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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	205834
Supplement #:	17
Drug Name:	Harvoni® (Ledipasvir/Sofosbuvir 90/400 mg or 4 x 22.5/100 mg)
Indication(s):	Treatment of adolescents and children with chronic hepatitis C virus infection
Applicant:	Gilead Sciences, Inc.
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1. EXECUTIVE SUMMARY

Harvoni is a fixed-dose combination tablet of ledipasvir (LDV) and sofosbuvir (SOF) (90/400 mg). Harvoni-containing regimens are approved to treat adult subjects infected with HCV genotype (GT) 1, 4, 5 or 6 based on observed SVR12 rates above 90%. The applicant has submitted a supplemental NDA in order to extend the indication of Harvoni to adolescents 12 to < 18 years old.

The submission was based on the interim clinical study report for the adolescent group in an ongoing Phase 2 study, GS-US-337-1116. The study was an open-label and single arm trial to evaluate Harvoni with and without ribavirin in treatment of pediatric patients. Although the study included two age groups, only Group 1 consisting of adolescents 12 to <18 was provided in this submission. Group 1 enrolled 100 adolescent subjects infected with HCV GT1. All of the subjects received 12 weeks of Harvoni. The primary efficacy endpoint was the sustained virologic response (SVR12) rate defined as the proportion of subjects who had HCV RNA below the lower limit of quantitation 12 weeks after the end of treatment. The study results demonstrated that 12 weeks of Harvoni regimen led to a 98% SVR12 rate. However, only one subject had cirrhosis at baseline. Therefore, the reviewer concluded that the results from Group 1 provided sufficient evidence to support the regimen of Harvoni for 12 weeks in treatment of adolescent subjects with HCV GT1 infection without cirrhosis but did not provide enough evidence to support the regimen in treatment of adolescent cirrhotic subjects with HCV GT1 infection.

There were no major statistical issues.

2. INTRODUCTION

2.1 Overview

Treatment of adult subjects infected with HCV has been changing rapidly in the recent years. HCV treatment contained interferon (IFN) and ribavirin (RBV) before the year 2013. Since then, several IFN-free DAA-based regimens have been approved for HCV infection in adult subjects. Compared with the IFN-containing treatments, the IFN-free DAA-based therapies resulted in much higher SVR12 rates and fewer adverse events. However, no IFN-free DAA-containing regimens have been approved for pediatric patients. Therefore, the applicant conducted a study, i.e., GS-US-337-1116 to evaluate the pharmacokinetics (PK), efficacy, and safety of treatment with Harvoni with and without RBV for adolescents and children with HCV infection. The study consisted of adolescents 12 to < 18 years old (referred to as Group 1) and children 3 to < 12 years old (referred to as Group 2). This submission only included interim clinical study report for Group 1. Therefore, this review focuses on the efficacy results for Group 1.

Table 1: List of Study Included in Review

Trial ID	Design	Study Population	Treatment/ Sample Size	Endpoint/Analysis
GS-US-337-1116	multi-center, open-label, multi-cohort	pediatric subjects aged 3 to <18 years with chronic genotype 1, 3, 4, 5 or 6 infection	Group 1: adolescents of 12 to < 18 years old; Harvoni for 12 weeks, n=100 Group 2: children of 3 to < 12 years old Of note, Group 2 results were not included in this submission.	The primary efficacy endpoint was SVR12 rate. There was no formal hypothesis testing proposed.

2.2 Data Sources

The data were located in \\CDSESUB1\evsprod\NDA205834\0153\m5\datasets\gs-us-337-1116. In response to the review team's comments related to the inconsistency of SVR12 results between the submitted interim clinical study result for GS-US-337-1116 and the published study results (Balisteri *et al* 2016), the updated SVR12 results provided by the applicant on January 2017 can be accessed at \\CDSESUB1\evsprod\NDA205834\0166\m1\us\111-info-amendment.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data in this NDA is good. During the course of review, the medical reviewer noticed inconsistent SVR12 rates between the submitted interim clinical study report and the manuscript "The Safety and Effectiveness of Ledipasvir-Sofosbuvir in Adolescents 12 to 17 Years Old With Hepatitis C Virus Genotype 1 Infection" (Balisteri *et al* 2016). An Information Request was issued to the applicant. The applicant clarified that one subject was lost to follow up after the Week 4 study visit through the Week 12 post-treatment visit but returned for the post-treatment Week 24 visit. The subject achieved SVR24 and therefore was considered as having achieved SVR12. The applicant provided the updated SVR12 results.

