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APPLICATION NUMBER:

205834Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW: Eric F. Donaldson, Ph.D.
NDA#: 205834 **SDN** 002 **DATE REVIEWED:** 06/27/2014

Reviewer: Eric F. Donaldson, Ph.D.
Date Submitted: 02/10/14 **Date Assigned:** 02/10/14
Date Received: 02/10/14

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

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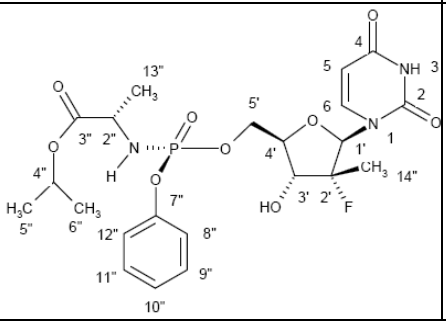
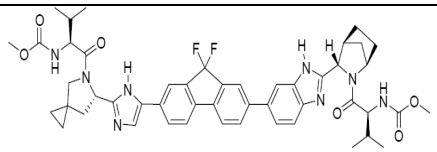
Amendments:

SDN	Date Submitted	Date Received	Date Assigned
002	02/10/2014	02/10/2014	02/10/2014

Related/Supporting Documents: IND115268, IND106739, NDA204671

Product Names	**Sofosbuvir (GS-7977)**	**Ledipasvir (GS-5885)**
Structures		
Chemical Names	(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	Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate
Molecular formula	$C_{22}H_{29}FN_3O_9P$	$C_{49}H_{54}F_2N_8O_6$
Molecular weight	529.46	889.00 Da

Drug category: Antiviral

Indication: Fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor and sofosbuvir, an HCV uridine nucleotide analog NS5B polymerase inhibitor, which is indicated for the treatment of chronic hepatitis C virus genotype 1 infection.

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Dosage Form/Route of administration: Oral

Dispensed: Rx

Abbreviations: BL, baseline; DAA, direct acting antiviral; EC_{50}, effective concentration at 50%; FC, fold-change; FDA, Food and Drug Administration; GT, genotype; HCV, hepatitis C virus; HSA, human serum albumin; IC_{50}, inhibitory concentration at 50%; IFN, recombinant human interferon α; mt, mitochondria; NGS, next generation sequencing; NAPI, nucleos(t)ide analog polymerase inhibitor; NNAPI, non-nucleoside analog polymerase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; PBL, peripheral blood lymphocytes; PDVF, protocol defined virologic failure; PEG, pegylated human interferon; PR, protease; P/R, pegylated interferon/ribavirin; RAV, resistance-associated variant; RBV, ribavirin; SDM, site-directed mutants; SOF, sofosbuvir; SVR, sustained virologic response; WT, wild-type.

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EXECUTIVE SUMMARY

This review focused on the next generation sequencing (NGS) data provided in support of NDA 205834 for the fixed-dose combination (FDC) of ledipasvir (LDV) and sofosbuvir (SOF; LDV/SOF) indicated for the treatment of hepatitis C virus (HCV) genotype (GT) 1 infection. Overall, assessment of the NGS data by the Division of Antiviral Products (DAVP) indicated that the data and analysis provided by the sponsor, Gilead Sciences (GSI), was acceptable and this NDA is approvable with respect to virology.

SOF (NDA 204671; approved December 2013) is a nucleotide prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is converted to the active uridine triphosphate form (GS-461203) within hepatocytes. It is an inhibitor of the NS5B RNA dependent RNA polymerase. 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 µM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.062 µM for genotype 1a (range 0.029-0.128 µM; N=67), 0.102 µM for genotype 1b (range 0.045-0.170 µM; N=29), 0.029 µM for genotype 2 (range 0.014-0.081 µM; N=15) and 0.081 µM for genotype 3a (range 0.024-0.181 µM; N=106). In infectivity assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a viruses were 0.03 µM and 0.02 µM, respectively.

LDV is a new molecular entity that inhibits HCV replication by interfering with the viral NS5A protein. It has antiviral activity against HCV genotype 1a and 1b replicons, with EC_{50} values of 0.031 nM and 0.004 nM, respectively. In addition, LDV has EC_{50} values ranging from 0.15 to 530 nM against genotypes 2 to 6 replicons. LDV has an EC_{50} value of 21 nM against the GT2a JFH-1 replicon with L31 in NS5A, but has a reduced activity with an EC_{50} value of 249 nM against the GT2a J6 HCV strain with M31, a common resistance-associated substitution in GT 1. LDV has less antiviral activity compared to GT1 against genotypes 4a, 5a, and 6a, with EC_{50} values of 0.39 nM, 0.15 nM and 1.1 nM, respectively. LDV has substantially lower activity against genotypes 3a and 6e with EC_{50} values of 168 nM and 264 nM, respectively.

