Clinical, Clinical Virology, and Cross-Discipline Team Leader Summary Review

Date	November 22, 2024
From	Timothy Jancel, PharmD, MHS Patrick Harrington, PhD Jules O'Rear, PhD Stephanie Troy, MD
Subject	Clinical, Virology, and Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	Sovaldi • NDA 204671 / S19 • NDA 212480 / S-04 Harvoni • NDA 205834 / S36 • NDA 212477 / S-06
Applicant	Gilead Sciences, Inc.
Date of Submission	June 27, 2024
PDUFA Goal Date	December 27, 2024
Proprietary Name	Sovaldi Harvoni
Established or Proper Name	Sofosbuvir (Sovaldi) Ledipasvir and sofosbuvir (Harvoni)
Dosage Form(s)	Sovaldi • Tablet (400 mg, 200 mg of sofosbuvir) • Pellets (200 mg, 150 mg of sofosbuvir) Harvoni • Tablet ▪ 90 mg of ledipasvir and 400 mg of sofosbuvir ▪ 45 mg of ledipasvir and 200 mg of sofosbuvir • Pellets ▪ 45 mg of ledipasvir and 200 mg of sofosbuvir ▪ 33.75 mg of ledipasvir and 150 mg of sofosbuvir
Applicant Proposed Indication(s)/ Population(s)	Treatment of chronic hepatitis C virus in adult and pediatric patients
Applicant Proposed Dosing Regimen(s)	Refer to labeling
Recommendation on Regulatory Action	*Approval*

INTRODUCTION

On June 28, 2023, the Applicant submitted the final Clinical Study Report (CSR) for Study GS-US-334-1113 (Study 1113), which was conducted in response to Pediatric Research Equity Act (PREA) postmarking requirements (PMRs) 2110-2 (NDA 204671, Sovaldi) and 2780-2 (NDA 205834, Harvoni). The Applicant stated that they did not intend to use the final results from Study 1113 to update labeling for Sovaldi or Harvoni. After a PREA Non-Compliance Letter was sent to the Applicant on May 22, 2024, the Applicant subsequently submitted labeling supplements for Sovaldi and Harvoni with updates to 6.1 *Clinical Trials Experience* and 8.4 *Pediatric Use* on June 27, 2024.

This Summary Review assesses the Applicant's submissions and proposed labeling for Sovaldi and Harvoni. In addition, please refer to the following reviews in DARRTS: Clinical Virology Review (July 27, 2023) and Clinical Review (May 23, 2024).

BACKGROUND

Sovaldi (sofosbuvir, SOF) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor. Harvoni is a fixed-dose combination (FDC) tablet of SOF and ledipasvir (LDV), an HCV NS5A inhibitor.

The approval letters for NDAs 204671 (Sovaldi) and 205834 (Harvoni) included the following PREA PMRs:

> NDA 204671 / PMR 2110-2 (December 06, 2013)
> *Collect and analyze long-term safety data for subjects enrolled in the pediatric SOVALDI (sofosbuvir) pharmacokinetic, safety and efficacy trial described in 2110-1. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of sofosbuvir in pediatric subjects, including growth assessment, sexual maturation and characterization of sofosbuvir resistance-associated substitutions in viral isolates from subjects failing therapy.*
>
> *Final Protocol Submission: 10/2014*
> *Trial Completion: 02/2023*
> *Final Report Submission: 08/2023*
>
> For reference, PMR 2110-1 stated the following:
> *Conduct a trial to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOVALDI (sofosbuvir) as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.*
>
> NDA 205834 / PMR 2780-2 (October 10, 2014)
> *Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.*
>
> *Final Protocol Submission: 05/15/2014*
> *Trial Completion: 02/28/2023*
> *Final Report Submission: 08/31/2023*
>
> *Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies.*

On June 28, 2023, the Applicant submitted the final CSR (Report Body) for Study 1113, *A Long-Term Follow-up Registry for Adolescent and Pediatric Subjects Who Received a Gilead Hepatitis C Virus Direct Acting Antiviral (DAA) in Gilead-Sponsored Chronic Hepatitis C Infection Trials*. The Applicant stated that the submission of this CSR completed the fulfillment of PREA PMRs 2110-2

(Sovaldi) and 2780-2 (Harvoni), and they did not intend to use Study 1113 to update Sovaldi or Harvoni labeling. However, reports of required pediatric postmarketing studies must be submitted as an NDA or as a supplement to the approved NDA with the proposed labeling changes the Applicant believes are warranted based on the data derived from this study. Therefore, the CSR for Study 1113 did not fulfill PREA PMRs 2110-2 and 2780-2.

On May 22, 2024, the Applicant was issued a PREA Non-Compliance Letter and was also asked to submit draft labeling as supplements, incorporating changes since the last approval of the Prescribing Information and FDA-approved patient labeling. Subsequently, on June 27, 2024, labeling supplements were submitted for Sovaldi and Harvoni.

