, 96.4%)
≥ 65 years	100% (9/9)	(66.4%, 100%)	84.6% (11/13)	(54.6%, 98.1%)	100% (8/8)	(63.1%, 100%)
Sex at birth						
Male	84.1% (37/44)	(69.9%, 93.4%)	94.5% (52/55)	(84.9%, 98.9%)	89.1% (41/46)	(76.4%, 96.4%)
Female	95.8% (23/24)	(78.9%, 99.9%)	100% (13/13)	(75.3%, 100%)	96.0% (24/25)	(79.6%, 99.9%)
Race						
Black or African American	66.7% (4/6)	(22.3%, 95.7%)	100% (5/5)	(47.8%, 100%)	100% (5/5)	(47.8%, 100%)
White	89.5% (51/57)	(78.5%, 96.0%)	95.1% (58/61)	(86.3%, 99.0%)	90.8% (59/65)	(81.0%, 96.5%)
Other	100% (5/5)	(47.8%, 100%)	100% (2/2)	(15.8%, 100%)	0/0	n/a
Ethnicity						
Hispanic or Latino	100% (9/9)	(66.4%, 100%)	100% (9/9)	(66.4%, 100%)	100% (9/9)	(66.4%, 100%)
Not Hispanic or Latino	86.4% (51/59)	(75.0%, 94.0%)	94.9% (56/59)	(85.9%, 98.9%)	90.3% (56/62)	(80.1%, 96.4%)
BMI at baseline						
< 30 kg/m²	89.7% (35/39)	(75.8%, 97.1%)	93.0% (40/43)	(80.9%, 98.5%)	93.3% (42/45)	(81.7%, 98.6%)
≥ 30 kg/m²	86.2% (25/29)	(68.3%, 96.1%)	100% (25/25)	(86.3%, 100%)	88.5% (23/26)	(69.8%, 97.6%)

Source: Table 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

Table 40: SVR12 Rates by Selected Baseline Characteristics among GT1 Subjects in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
IL28B						
CC	85.7% (12/14)	(57.2%, 98.2%)	100% (13/13)	(75.3%, 100%)	100% (10/10)	(69.2%, 100%)
CT	87.8% (36/41)	(73.8%, 95.9%)	94.9% (37/39)	(82.7%, 99.4%)	92.7% (38/41)	(80.1%, 98.5%)
TT	92.3% (12/13)	(64.0%, 99.8%)	93.8% (15/16)	(69.8%, 99.8%)	88.9% (16/18)	(65.3%, 98.6%)
Baseline HCV RNA (IU/mL)						
< 800,000	92.3% (24/26)	(74.9%, 99.1%)	100% (31/31)	(88.8%, 100%)	92.5% (37/410)	(79.6%, 98.4%)
≥ 800,000	85.7% (36/42)	(71.5%, 94.6%)	91.9% (34/37)	(78.1%, 98.3%)	90.3% (28/31)	(74.2%, 98.0%)
Baseline ALT						
≤ 1.5 x ULN	79.3% (23/29)	(60.3%, 92.0%)	94.4% (34/36)	(81.3%, 99.3%)	91.2% (31/34)	(76.3%, 98.1%)
> 1.5 x ULN	94.9% (37/39)	(82.7%, 99.4%)	96.9% (31/32)	(83.8%, 99.9%)	91.9% (34/37)	(78.1%, 98.3%)
Baseline CPT score						
CPT A	100% (3/3)	(29.2%, 100%)	100% (4/4)	(39.8%, 100%)	85.7% (6/7)	(42.1%, 99.6%)
CPT B	87.7% (57/65)	(77.2%, 94.5%)	95.2% (59/69)	(86.5%, 99.0%)	91.5% (54/59)	(81.3%, 97.2%)
CPT C	0/0	n/a	100% (2/2)	(15.8%, 100%)	100% (5/5)	(47.8%, 100%)
Baseline MELD score						
< 10	88.9% (24/27)	(70.8%, 97.6%)	100% (21/21)	(83.9%, 100%)	95.0% (19/20)	(75.1%, 99.9%)
10 – 15	86.8% (33/38)	(71.9%, 95.6%)	93.2% (41/44)	(81.3%, 98.6%)	89.1% (41/46)	(76.4%, 96.4%)
16 – 20	100% (3/3)	(29.2%, 100%)	100% (3/3)	(29.2%, 100%)	100% (5/5)	(47.8%, 100%)
21 – 25	0/0	n/a	0/0	n/a	0/0	n/a
Prior HCV treatment history						
TN	91.7% (22/24)	(73.0%, 99.0%)	92.6% (25/27)	(75.7%, 99.1%)	89.2% (33/37)	(74.6%, 97.0%)
TE	86.4% (33/44)	(72.6%, 94.8%)	97.6% (40/41)	(87.1%, 99.9%)	94.1% (32/34)	(80.3%, 99.3%)

