CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212480Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

VIROLOGY REVIEW
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
NDA 204671 SDN 460; NDA 212480 SDN 1
Review Completed: 05/29/19

Reviewer: LALJI MISHRA, Ph.D.
Date Submitted: 02/28/19
Date Received: 02/28/19
Date Assigned: 03/5/19

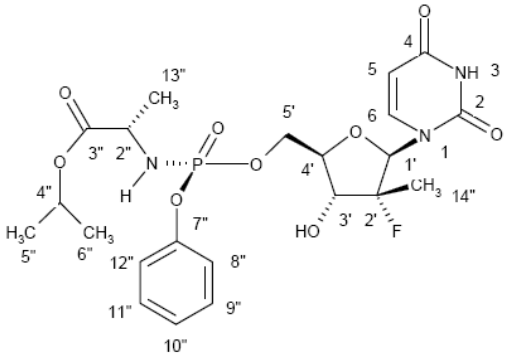
Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Product Names:

a. **Proprietary:** SOVALDI®
b. **Non-proprietary:** sofosbuvir
c. **Chemical:**

Sofosbuvir: (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy) phosphorylamino) propanoate

Structure



SOFOSBUVIR

Molecular Formula: $C_{22}H_{29}FN_3O_9P$
Molecular Weight: 529.46
Drug Category: Antiviral

Indication:

- Adult patients with genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis as a component of combination antiviral treatment regimen.
- Pediatric patients 3 years of age and older with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin.

Dosage Form/Route of Administration: Oral/tablet or granules

For adult (b) (4) one 400 mg tablet taken once daily with or without food.
For pediatric patients 3 years (b) (4) 150 mg to 400 mg sofosbuvir tablet, or oral granules per day with or without food.

Additional submissions reviewed:

Supplement #	Date of Correspondence	Date of Receipt	Date Assigned
N204671 SDN 463	03/14/19	03/14/19	03/14/19
N204671 SDN 470	07/10/19	07/10/19	07/10/19
N212480 SDN 001	02/28/19	02/28/19	03/5/19
N212480 SDN 002	03/14/19	03/14/19	03/14/19
N212480 SDN 011	07/10/19	07/10/19	07/10/19

Abbreviations:

BLAST, basic local alignment search tool; EC_{50}, effective concentration at 50%; FDC, fixed-dose combination; FU, follow-up visit; GT, genotype; HBV, hepatitis B virus; HBcAb, hepatitis B virus core antibody; HBsAb, antibody against hepatitis B virus surface protein; HBsAg, hepatitis B virus surface protein antigen; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; IFN, recombinant human interferon; LiPA, line probe assay; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; SVR4, 12 and 24, sustained virologic response at 4 , 12 and 24 weeks after end of treatment

BACKGROUND

Gilead Sciences Inc. (GSI) has submitted an efficacy supplement to NDA 204671 in support of the approval of SOVALDI tablets for use in the treatment of hepatitis C virus (HCV) infection in pediatric patients. In addition, GSI has submitted an original NDA 212480 in support of the marketing approval of SOVALDI oral granules for the treatment of HCV infection in pediatric patients. SOVALDI is currently indicated for the treatment of HCV infection in adults and pediatric patients 12 years of age and older or weighing at least 35 kg. In support of the marketing approval and proposed labeling changes, the sponsor has submitted results of Study GS-US-334-1112 entitled “A Phase 2, Open-Label, Multicenter, Multi-cohort Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir + Ribavirin in Adolescents and Children with Genotype 2 or 3 Chronic HCV Infection”.

Study GS-US-334-1112 is also submitted in fulfillment of PMR 2110-1 which states the following:

Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOVALDI in pediatric subjects 3 to 17 years of age with chronic hepatitis C.

The original NDA for SOVALDI tablets was approved by the FDA for the treatment of chronic hepatitis C virus genotype 1 infection on 6th December 2013.