3.2 Evaluation of Efficacy

3.2.1 Study Design

GS-US-337-1116 was a phase 2, open-label, multi-cohort, 2-part study to evaluate the safety and efficacy of Harvoni with and without RBV in pediatric subjects aged 3 to < 18 years with chronic genotype 1, 3, 4, 5 or 6 HCV infection. The study consisted of a PK lead-in phase and a treatment phase. Although the study evaluated included pediatric subjects as young as 3 years of

age, this submission only included data for Group 1, consisting of adolescents 12 to <18 weighing ≥ 45 kg. The interim analyses were done after all subjects in Group 1 had completed the post-treatment Week 12 visit or had prematurely discontinued from the study.

In the PK lead-in phase in Group 1, the regimen of LDV/SOF 90/400 mg was evaluated and confirmed by analyzing PK, safety and antiviral activity of LDV/SOF through 10 days. Subjects in the PK lead-in phase were required to be treatment naïve (TN) without a history of cirrhosis.

Subjects who completed the PK lead-in phase were immediately enrolled into the treatment phase with no interruption of study drug administration. An additional 90 subjects were planned to be recruited in the treatment phase. Up to 40 subjects were allowed to be treatment experienced (TE). The planned treatment regimens and durations were based on country of enrollment, genotype, treatment experience, and cirrhosis status as shown in Table 2. All subjects were to complete post-treatment Weeks 4, 12 and 24 visits regardless of their treatment duration. Of note, although the study was designed to enroll subjects with different HCV genotypes, all subjects in Group 1 had HCV GT1 infection.

Table 2: Planned Treatment Regimens in Group 1 in GS-US-337-1116

	United Kingdom	United States/Australia/New Zealand
Treatment Naive with or without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6[a]	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Treatment Experienced without Cirrhosis		
Genotype 1	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotypes 4, 5, or 6[a]	LDV/SOF 12 weeks	LDV/SOF 12 weeks
Genotype 3	LDV/SOF + RBV 24 weeks	N/A
Treatment Experienced with Cirrhosis		
Genotype 1	LDV/SOF 24 weeks	LDV/SOF 24 weeks
Genotypes 4, 5, or 6[a]	LDV/SOF 24 weeks	LDV/SOF 12 weeks
Genotype 3	LDV/SOF + RBV 24 weeks	N/A

a During the enrollment period for Group 1, screening included genotypes 1, 3, and 4 according to the original protocol and amendments 1 to 3 (Section 7.2).

Source: Table 7-1 in GS-US-337-1116 Interim Clinical Study Report

There were no control arm or pre-specified hypothesis testing proposed to evaluate efficacy. However according to the FDA Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry Revision 2 published in May 2016, pediatric trials in general are to provide confirmatory PK data and a safety database of about 100 patients. With respect to efficacy, pediatric extrapolation of efficacy is acceptable for HCV drugs since the course of HCV infection and the effects of DAAs are sufficiently similar between

adult and pediatric populations. Pediatric trials are to assess whether SVR rates are comparable to those observed in adult trials.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Table 3 shows the patient disposition. All enrolled subjects received at least one dose of study medicine. Among all treated subjects, only one subject (subject 09907-52140) discontinued the study drug prematurely.

Table 3: Patient Disposition in GS-US-337-1116

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis	**Treatment-experienced Without cirrhosis**	**Total**
Number of enrolled	80	20	100
Number of treated	80 (100%)	20 (100%)	100 (100%)
Discontinued study drug	1 (1.3%)	0	1 (1.0%)
Lost to follow-up	1 (1.3%)	0	1 (1.0%)

Source: Table 8-2 in GS-US-337-1116 Interim Clinical Study Report

Patient demographics are provided in Table 4. Among the 100 adolescent subjects enrolled in the study, the mean (standard deviation [SD]) age was 15 (1.7) years. The majority were females (63%), white (90%) and enrolled in the US sites (91%).