Source: Table 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

Table 41: SVR12 Rates by Demographics among GT3 Subjects in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
Age at baseline (years)						
< 65 years	50.0% (7/14)	(23.0%, 77.0%)	84.6% (11/13)	(54.6%, 98.1%)	45.5% (5/11)	(16.7%, 76.6%)
≥ 65 years	0/0	n/a	0/0	n/a	100% (1/1)	(2.5%, 100%)
Sex at birth						
Male	37.5% (3/8)	(8.5%, 75.5%)	71.4% (5/7)	(29.0%, 96.3%)	54.5% (6/11)	(23.4%, 83.3%)
Female	66.7% (4/6)	(22.3%, 95.7%)	100% (6/6)	(54.1%, 100%)	0% (0/1)	(0.0%, 97.5%)
Race						
Black or African American	0/0	n/a	0/0	n/a	0% (0/1)	(0.0%, 97.5%)
White	50% (7/14)	(23.0%, 77.0%)	83.3% (10/12)	(51.6%, 97.9%)	50% (5/10)	(18.7%, 81.3%)
Other	0/0	n/a	100% (1/1)	(2.5%, 100%)	100% (1/1)	(2.5%, 100%)
Ethnicity						
Hispanic or Latino	33.3% (1/3)	(0.8%, 90.6%)	100% (3/3)	(29.2%, 100%)	100% (3/3)	(29.2%, 100%)
Not Hispanic or Latino	54.5% (6/11)	(23.4%, 83.3%)	80.0% (8/10)	(44.4%, 97.5%)	33.3% (3/9)	(7.5%, 70.1%)
BMI at baseline						
< 30 kg/m²	28.6% (2/7)	(3.7%, 71.0%)	87.5% (7/8)	(47.3%, 99.7%)	75.0% (3/4)	(19.4%, 99.4%)
≥ 30 kg/m²	71.4% (5/7)	(29.0%, 96.3%)	80.0% (4/5)	(28.4%, 99.5%)	37.5% (3/8)	(8.5%, 75.5%)