Study GS-US-334-1112

Title: A Phase 2, Open-Label, Multicenter, Multi-cohort, Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir + Ribavirin in Adolescents and Children with Genotype 2 or 3 Chronic HCV Infection

OBJECTIVES

Primary

- **Pharmacokinetic (PK) lead-in phase:** To evaluate the steady state PK and confirm the dose of SOF in HCV-infected pediatric subjects
- **Treatment phase:** To evaluate the safety and tolerability of SOF+RBV for 12 or 24 weeks in HCV-infected pediatric subjects with genotype 2 or 3 HCV infection, respectively

Secondary

- **PK lead-in phase:** To evaluate the safety and tolerability of SOF+RBV for 7 days in HCV-infected pediatric subjects

Treatment phase:

- To determine the antiviral efficacy of SOF+RBV treatment in subjects with genotype 2 or genotype 3 HCV infection separately, as assessed by the proportion of subjects with sustained virologic response (SVR) 12 weeks after completion of treatment (SVR12)
- To determine the antiviral efficacy of SOF+RBV treatment in subjects with genotype 2 or genotype 3 HCV infection separately, as assessed by the proportion of subjects with SVR 4 and 24 weeks after completion of treatment (SVR4 and SVR24)
- To evaluate the kinetics of circulating HCV RNA during treatment and after completion of treatment
- To evaluate the emergence of viral resistance to SOF during treatment and after completion of treatment
- To evaluate the palatability of SOF oral granules at Day 1, as applicable.
- To evaluate the effect of growth and development on pediatric subjects during and after Treatment

The exploratory objective of this study was as follows:

To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy and/or tolerability of medical therapies through genetic discovery research (e.g., pharmacogenomics), in subjects who provided their separate and specific consent

Study Design

Please note the efficacy results and resistance analyses presented in this NDA submission for subjects 12 to 18 years are the same as previously reviewed by Dr. Lisa K. Naeger. Please refer to Virology Review of NDA 204671 SDN 337 dated 01/09/17 for efficacy and resistance analysis for subjects 12 to 18 years enrolled in study GS-US 344-1112.

This review includes efficacy and resistance analysis for subjects 6 to <12 years and 3 to <6 years enrolled in study GS-US 344-1112.

This is an open-label, multi-cohort, 2-part study evaluating the PK, safety, and efficacy of SOF+RBV in chronic HCV-infected pediatric subjects with genotype 2 or genotype 3 HCV infection.

Approximately 100 subjects were planned to be enrolled: approximately 50 adolescent subjects 12 to <18 years old and approximately 50 pediatric subjects 3 to <12 years old. Subjects could be either treatment naive or treatment experienced, with up to 20 subjects allowed to be treatment experienced.

Subjects in 3 age groups were enrolled in a sequential fashion: 12 to <18 years old, followed by 6 to <12 years old, and 3 to <6 years old.
Subjects received the following regimen based on HCV genotype:
-Subjects with genotype 2 HCV infection: SOF+RBV for 12 weeks
-Subjects with genotype 3 HCV infection: SOF+RBV for 24 weeks

The study consisted of a PK lead-in phase and a treatment phase.

PK Lead-in Phase

The PK lead-in phase evaluated and/or confirmed the dose of SOF by analyzing PK and safety of SOF administered in combination with RBV through 7 days of dosing for each cohort. Three cohorts, each with at least 10 treatment-naive subjects with genotype 2 or genotype 3 HCV infection, were sequentially enrolled:

- Cohort 1: 12 to <18 years old weighing ≥45 kg
- Cohort 2: 6 to <12 years old weighing ≥17 kg and <45 kg
- Cohort 3: 3 to <6 years old

Weight limits were defined for the subjects enrolled in the PK lead-in phase cohorts only. Weight limits for Cohort 1 and Cohort 2 did not apply to additional subjects of each age group enrolled in the treatment phase.

Intensive PK and safety results through Day 7 of treatment for each cohort were reviewed to confirm the appropriateness of the evaluated SOF dose prior to initiating the treatment phase of that age group and determining the age-appropriate dose to be evaluated in the PK lead-in phase of the next age group.