Data from three phase 3 studies, including Study GS-US-337-0102 (ION-1; treatment-naïve subjects), Study GS-US-337-0108 (ION-3; treatment-naïve non-cirrhotic subjects), and Study GS-US-337-0109 (ION-2; treatment-experienced subjects) and two phase 2 studies, including Study P7977-0532 (ELECTRON) and Study GS-US-337-0118 (LONESTAR) were submitted for resistance analyses. Cell culture selection experiments were performed using the HCV GT1a and GT1b replicon systems to identify resistance-associated substitutions that emerged in NS5A in response to LDV. These experiments, along with phenotypic assessments, showed that Q30E and Y93H were associated with resistance to LDV in the HCV GT1a replicon and Y93H was the predominant resistance-associated substitution in the GT1b replicon (see the review of Clinical Virology Reviewer Lisa Naeger, Ph.D. for complete details). In the phase 2 and phase 3 clinical trials, additional resistance-associated substitutions were identified and phenotyped by the sponsor. According to

HCV GT1a and A92K or Y93H that emerges in HCV GT1b confer >1,000-fold reductions in susceptibility to LDV in cell culture. The L31M, L31I, L31V, Q30H, Q30R, Q30G, or P32L substitutions that emerge in HCV GT1a and the P58D substitution that emerges in HCV GT1b are in the 100- to 1,000-fold resistance category. The K24R, K24G, K24N, M28T, Q30L, Q30T, S38F, A92T, or Y93F substitutions that emerge in GT1a and the L31M, L31V, L31I, or P32L substitutions that emerge in GT1b are in the <100-fold resistance category. Based on these results, the LDV resistance analysis focused on, but was not limited to, these NS5A positions. NS5A polymorphisms at amino acid positions K24, M28, Q30, L31, P32L, H58, A92, and Y93 were analyzed in the FDA virology resistance analysis. Substitutions or mixtures of substitutions at these NS5A positions were detected at baseline in 23% (370/1615) of the subjects in the phase 3 studies (ION-1, ION-2, and ION-3).

For the virology analyses, relapse rates were used as the measure of efficacy outcome for the three phase 3 studies and the two phase 2 studies. The overall relapse rate was 2.7% in all the studies submitted. In GT1a subjects, the relapse rate was 3% (41/1378). In GT1b subjects, the relapse rate was 1.7% (7/411). When the effect of individual baseline NS5A polymorphisms on relapse rates was examined, the highest relapse rates were seen in subjects with baseline polymorphisms at positions Q30, L31, and Y93 where relapse rates were 6.6% (5/76), 10% (5/50), and 15% (8/54), respectively. Relapse rates for subjects with one baseline NS5A resistance-associated polymorphism were 3.6%, but were higher for subjects with 2 or 3 baseline NS5A resistance-associated polymorphisms with relapse rates of 9.5% and 9%, respectively.

There were a total of 50 subjects (GT1a=42 and GT1b=8) who failed treatment with the FDC of LDV/SOF and who comprised the resistance analysis population that was analyzed by next generation sequencing. The most common substitutions associated with resistance to LDV (as determined comparing three variant detection algorithms and only counting those detected by two) were at positions Y93 (n=19; GT1a=15 and GT1b=4), Q30 (n=14; GT1a=14 and GT1b=0), M28 (n=10; GT1a=9 and GT1b=1), L31 (n=6; GT1a=6 and GT1b=0), and H58 (n=3, GT1a=3 and GT1b=0).

For SOF resistance, there were several substitutions associated with resistance that had been identified in the review of SOF (NDA 204671), including positions S62 (n=23; GT1a=23 and GT1b=0), D61 (n=9; GT1a=9 and GT1b=0), E440 (n=8; GT1a=1 and GT1b=7), V321 (n=3; GT1a=2 and GT1b=1), L159 (n=1; GT1a=1 and GT1b=0), S282 (n=1; GT1a=1 and GT1b=0), and L320 (n=1; GT1a=1 and GT1b=0) that emerged in these studies. In addition, two additional amino acid positions had substitutions that were treatment emergent, including A112 (n=3, GT1a=3 and GT1b=0) and E237 (n=2; GT1a=2 and GT1b=0). Of note, in this dataset, substitutions at positions HCV GT1a NS5B_S62 and HCV GT1b NS5B_E440 appeared to be polymorphic and not associated with resistance as compared to the SOF dataset that was used to identify these positions (SOF NDA 204671, original review and addendum). However, the D61G substitution was treatment emergent and detected in the NS5B HCV protein of several subjects infected with HCV GT1a who failed treatment with the LDV/SOF FDC. This same substitution was detected and associated with treatment failure among subjects infected with HCV GT1a in the Liver Pre-Transplant Study P7977-2025 (reviewed in SOF NDA 204671 addendum). Additional substitutions that should be phenotypically evaluated for SOF resistance include, NS5B_A112T, NS5B_E237G, and NS5B_S473T.

BACKGROUND AND SUMMARY

Sofosbuvir is a nucleotide prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is converted to the active uridine triphosphate form (GS-461203) within the hepatocyte. 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 µM. The median EC_{50} values of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates were 0.062 µM for genotype 1a (range 0.029-0.128 µM; N=67), 0.102 µM for genotype 1b (range 0.045-0.170 µM; N=29), 0.029 µM for genotype 2 (range 0.014-0.081 µM; N=15) and 0.081 µM for genotype 3a (range 0.024-0.181 µM;

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