Source: Table 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

Table 42: SVR12 Rates by Selected Baseline Characteristics among GT3 Subjects in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	**95% CI**	**SVR12 rate**	**95% CI**	**SVR12 rate**	**95% CI**
IL28B						
CC	50.0% (2/4)	(6.8%, 93.2%)	100% (6/6)	(54.1%, 100%)	71.4% (5/7)	(29.0%, 96.3%)
CT	50.0% (4/8)	(15.7%, 84.3%)	80.0% (4/5)	(28.4%, 99.5%)	20.0% (1/5)	(0.5%, 71.6%)
TT	50.0% (1/2)	(1.3%, 98.7%)	50.0% (1/2)	(1.3%, 98.7%)	0/0	n/a
Baseline HCV RNA (IU/mL)						
< 800,000	50% (2/4)	(6.8%, 93.2%)	60.0% (3/5)	(14.7%, 94.7%)	66.7% (2/3)	(9.4%, 99.2%)
≥ 800,000	50% (5/10)	(18.7%, 81.3%)	100% (8/8)	(63.1%, 100%)	44.4% (4/9)	(13.7%, 78.8%)
Baseline ALT						
≤ 1.5 x ULN	50.0% (4/8)	(15.7%, 84.3%)	83.3% (5/6)	(35.9%, 99.6%)	37.5% (3/8)	(8.5%, 75.5%)
> 1.5 x ULN	50.0% (3/6)	(11.8%, 88.2%)	85.7% (6/7)	(42.1%, 99.6%)	75.0% (3/4)	(19.4%, 99.4%)
Baseline CPT score						
CPT A	0/0	n/a	100% (2/2)	(15.8%, 100%)	0/0	n/a
CPT B	50.0% (7/14)	(23.0%, 77.0%)	80.0% (8/10)	(44.4%, 97.5%)	50.0% (6/12)	(21.1%, 78.9%)
CPT C	0/0	n/a	100% (1/1)	(2.5%, 100%)	0/0	n/a
Baseline MELD score						
< 10	28.6% (2/7)	(3.7%, 71.0%)	100% (5/5)	(47.8%, 100%)	75.0% (3/4)	(19.4%, 99.4%)
10 – 15	66.7% (4/6)	(22.3%, 95.7%)	75.0% (6/8)	(34.9%, 96.8%)	37.5% (3/8)	(8.5%, 75.5%)
16 – 20	0/0	n/a	0/0	n/a	0/0	n/a
21 – 25	100% (1/1)	(2.5%, 100%)	0/0	n/a	0/0	n/a
Prior HCV treatment history						
TN	50.0% (3/6)	(11.8%, 88.2%)	80.0% (8/10)	(44.4%, 97.5%)	60.0% (3/5)	(14.7%, 94.7%)
TE	50.0% (4/8)	(15.7%, 84.3%)	100% (3/3)	(29.2%, 100%)	42.9% (3/7)	(9.9%, 81.6%)

Source: Table 15.9.2.1.5 in ASTRAL-4 Interim Clinical Study Report

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues.

5.2 Collective Evidence

The NDA included the interim CSR for four pivotal studies, i.e, ASTRAL-1 to 4. These four studies were randomized and multicenter trials with the same primary efficacy endpoint of SVR12 rate. ASTRAL-1 randomized HCV GT1, 2, 4, and 6 subjects with and without compensated cirrhosis to receive either 12 weeks of SOF/VEL or placebo. Subjects infected with HCV GT5 were assigned 12 weeks of SOF/VEL. The placebo arm was for purpose of comparative safety only since none of placebo subjects were expected to achieve SVR12. ASTRAL-2 was an active-controlled trial conducted in HCV GT2 subjects with and without compensated cirrhosis to compare 12 weeks of SOF/VEL with the standard of care of SOF plus RBV for 12 weeks. ASTRAL-3 had a similar design to ASTRAL-2 but was conducted in HCV GT3 subjects with and without compensated cirrhosis. The study compared 12 weeks of SOF/VEL against an approved regimen of 24 weeks of SOF plus RBV. ASTRAL-4 investigated three SOF/VEL-containing regimens in HCV subjects with decompensated cirrhosis. The three regimens in the study included 12 weeks of SOF/VEL, 12 weeks of SOF/VEL plus RBV, and 24 weeks of SOF/VEL. The active-controlled design was not feasible for subjects with decompensated cirrhosis because no IFN-free DAA-based regimens were approved for the patient population.

In ASTRAL-1to 3, SVR12 rates above 95% were observed for 12 weeks of treatment with, and the SVR12 rates were significantly higher than the pre-specified threshold or the rate for the active control. In ASTRAL-1, the SVR12 rate for 12 weeks of SOF/VEL was as high as 99% in subjects infected with HCV GT1, 2, 4, 5 and 6 which was significantly superior to the pre-specified threshold of 85%. In ASTRAL-2, 12 weeks of SOF/VEL resulted in a significantly higher SVR12 rate than 12 weeks of SOF + RBV in subjects with HCV GT2 infection (99% vs. 94%). The results in ASTRAL-3 demonstrated that the 12-week SOF/VEL treatment was significantly superior to the 24-week SOF + RBV treatment in SVR12 rate among subjects infected with HCV GT3 (95% vs. 80%). Baseline cirrhotic status and previous HCV treatment history were the two randomization factors in ASTRAL-3. The pre-specified subgroup analyses demonstrated that, compared with 24-week SOF + RBV, the SVR12 rate for 12 weeks of SOF/VEL was approximately 25.0% higher (95% CI: [12%, 37%]) in HCV GT3 subjects with cirrhosis and 27% higher (95% CI: [12%, 40%]) among HCV GT3 TE subjects (Table 34). Results from ASTRAL-1 to 3 provided sufficient evidence that SOF/VEL for 12 weeks was effective in treatment of HCV infection without decompensated cirrhosis regardless of genotypes.