Treatment Phase

Subjects who participated in the PK lead-in phase were immediately rolled over into the treatment phase with no interruption of study drug administration. The first visit in the treatment phase for these subjects was the Week 2 visit.

Additional treatment-naive or treatment-experienced subjects with genotype 2 or genotype 3 HCV infection were enrolled into the treatment phase upon confirmation of the age-appropriate SOF dose from the PK lead-in phase. Weight limits for Cohort 1 and Cohort 2 did not apply to additional subjects of each age group enrolled in the treatment phase. The treatment phase was initiated sequentially by age group as defined in Cohort 1, 2, and 3 of the PK lead-in phase. No additional subjects were enrolled in the treatment phase in the 3 to <6 year old cohort.

After completing all required study visits, subjects who attained SVR24, or those who did not attain SVR24 and did not initiate experimental or approved anti-HCV therapy, could enroll in a long term registry (Study GS-US-334-1113) for assessment of growth, quality of life, and long-term viral suppression (if applicable).

Microbiology Specific Inclusion Criteria

Subjects who met all of the following inclusion criteria were eligible for participation in the study:

1. Ages 3 years to <18 years (consent of parent or legal guardian required).
2. PK lead-in only: subjects in Cohort 1 (age 12 to <18 years old) must weigh ≥45 kg.
3. PK lead-in only: subjects in Cohort 2 (age 6 to <12 years old) must weigh ≥17 kg and <45 kg.
4. PK lead-in only: all subjects must be treatment naïve.
5. Treatment experienced subjects: must have had prior treatment failure to a regimen including IFN either with or without RBV that was completed at least 8 weeks prior to Baseline/Day 1.
6. HCV infection documented by either:
   a) a positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test at least 6 months prior to the Day 1 visit, or
   b) a liver biopsy performed prior to the Day 1 visit with evidence of chronic HCV infection.

7. Infection with HCV genotype 2 or genotype 3 as determined at screening.
8. HCV RNA ≥1000 IU/mL at screening.

Microbiology Specific Exclusion Criteria

Subjects with any of the following exclusion criteria were not eligible for participation in the study:

1. Decompensated liver disease defined as international normalized ratio (INR) >1.2 x the upper limit of normal (ULN), platelets <50,000/mm^3, serum albumin <3.5 g/dL, or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy, varicea hemorrhage).
2. Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency).
3. Evidence of hepatocellular carcinoma or other malignancy (with the exception of certain resolved skin cancers).
4. Coinfection with HIV-1, acute hepatitis A virus (HAV), or hepatitis B virus (HBV).
5. Known hypersensitivity to the study drugs, the metabolites or formulation excipients.

Treatments Administered

Treatment Regimen:

Following screening and confirmation of eligibility by the investigator, 106 subjects (52 subjects 12 to <18 years old, 41 subjects 6 to <12 years old, and 13 subjects 3 to <6 years old) were assigned to the following regimen based on HCV genotype:

- Subjects with genotype 2 HCV infection: SOF+RBV for 12 weeks
- Subjects with genotype 3 HCV infection: SOF+RBV for 24 weeks

SOF dosages:

- Subjects 12 to <18 years old enrolled in the PK lead-in phase or in the treatment phase: SOF 400 mg orally once daily + weight-based RBV orally divided twice daily
  - Subjects completed a swallowability assessment at screening up to Day 1 using placebo-to-match tablets to assess acceptability of the 400-mg tablet.
  - Subjects who were determined unable to swallow the placebo-to-match SOF 400-mg tablet repeated the assessment with a placebo-to-match for the SOF 100-mg tablet size. The tablet size determined the number of tablets to be administered each day (1 × 400 mg tablet, or 4 × 100 mg tablets).
  - Subjects unable to swallow the placebo-to-match SOF 100-mg tablet received the granule formulation (8 × 50-mg capsules containing the SOF granules). Prior to administration, the SOF granules were removed from the capsules and administered orally with water or food.