REVIEW

Please refer to the following reviews of Study 1113 in DARRTS for full details:

- Clinical Review (May 23, 2024)
- Clinical Virology Review (July 27, 2023)

Clinical Summary
We agree with the Applicant's conclusions from Study 1113. No notable effects of Sovaldi and Harvoni were observed during the follow-up on growth of participants as assessed by changes from baseline through end of study on height, weight, and body mass index percentiles and Z-scores for any age group or on the development and sexual maturation of participants as assessed by changes from baseline through end of study in Tanner pubertal stages. In addition, all participants who were enrolled in Study 1113 and had achieved sustained virologic response at 12 weeks (SVR12) in the parent study maintained SVR through end of the registry.

Clinical Virology Summary
We agree with the Applicant's conclusion that all participants who were enrolled in Study 1113 and had achieved SVR12 in the parent study maintained SVR through the end of the registry. Across all trials of sofosbuvir-based regimens represented in the long-term follow-up study, participants were followed for a median duration of 1450 days (~4 years) after achieving SVR12.

During the review of this application, we noted that the following statement in Section 12.4 *Microbiology* of the Harvoni labeling is no longer accurate: *"No data are available on the persistence of ledipasvir or sofosbuvir resistance-associated substitutions."* One pediatric participant in Study 1113 who did not achieve SVR12 (relapse) following ledipasvir/sofosbuvir treatment in parent treatment study GS-US-337-1116 had virus at the time of relapse with a treatment-emergent, NS5A Y93H ledipasvir resistance-associated substitution, and Y93H remained detected through at least Week 144 of follow-up. Furthermore, multiple other studies of ledipasvir and other HCV NS5A inhibitors have demonstrated that NS5A resistance-associated substitutions can persist for an extended duration after virologic failure (e.g., see Wyles et al., 2018). Therefore, this section of labeling was updated accordingly (see below).

CONCLUSIONS

We agree with the Applicant's assessment and have agreed to final labeling changes.

RECOMMENDATIONS

The following final labeling changes were agreed to with the Applicant:

Sovaldi

- 6.1 *Clinical Trials Experience*
  In a 5-year follow-up study, 88 of the 106 subjects from the Phase 2 open-label clinical trial (Study 1112) were followed for a median (Q1, Q3) duration of 239 (179, 244) weeks. No notable effects on growth assessed by changes from baseline through end of study were observed for height, weight, BMI percentiles, and Z-scores for any age group. No notable effects were observed on the development of secondary sexual characteristics of subjects as assessed by changes from baseline through end of study in Tanner pubertal stages *[see Use in Specific Populations (8.4)]*.
- 8.4 *Pediatric Use*
  In a 5-year follow-up study, the long-term effects of SOVALDI on pediatric growth were assessed in 88 pediatric subjects 3 years of age and older treated with SOVALDI in Study 1112. No notable effects on growth from baseline through end of study were observed *[see Adverse Reactions (6.1)]*. All subjects who had achieved SVR12 maintained SVR through end of study.

Harvoni

- 6.1 *Clinical Trials Experience*
  In a 5-year follow-up study, 178 of the 226 subjects from the Phase 2 open-label clinical trial (Study 1116) were followed for a median (Q1, Q3) duration of 239 (143, 244) weeks. No notable effects on growth assessed by changes from baseline through end of study were observed for height, weight, BMI percentiles, and Z-scores for any age group. No notable effects were observed on the development of secondary sexual characteristics of subjects as assessed by changes from baseline through end of study in Tanner pubertal stages *[see Use in Specific Populations (8.4)]*.
- 8.4 *Pediatric Use*
  In a 5-year follow-up study, the long-term effects of HARVONI on pediatric growth were assessed in 178 pediatric subjects 3 years of age and older treated with HARVONI in Study 1116. No notable effects on growth from baseline through end of study were observed *[see Adverse Reactions (6.1)]*. All subjects who had achieved SVR12 maintained SVR through end of study.
- 12.4 *Microbiology*
  Persistence of Resistance-Associated Substitutions
  Certain NS5A inhibitor resistance-associated substitutions have been found to persist for >1 year in some patients. The long-term clinical impact of the emergence or persistence of virus containing ledipasvir or sofosbuvir resistance-associated substitutions is unknown.

  Previously:
  Persistence of Resistance-Associated Substitutions
  No data are available on the persistence of ledipasvir or sofosbuvir resistance-associated substitutions. NS5A resistance-associated substitutions for other NS5A inhibitors have been found to persist for >1 year in some patients. The long-term clinical impact of the emergence or persistence of virus containing ledipasvir or sofosbuvir resistance-associated substitutions is unknown.

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/s/

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