CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 8, 2014
From	Kimberly Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205834
Applicant	Gilead Sciences
Date of Submission	February 8, 2014
PDUFA Goal Date	October 10, 2014
Proprietary Name / Established (USAN) names	Harvoni (Ledipasvir/Sofosbuvir)
Dosage forms / Strength	Fixed Dose Combination Tablet (ledipasvir 90 mg/sofosbuvir 400 mg)
Proposed Indication(s)	Treatment of chronic hepatitis C infection
Recommended:	Approval pending satisfactory outcome from CMC inspections

1. Introduction

This cross-discipline team leader review presents the main findings for ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination (FDC) tablet for the treatment of chronic hepatitis C (CHC) genotype 1 infection. Ledipasvir (LDV) is a hepatitis C virus (HCV) inhibitor targeting the HCV NS5A protein, which is required for RNA replication and assembly of HCV virions. Sofosbuvir (SOF) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. SOF was approved on December 6, 2013, as a part of a combination regimen for the treatment of CHC genotype 1, 2, 3, and 4 infection and is the only NS5B inhibitor approved. LDV is the first direct acting antiviral agent (DAA) in the NS5A drug class submitted for marketing approval.

The Applicant submitted data from three Phase 3 trials in subjects with CHC genotype 1 infection who were treatment-naïve and in subjects who previously failed treatment with either pegylated interferon alfa and ribavirin (PR) or an HCV protease inhibitor in combination with PR. Data from these trials included subjects with and without cirrhosis.

This review highlights the safety and efficacy, virology, clinical pharmacology findings and overall benefit/risk assessment to support my recommendation for approval of this NDA. Brief comments regarding chemistry/manufacturing and controls and pharmacology/toxicology are also presented.

2. Background

Chronic HCV infection is a serious and life-threatening condition and can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV infection is a global health problem with an estimated 170 million individuals infected worldwide. In the United States, approximately 3 million people have chronic HCV infection.

The majority of cases of chronic HCV infection in the United States are genotype 1 (70-75%, predominately genotype 1a). The treatment of genotype 1 infection has rapidly evolved over the past three years. HCV drug development has focused on DAAs, which are designed to target specific steps in the HCV replication cycle. Prior to 2011 the standard of care was PR for 48 weeks. A PR regimen is poorly tolerated due to associated toxicities such as flu-like illness, depression and cytopenia. Sustained virologic response (SVR) rates for PR range 40-45%. Since 2011 four different HCV DAAs were approved. The first DAAs approved in 2011 were NS3/4A protease inhibitors (PIs), boceprevir and telaprevir. With these approvals the standard of care changed from PR to boceprevir or telaprevir in combination with PR. These regimens resulted in improved efficacy SVR rates (60-70%); however, tolerability and toxicity of this regimen remains because PR is still part of the regimen. The standard of care again changed in 2013 with the approvals of simeprevir (NS3/4A protease inhibitor) and SOF. Although both were approved in combination with PR in genotype 1 HCV-infected patients the overall treatment duration was reduced and SVR rates of up to 90% were achieved.

As noted the current standard of care still includes treatment with PR for genotype 1 HCV-infected subjects. Therefore, there is an unmet need for safe and effective treatment options that do not contain PR. The LDV/SOF regimen represents some important milestones in HCV drug development. Specifically, LDV/SOF FDC is the first regimen for genotype 1 HCV infection that does not include PR and combines two drugs from different DAA classes, of which LDV is the first in class for NDA submission.

Breakthrough therapy designation was granted on July 22, 2013. This NDA received a priority review under PDUFA V and was not presented at the Antiviral Products Advisory Committee because LDV/SOF received breakthrough designation and the benefit/risk assessment did not appear controversial based on the review team's preliminary assessment of the top line trial results.

LDV/SOF FDC tablet has not been marketed outside the United States to date; a marketing application is currently under consideration by the EMA.

21 CFR 300.50 describes FDA's policy for the approval of fixed combination prescription drugs for humans. The Federal Food, Drug and Cosmetics Act states in part, "Two or more drugs may be combined in a single dosage form when each

component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug" 21 CFR 300.50(a). The regulations are interpreted to require a factorial analysis of proposed combination ingredients to demonstrate the combination is more effective than each component of the combination alone. For HCV drugs, however, studying the efficacy of an FDC in a clinical study with a factorial design in which the entire combination would be compared to its individual components is not feasible or ethical. This type of study design requires HCV-infected individuals to be exposed to suboptimal regimens that could quickly result in drug resistance not only to the drug or drugs under study, but in many cases to other drugs from within the same class. Suboptimal therapy may jeopardize the success of future therapeutic options for those patients exposed to single treatment or risk disease progression.