- Subjects 6 to <12 years old enrolled in the PK lead-in phase or in the treatment phase: SOF 200 mg orally once daily + weight-based RBV orally divided twice daily
  - Subjects completed a swallowability assessment at screening up to Day 1 using placebo-to-match tablets to assess acceptability of the 100-mg tablet.
  - Subjects unable to swallow the placebo-to-match SOF 100-mg tablet received the granule formulation (4 × 50-mg capsules containing the SOF granules). Prior to administration, the SOF granules were removed from the capsules and administered orally with water or food.
- Subjects 3 to <6 years old enrolled in the PK lead-in phase (no additional subjects were enrolled in the treatment phase):
  - If weight was ≥17 kg: SOF 200 mg orally once daily + weight-based RBV orally divided twice daily
  - if weight was <17 kg: SOF 150 mg orally once daily + weight-based RBV orally divided twice daily
  - Subjects received the granule formulation: 200 mg/day (4 × 50-mg capsules containing the SOF granule formulation) or 150 mg/day (3 × 50-mg capsules containing the SOF granule formulation). Prior to administration, the SOF granules were removed from the capsules and administered orally with water or food.

RBV dosages:

Weight-based RBV divided dose is described in Section 5.3.2 of the protocol (NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 42).

Assay Methodology

HCV antibody, HIV-1, HIV-2 antibody, HBs antigen, and HAV antibody tests were performed at screening

Determination of HCV genotype and subtype

HCV genotype and subtype was determined at screening by the Siemens VERSANT® HCV Genotype INNO-Line Probe 2.0 Assay. Additionally, subtype was confirmed by BLAST analyses of NS5A and NS5B sequences.

Plasma samples were collected at Day 1 and on Weeks 1, 2, 4, 8, 12,16, 20, 24 and at an early termination and at post-treatment Weeks 4, 12 and 24 and stored for potential HCV sequencing and other virology studies.

HCV RNA Quantification

Blood samples were collected to determine serum levels of HCV RNA at screening, baseline/Day 1, and at each study visit during the on-treatment and posttreatment periods.

The COBAS® AmpliPrep/COBAS®TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The lower limit of quantitation (LLOQ) of the assay was 15 IU/mL.

HCV RNA was quantified at baseline/Day 1, Day 3, at Weeks 1, 2, 4, 8, 12, 16, 20, 24 and at early termination and at post-treatment week 4, 12 and 24.

Viral Resistance Monitoring

The HCV nonstructural protein (NS)5B coding regions were amplified by (b) (4) using standard reverse transcription polymerase chain reaction (RT-PCR) technology. Following amplification, the polymerase chain reaction (PCR) products were deep sequenced with a 1% cutoff.

Baseline NS5B deep sequencing analysis was performed for all subjects. For resistance-associated variant (RAV) analysis was performed at a 15% assay cutoff.

Comment

The sponsor stated that a 15% cutoff was found to be more clinically meaningful (NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 53).

For subjects with virologic failure, deep sequencing of HCV NS5B was performed at the first virologic failure time point with HCV RNA >1000 IU/mL. Amino acid substitutions in NS5B for the samples collected at virologic failure were compared with the respective baseline sequence for each subject and reported using a 15% cutoff.

Virology Data

Electronic HCV baseline or postbaseline sequencing data were extracted directly from the (b) (4) to Gilead. The Gilead Clinical Virology team processed all sequencing data and stored the results electronically in the Gilead Virology Database.

HCV RNA Result Reporting Conventions

When the calculated HCV RNA value was within the linear range of the assay, then the result was reported as the "<<numeric value>>IU/mL." In this report, this result is referred to as the numeric result or as "≥ LLOQ detected" for a categorical result.

When HCV RNA was not detected, the result was reported as "No HCV RNA detected" or "target not detected." In this report, this result is referred to as "< LLOQ target not detected" or "< LLOQ TND."

When the HCV RNA IU/mL was < LLOQ of the assay, the result was reported as "<15 IU/mL HCV RNA detected." In this report, this result was referred to as "< LLOQ detected."

The overall category of HCV RNA <LLOQ included "<LLOQ TND" and "<LLOQ detected."