Table 4: Patient Demographics in GS-US-337-1116

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis (N=80)	**Treatment-experienced Without cirrhosis (N=20)**	**Total (N=100)**
Age (years)			
Mean (SD)	15 (1.7)	15 (1.7)	15 (1.7)
Median	15	15	15
Q1, Q3	13, 16	13, 16	13, 16
Min, Max	12, 17	12, 17	12, 17
Gender			
Male	30 (37.5%)	7 (35%)	37 (37.0%)
Female	50 (62.5%)	13 (65%)	63 (63.0%)
Race			
Black or African American	7 (8.8%)	0	7 (7.0%)
White	71 (88.8%)	19 (95.0%)	90 (90.0%)
Asian	2 (2.5%)	0	2 (2.0%)
Not disclosed	0	1 (5.0%)	1 (1.0%)
Ethnicity			
Hispanic or Latino	10 (12.5%)	3 (15.0%)	13 (13.0%)
Not Hispanic or Latino	68 (85.0%)	17 (85.0%)	85 (85.0%)
Not disclosed	2 (2.5%)	0	2 (2.0%)

Source: Table 8-2 in GS-US-337-1116 Interim Clinical Study Report
[1]summarized by the statistical reviewer

(to be continued)

Table 4: Patient Demographics in GS-US-337-1116 (continued)

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis (N=80)	**Treatment-experienced Without cirrhosis (N=20)**	**Total (N=100)**
Country1			
Australia	7 (8.8%)	1 (5.0%)	8 (8.0%)
United Kingdom	0	1 (5.0%)	1 (1.0%)
United States	73 (91.3%)	18 (90.0%)	91 (91.0%)
Baseline Body Mass Index (kg/m^2)			
Mean (SD)	22.9 (5.55)	23.2 (4.37)	23.0 (5.32)
Median	20.9	22.2	21.0
Q1, Q3	18.6, 26.0	19.9, 24.7	19.0, 25.9
Min, Max	13.1, 36.6	17.6, 31.7	13.1, 36.6

Source: Table 8-2 in GS-US-337-1116 Interim Clinical Study Report

Table 5 shows selected baseline disease characteristics. All subjects had GT1 HCV infection, with 81% having GT1a HCV infection and 19% having GT1b HCV infection. Overall, 80% of the treated subjects were treatment-naïve and 20% were treatment-experienced. There was only one subject with cirrhosis at baseline, and 57% of subjects had missing information on their cirrhotic status at baseline. The majority of the subjects had non-CC (CT or TT) IL28B alleles (76%) and baseline ALT ≤ 1.5 x ULN (74%). The mean (SD) HCV RNA value at baseline was 6.0 (0.55) $\log_{10}$ IU/mL.

Table 5: Selected Baseline Disease Characteristics in GS-US-337-1116

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis (N=80)	**Treatment-experienced Without cirrhosis (N=20)**	**Total (N=100)**
HCV genotype			
GT1a	66 (82.5%)	15 (75.0%)	81 (81.0%)
GT1b	14 (17.5%)	5 (25.0%)	19 (19.0%)
Cirrhosis			
No	31 (38.8%)	11 (55.0%)	42 (42.0%)
Yes	1 (1.3%)	0	1 (1.0%)
Unknown	48 (60.0%)	9 (45.0%)	57 (57.0%)
IL28B			
CC	20 (25.0%)	4 (20.0%)	24 (24.0%)
CT	42 (52.5%)	11 (55.0%)	53 (53.0%)
TT	18 (22.5%)	5 (25.0%)	23 (23.0%)
Baseline HCV RNA ($\log_{10}$IU/mL)			
Mean (SD)	6.0 (0.55)	6.1 (0.56)	6.0 (0.55)
Median	6.0	6.3	6.0
Q1, Q3	5.6, 6.4	5.6, 6.6	5.6, 6.4
Min, Max	4.7, 7.0	5.0, 6.8	4.7, 7.0
< 800,000 IU/mL	36 (45.0%)	9 (45.0%)	45 (45.0%)
≥ 800,000 IU/mL	44 (55.0%)	11 (55.0%)	55 (55.0%)