ASTRAL-4 showed the regimen of SOF/VEL + RBV for 12 weeks had the highest SVR12 rate (94%) compared with SOF/VEL for 12 weeks (83%) and SOF/VEL for 24 weeks (86%). The SVR12 rates of all three treatment groups were clearly superior to the assumed spontaneously

rate of 1%. Pairwise comparisons in SVR12 rate among the three treatment groups were not pre-specified. However, the reviewer's exploratory analyses showed that 12-week SOF/VEL + RBV had a nominally significantly higher SVR12 rate than 12-week SOF/VEL (p=0.031 based on Fisher's exact test) and not a significant finding compared to 24-week SOF/VEL (p=0.056 based on Fisher's exact test). Further exploratory subgroup analyses suggested the highest SVR12 rate observed in the 12-week SOF/VEL group was driven by the subjects with HCV GT1 and GT3 infections because the majority of the subjects in the study had GT1 (78%) and GT3 (15%) infections (Table 37). There was limited data for subjects with HCV GT2 and 4 infections. The study included only 12 GT2 subjects and eight GT4 subjects. Therefore, the differences in SVR12 rates across the three groups were not apparent in these two genotypes to draw any meaningful conclusions. Meanwhile, the study did not provide any evidence for GT5 and 6 infections since there were no GT5 subjects and only one GT6 subject in the study. A similar concern is that the higher SVR12 rate for SOF/VEL for 12 weeks versus the other two regimens was driven by the subjects with CPT class B cirrhosis because approximately 90% of subjects in ASTRAL-4 had CPT class B cirrhosis at baseline. There were only 16 subjects with CPT class A cirrhosis and 11 subjects with CPT class C cirrhosis in total. The sample sizes for subjects with CPT class A and C cirrhosis in the study were limited to make any reliable conclusion on the optimal regimen in these two classes.

5.3 Conclusions and Recommendations

The results from ASTRAL-1 to 3 indicated that the 12-week SOF/VEL regimen was effective in treatment of HCV infected-subjects with and without compensated cirrhosis. Based on the findings from ASTRAL-4, 12-week SOF/VEL + RBV regimen can be considered effective in treatment of subjects with HCV GT1 and 3 infections and CPT B cirrhosis. There were limited data for subjects with HCV GT 2, 4, 5, and 6 infections in ASTRAL-4 to determine the optimal regimen for these subsets. Similarly, the sample sizes for subjects with CPT A and C cirrhosis in ASTRAL-4 were too small to conclude the optimal regimen for the subgroups.

5.4 Labeling Recommendations

There is internal discussion on whether to recommend addition of RBV to SOF/VEL + RBV for 12 weeks in GT3 subjects with compensated cirrhosis. The reviewer is concerned about the insufficient data to support the recommendation. The treatment of 12 weeks of SOF/VEL + RBV was not evaluated in GT3 subjects with compensated cirrhosis in any Phase 3 studies. A randomized, open-label, dose-ranging Phase 2 trial (Study 0109) recruited 52 GT3 cirrhotic subjects. The study results showed that, among GT3 cirrhotic subjects, the SVR12 rate was 96% (25/26) with 95% CI of (70%, 98%) for 12-week SOF/VEL + RBV and 88% (23/26) with 95% CI of (80%, 100%) for 12-week SOF/VEL. Although adding RBV increased SVR12 rate by 8%, the treatment difference was not significant with 95% CI of (-28%, 10%) due to small sample sizes. Of note, the applicant is planning to conduct a (b) (4) trial (b) (4) to evaluate the regimens (b) (4) in subjects with GT3 HCV infection and (b) (4) cirrhosis. (b) (4)

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/s/

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