For numerical HCV RNA data, values < LLOQ were set to the LLOQ minus 1 (i.e., 14 HCV RNA IU/mL). HCV RNA values returned as "No HCV RNA detected" were also set to 14 IU/mL.

Primary Efficacy Endpoint

The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of the study drug, in the Full Analysis Set.

Secondary Efficacy Endpoints

Proportion of Subjects with SVR4 and SVR24

The proportions of subjects with SVR4 and SVR24, defined as HCV RNA < LLOQ at 4 and 24 weeks, respectively, after discontinuation of study drug, were summarized.

Virologic Failure

Virologic outcomes, including the proportion of subjects with SVR12, overall virologic failure (with subgroups for on-treatment virologic failure and relapse), and other (those who did not achieve SVR12 and did not meet virologic failure criteria) were summarized. On-treatment virologic failure (breakthrough, rebound, and nonresponse) and relapse were defined as follows:

- On-treatment virologic failure:
  - Breakthrough: HCV RNA ≥LLOQ after having previously had HCV RNA <LLOQ, while on treatment, confirmed with 2 consecutive values (note: the second confirmation value could have been posttreatment), or last available on-treatment measurement with no subsequent follow-up values
  - Rebound: >$\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note: the second confirmation value could have been posttreatment), or last available on-treatment measurement with no subsequent follow-up values
  - Nonresponse: HCV RNA persistently ≥ LLOQ through 8 weeks of treatment

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

I. Disposition of Study Subjects

- **6 to <12 Years Old**

All 41 subjects that (sic) were enrolled received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set (13 subjects with genotype 2 HCV infection treated for 12 weeks and 28 subjects with genotype 3 HCV infection treated for 24 weeks).

All subjects (100.0%) completed study treatment.

The majority of subjects had been infected through vertical transmission (97.6%). Among subjects with genotype 2 HCV infection (n=13), 7 had the genotype 2b subtype, 4 had the genotype 2a/2c subtype, and 2 could not be subtyped at screening. Among the subjects with genotype 3 infection (n=28), all were genotype 3a. The majority of subjects had non-CC (CT or TT) IL28B alleles (65.9%), and HCV RNA <800,000 IU/mL (53.7%) with a mean (SD) baseline HCV RNA value of 5.7 (1.07) $\log_{10}$ IU/mL. No subjects had known cirrhosis based on prior biopsy. The mean (SD) baseline ALT value was 54 (87.7) U/L; and 22.0% of subjects had baseline ALT values> 1.5 x ULN.

- **3 to <6 Years Old**

All 13 subjects that (sic) were enrolled received at least 1 dose of study drug and were included in the Safety Analysis Set and Full Analysis Set (5 subjects with genotype 2 HCV infection treated for 12 weeks and 8 subjects with genotype 3 HCV infection treated for 24 weeks).

Twelve of 13 subjects (92.3%) completed study treatment. One subject prematurely discontinued study treatment due to AEs of product use issue (the subject spit up the dose) and abnormal product taste.

The majority of subjects in the 2 treatment groups had been infected through vertical transmission (84.6%). Among subjects with genotype 2 HCV infection (n=5), 4 had the genotype 2b subtype, and HCV from 1 subject could not be subtyped at screening. Among subjects with genotype 3 HCV infection (n=8), all had the genotype 3a subtype. The majority of subjects had non-CC (CT or TT) IL28B alleles (76.9%). The majority of subjects had HCV RNA <800,000 IU/mL (76.9%) and a mean (SD) baseline HCV RNA value of 5.4 (0.81) $\log_{10}$ IU/mL. No subjects had known cirrhosis based on prior biopsy. The mean (SD) baseline ALT value was 31 (17.5) U/L; and 7.7% of subjects had baseline ALT values > 1.5 x ULN.

II. Efficacy Evaluations

II (a). 6 to <12 Years Old

The key efficacy endpoint was SVR12, defined as HCV RNA <LLOQ 12 weeks after completion of treatment with the study drug, in the Full Analysis Set.