Source: Table 8-5 in GS-US-337-1116 Interim Clinical Study Report

(to be continued)

Table 5: Selected Baseline Disease Characteristics in GS-US-337-1116

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis (N=80)	**Treatment-experienced Without cirrhosis (N=20)**	**Total (N=100)**
Baseline ALT			
≤ 1.5 x ULN	61 (76.3%)	13 (65.0%)	74 (74.0%)
> 1.5 x ULN	19 (23.8%)	7 (35.0%)	26 (26.0%)
Responses to prior HCV treatment			
Nonresponder	0	13 (65.0%)	13 (65.0%)
Relapse/breakthrough	0	6 (30.0%)	6 (30.0%)
Unknown (Interferon intolerant)	0	1 (5.0%)	1 (5.0%)

Source: Table 8-5 in GS-US-337-1116 Interim Clinical Study Report

3.2.3 Statistical Methodologies

The efficacy analyses were performed in pediatric subjects who received at least one dose of Harvoni (referred as "All Treated" in this report). The SVR12 rate along with the 95% exact confidence interval based on the Clopper-Pearson method were calculated.

3.2.4 Results and Conclusions

Table 6 summarizes the applicant's results for the virologic outcome at posttreatment Week 12. The results were confirmed by the reviewer. Overall, the SVR12 rate was 98% with 95% CI of (93.0%, 99.8%). No subject experienced on-treatment virologic failure or relapse. Furthermore, the SVR12 rate was 97.5% with 95% CI of (91.3%, 99.7%) in treatment-naïve subjects and 100% with 95% CI of (83.2%, 100%) in treatment-experienced subjects.

Table 6: Applicant's Results for SVR12 (All Treated)

	Harvoni 12 weeks		
	Treatment-naïve with or without cirrhosis (N=80)	**Treatment-experienced without cirrhosis (N=20)**	**Total (N=100)**
SVR12 [95% exact CI[1]]	97.5% (78/80) [91.3%, 99.7%]	100% (20/20) [83.2%, 100%]	98.0% (98/100) [93.0%, 99.8%]
Not achieving SVR12			
On-treatment failure	0% (0/80)	0% (0/20)	0% (0/100)
Relapse	0% (0/80)	0% (0/20)	0% (0/100)
Other	2.5% (2/80)	0% (0/20)	2.0% (2/100)

Source: Tables 2 and 3 in applicant's responses on January to FDA request for information dated 06 January 2017 (\\CDSESUB1\evsprod\NDA205834\0166\m1\us\111-info-amendment)

[1]based on the Clopper-Pearson method

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There were only two subjects that did not achieve SVR12. The high response rates and small sample sizes in most of the subgroups precluded any meaningful interpretations based on the subgroup analyses.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues.

5.2 Collective Evidence

The submission was based on the interim clinical study report for Study GS-US-337-1116. The study was an open-label, single arm trial to evaluate Harvoni with and without ribavirin in treatment of pediatric patients. The submission included data for HCV GT1 adolescent subjects 12 to <18 years old. The study demonstrated that 12 weeks of the Harvoni regimen resulted in high SVR12 response rates for the 100 enrolled subjects. Specifically, SVR12 rates of 97.5% with 95% CI of (91.3%, 99.7%) and 100% with 95% CI of (83.2%, 100%) were observed in treatment-naïve and treatment-experienced adolescent subjects, respectively.

5.3 Conclusions and Recommendations

The results provided evidence to support the regimen of Harvoni for 12 weeks in treatment of adolescent subjects with HCV GT1 infection without cirrhosis. However, the study did not provide adequate evidence to support the regimen for the treatment of adolescent subjects with HCV GT1 infection with cirrhosis since only one subject in the study had cirrhosis at baseline.

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