In this scenario where components of the combination cannot be administered individually (more than few days) due to rapid development of resistance, other evidence to show the contribution of each agent to the combination is needed. The evidence to show the contribution of each agent to the combination comes from (1) the approval of SOF 400 mg QD as part of a combination regimen for genotype 1 subjects (NDA 204671), (2) monotherapy and dose ranging trial results for LDV and (3) the comparison of SVR rates between SOF+ PR and LDV/SOF.

The SVR12 rate for genotype 1 subjects receiving SOF + PR in one Phase 3 trial for 12 weeks was 89%. LDV proof-of-concept was established in a 3-day dose-ranging monotherapy trial evaluating LDV doses 1, 3, 10, 30 and 90 mg once daily. Results show a dose dependent response (reduction in HCV RNA) for doses 1 mg through 30 mg. No evidence of additional antiviral activity at 90 mg was seen; however, HCV RNA suppression was sustained for a longer period compared to the 30 mg dose. A phase 2 dose-ranging trial (GS-US-248-0120) LDV 30 mg and 90 mg in combination with two other investigational DAAs (vedroprevir and tegobuvir) with RBV for 12 and 24 weeks was conducted. LDV 90 mg group for 12 or 24 weeks had numerically higher SVR rates compared with LDV 30 mg group for 24 weeks, though not statistically different. However, the incidence of virologic breakthrough in the LDV 90 mg group was approximately half of that observed in the LDV 30 mg group. These data show the contribution of LDV to the regimen via dose response.

As mentioned the SVR rate in genotype 1 treatment-naïve subjects with SOF+PR for 12 weeks is 89%. In comparison, the SVR rate for LDV/SOF in treatment-naïve genotype 1 subjects from Phase 3 trials ranges from 94% - 99%. Collectively these data (monotherapy, dose ranging and Phase 3 cross-trial comparison results) show the contribution of LDV to the LDV/SOF FDC and satisfy 21 CFR 300.50. Based on cross trial comparison, SVR rates are numerically improved when LDV is combined with SOF compared to SOF+PR, thereby eliminating the need for a PR based regimen.

3. CMC/Device

Collectively the CMC review team cannot recommend approval of LDV/SOF at this time due to pending facilities review and inspections and agreement to monitor for the (b) (4) content of LDV. Addenda to reviews are expected following receipt and review of the final outcomes of the inspections.

- **General product quality considerations**

LDV/SOF FDC is a new molecular entity. LDV/SOF is for oral administration and each tablet contains 90 mg of LDV and 400 mg of SOF.

According to the CMC reviewer, Dr. George Lunn, the data presented in the NDA and amendments are adequate to assure composition, manufacturing process, and specifications for LSV/SOF FDC are appropriate. The expiration dating period of 24 months when stored below 30 degrees Celsius is supported by adequate data. No product quality microbiology issues were identified by Dr. Steven Donald. The proposed labeling is adequate pending minor revisions. The specified impurities were reviewed by Dr. Mark Powley and deemed adequate from a pharmacology/toxicology perspective.

The dissolution method and dissolution acceptance criterion were acceptable for both LDV and SOF. Adequate data were provided to support the discriminating ability of the dissolution method. The Applicant agreed to monitor for the (b) (4) content of the LDV component.

- **Facilities review/inspection**

The facilities review and inspections are pending.

4. Nonclinical Pharmacology/Toxicology

The preclinical evaluation of SOF was conducted for NDA 204671. This review focuses on the preclinical evaluation of LDV and the 2-year SOF carcinogenicity studies. The preclinical evaluation includes over 44 studies to assess the safety, pharmacology, pharmacokinetics, general toxicity, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and local tolerance, in mice, rats, dogs, rabbits and monkeys. Repeat dose studies were conducted in mice (4 weeks), rats (26 weeks), and dogs (39 weeks). Dr. Christopher Ellis recommended approval for this NDA based on the nonclinical pharmacology/toxicology findings.

- **General nonclinical pharmacology/toxicology considerations**

According to Dr. Ellis's assessment, no clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats and dogs for 1, 6, and 9 months respectively. No overlapping toxicities between LDV and SOF were noted. A potential LDV-related mild hepatobiliary signal was noted as evident by increases in ALT or

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