At screening, for eligibility HCV genotype was determined by Line Probe assay. Genotype and subtype were subsequently determined by BLAST analyses of NS5B sequences from deep sequencing.

BLAST analyses of NS5B sequences provided the HCV subtype for 2 subjects whose HCV subtype was undetermined by Line Probe assay. In addition, BLAST analyses of NS5B sequences provided a refinement of HCV subtype for 4 subjects whose HCV subtype were initially determined as 2a/2c at screening by Line Probe assay. HCV genotype/subtype was confirmed for the other 35 subjects. Table 1 summarizes the HCV subtype determination and refinement based on BLAST analysis

Table 1: Summary of BLAST Sequencing-based Subtype Updates for Subjects 6 to <12 Years Old (Source: NDA 204671 SDN 460 , Study GS-US-334-1112 Final Clinical Study Report, Page 122 Table 40)

HCV Subtype at Screening	Number of Subjects	BLAST Sequencing-Based HCV Genotype
2	2	2a (n = 1) 2i (n = 1)
2a/2c	4	2a (n = 2) 2c (n= 2)

Table 2 presents SVR12 and SVR24 by sequence based BLAST HCV genotype/subtype. Overall, 41 of 41 subjects in the Resistance Analysis Population achieved SVR12 .

Table 2: SVR12 and SVR24 by BLAST Sequencing-based Genotype/Subtype for Subjects 6 to <12 Years Old (Source: NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 123 Table 41)

Subtype	Number of Subjects N = 41	SVR12 and SVR24 n/N (%)
GT2 Total	**13**	**13/13 (100%)**
2a	3	3/3 (100%)
2b	7	7/7 (100%)
2c	2	2/2 (100%)
2i	1	1/1 (100%)
GT3 Total	**28**	**28/28 (100%)**
3a	28	28/28 (100%)
Total	**41**	**41/41 (100%)**

GT = genotype

Table 2 shows that all subjects with genotype 2 HCV infection treated for 12 weeks with SOF+RBV and subjects with genotype 3 HCV infection treated for 24 weeks with SOF+RBV achieved SVR12. The concordance between SVR12 and SVR24 was 100.0% for both treatment groups.

No subject had on-treatment virologic failure i, e., breakthrough, rebound, or nonresponse) or relapsed

II (b). 3 to <6 Years Old

Sequence-based BLAST analyses of NS5B sequences provided HCV subtype for 1 subject for whom HCV subtype was not determined at screening by Line Probe assay. HCV genotype/subtype was confirmed for the other 11 subjects who could be sequenced.

Table 3 summarizes the subtype determination based on BLAST analysis.

Table 3: Summary of BLAST Sequencing-based Subtype Determination for Subjects 3 to <6 years old (Source: NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 133, Table 50)

HCV Subtype at Screening	Number of Subjects	BLAST Sequencing-Based HCV Genotype
2	1	2b (n = 1)

Table 4 presents the virologic outcome for 3 to <6 years old subjects.

Table 4.: Virologic Outcomes for 3 to <6 Years Old Subjects (Source: NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 126, Table 45)

	3 to < 6 Years Old SOF 200 mg or 150 mg + RBV	
	Genotype 2 12 Weeks (N=5)	Genotype 3 24 Weeks (N=8)
SVR12	4/5 (80.0%)	8/8 (100.0%)
Overall Virologic Failure	0/5	0/8
Other	1/5 (20.0%)	0/8

Results presented in Table 4 are summarized as follows:

- One of 5 subjects with genotype 2 HCV infection treated for 12 weeks (20.0%) did not achieve SVR12 due to premature discontinuation of the study. This subject is characterized as " other".
- Subjects with genotype 3 HCV infection who received SOF+RBV for 24 weeks: 8/8 subjects (100%) achieved SVR12.

- No subject had on-treatment virologic failure (i. e., breakthrough, rebound, or nonresponse) or relapsed

The sponsor stated that the SVR4 and SVR24 results for subjects with both genotype 2 and genotype 3 HCV infection treated for 12 and 24 weeks, respectively, were the same as the SVR12 results. For both subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype 3 HCV infection treated for 24 weeks, concordance between SVR12 and SVR24 was 100%.

III. Resistance Analysis

HCV NS5B Resistance-Associated Variants

The sponsor stated that for the purposes of this report, nucleoside analog polymerase inhibitor resistance-associated substitutions were defined as follows: S96T, N142T, L159F, E237G, S282T, S282 variant other than S282T, C/M289I/L, L320F/I/V, and V321A/I, and were reported at 15% assay cutoff.

In addition to the above substitutions, the following NS5B resistance-associated polymorphisms were searched for in resistance datasets

D61G, A112T, C316N and S473T (identified in previous study (b) (4)

III (a). NS5B Resistance-Associated Polymorphism in Baseline Isolates from Subjects 6 to <12 Years Old

Pretreatment full-length NS5B deep sequencing data were obtained from 40/41 subjects. A short fragment of NS5B was obtained for 1 subject with genotype 3 HCV infection.

At the 15% cutoff, NS5B resistance-associated polymorphisms were detected in baseline isolates from 2/41 subjects.

Table 6: Subjects 6 to <12 Years Old with Baseline NS5B Polymorphisms and Treatment Outcome Age Group) (Source: NDA 204671 SDN 460 Resistance Data for Study GS-US-334-1112 In DAVP Template Format)

Subject ID	HCV Subtype	Treatment	Cirrhosis (Y/N)	TN/TE	Baseline NS5B RAV	Treatment Outcome (Yes)
(b) (6)	2b	SOF+ RBV for 12 Weeks	Unknown	TN	M289I	SVR12/SVR24
	2b	SOF+ RBV for 12 Weeks	N	TN	M289I	SVR12/SVR24

Comments

1. Baseline isolates from 2/41 subjects in the 6 to <12 years age group had the NS5B resistance-associated polymorphism M289I.
2. Subjects with baseline polymorphism M289I achieved SVR12 and SVR24.
3. Baseline NS5B polymorphism did not impact SVR12 and SVR24 outcome**.**

III (b). NS5B Resistance-Associated Polymorphism in Baseline Isolates from Subjects 3 to <6 Years Old

The sponsor stated that one of the 13 subjects with virologic outcome of " other" was not included in the Resistance Analysis population. Full-length NS5B deep sequencing data were obtained for baseline isolates from 11 out of 12 subjects. Full-length and short-fragment NS5B amplification was not successful for 1 subject with genotype 3a HCV infection due to assay failure.

The sponsor stated that baseline isolates from none of 11 subjects harbored NS5B resistance-associated polymorphisms with a 15% cutoff. All subjects (11/11) included in the resistance analysis plan achieved SVR12 and SVR24 (NDA 204671 SDN 460, Study GS-US-334-1112 Final Clinical Study Report, Page 134, Table 51).

IV. Treatment-Emergent NS5B Substitution in a Virologic Failure Subjects (6 to <12 Years old and 3 to <6 Years Old)

No subject in 6 to <12 years and also in 3 to <6 years age group experienced on-treatment viral breakthrough or relapse through post treatment Week 12 or post-treatment Week 24. One of the 5 subjects (b) (6) with genotype 2 HCV infection in 3 to <6 years age group did not achieve SVR12 due to premature discontinuation of the study.

CONCLUSIONS

In this NDA submission, the efficacy and safety of sofosbuvir + ribavirin in 6 to <12 years and 3 to <6 years old pediatric subjects with chronic genotype 2 and 3 infection were evaluated. Forty-one subjects 6 to <12 years old received SOF+ RBV (dose depending on the body weight). Genotypes of HCV were first determined using INNO-Line Probe assay at screening and confirmed by BLAST analyses of NS5B sequences.

NS5B resistance-associated polymorphism M289I was detected only in baseline isolates from 2/41 (4.9%) subjects in 6 to <12 years age group. Baseline NS5B resistance-associated polymorphisms had no impact on SVR12 and SVR24 outcome. Subjects with NS5B baseline polymorphisms achieved SVR12/SVR24. All subjects(n=41) in 6 to <12 yeas age group (GT2, n=13 and GT3, n=28) achieved SVR12 and SVR24. There was a 100% concordance between SVR12 and SVR24. Similarly, 12/13 subjects in 3 to <6 years age group (GT2, n=4 and GT3, n= 8) achieved SVR12 and SVR24. One subject in the GT2 group (1/5) prematurely discontinued treatment. However, none of the other GT2 subjects (n=4) and none of the GT3 subjects (n=8)

experienced virologic failure (breakthrough, relapse through posttreatment Week 24 or nonresponse).

REFERENCES

Naeger, L.K. Virology Review of NDA 204671SE-006 SDN 377 dated 01/09/17.

MICROBIOLOGY LABEL

The sponsor did not propose any change in the Microbiology section of the label.
DAVP concurs with the current version of the microbiology label.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus *[see Microbiology (12.4)]*.

12.4 Microbiology

Mechanism of Action

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with IC_{50} values ranging from 0.7 to 2.6 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 micromolar. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.062 micromolar for genotype 1a (range 0.029–0.128 micromolar; N=67), 0.102 micromolar for genotype 1b (range 0.045–0.170 micromolar; N=29), 0.029 micromolar for genotype 2 (range 0.014–0.081 micromolar; N=15) and 0.081 micromolar for genotype 3a (range 0.024–0.181 micromolar; N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 micromolar, respectively. The presence of 40% human serum had no effect

on the anti-HCV activity of sofosbuvir. Evaluation of sofosbuvir in combination with interferon alpha or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. An M289L substitution developed along with the S282T substitution in genotype 2a, 5 and 6 replicons. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Trials

In a pooled analysis of 982 subjects who received SOVALDI in Phase 3 trials, 224 subjects had post-baseline NS5B genotypic data from next generation nucleotide sequencing (assay cutoff of 1%).

Treatment-emergent substitutions L159F (n=6) and V321A (n=5) were detected in postbaseline samples from GT3a-infected subjects across the Phase 3 trials. No detectable shift in the phenotypic susceptibility to sofosbuvir of subject isolates with L159F or V321A substitutions was seen. The sofosbuvir-associated resistance substitution S282T was not detected at baseline or in the failure isolates from Phase 3 trials. However, an S282T substitution was detected in one genotype 2b subject who relapsed at Week 4 post-treatment after 12 weeks of sofosbuvir monotherapy in the Phase 2 trial P7977- 0523 [ELECTRON]. The isolate from this subject displayed a mean 13.5-fold reduced susceptibility to sofosbuvir. For this subject, the S282T substitution was no longer detectable at Week 12 post-treatment by next generation sequencing with an assay cutoff of 1%.

In the trial done in subjects with hepatocellular carcinoma awaiting liver transplantation where subjects received up to 48 weeks of sofosbuvir and ribavirin, the L159F substitution emerged in multiple subjects with GT1a or GT2b HCV who experienced virologic failure (breakthrough and relapse). Furthermore, the presence of substitutions L159F and/or C316N at baseline was associated with sofosbuvir breakthrough and relapse post-transplant in multiple subjects infected with GT1b HCV. In addition, S282R and L320F substitutions were detected on-treatment by next generation sequencing in a subject infected with GT1a HCV with a partial treatment response.

The clinical significance of these substitutions is not known.

Cross Resistance

HCV replicons expressing the sofosbuvir-associated resistance substitution S282T were susceptible to NS5A inhibitors and ribavirin. HCV replicons expressing the ribavirin associated substitutions T390I and F415Y were susceptible to sofosbuvir. Sofosbuvir was active against HCV replicons with NS3/4A protease inhibitor, NS5B non-nucleoside inhibitor and NS5A inhibitor resistant variants.

RECOMMENDATION

With respect to virology, NDA 204671 SE-014 and NDA 212480 are approvable.

_____
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