CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Decisional Review for NDA 205834

Date	September 23, 2014
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 205834/Original Submission
Proprietary / Established (USAN) names	Harvoni™ [ledipasvir (LDV)/sofosbuvir (SOF)]
Dosage forms / strength	Fixed-dose combination, 90 mg/400 mg tablets, once daily
Proposed Indication(s)	Indicated for the treatment of chronic hepatitis C (CHC) in adults with Genotype 1 infection
Action	Approval

1. Introduction to Review: This Division Director's memorandum provides a topline summary of NDA 205834 for Gilead Sciences' New Drug Application (NDA) for the fixed-dose combination of ledipasvir, an NS5A inhibitor and sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor for treatment of adult patients with Genotype 1 (GT1) infection. This decisional review summarizes pertinent findings from the original NDA submission and FDA's multidisciplinary reviews and product labeling.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:
Chronic hepatitis C viral infection is a public health burden. Based on NHANES data from 2003-2010, it is estimated that 2.7- 3.9 million people in the United States are infected with the virus. Most are unaware that they are infected and consequently treatment is not reaching those in need. With chronic infection, it is projected that there will be an increase in cases of hepatocellular carcinoma (HCC) with an estimated peak incidence in 2019 of 14,000 cases/year and decompensated cirrhosis with a projected peak incidence in 2020 of >145,000 cases/year (Davis, et al., Gastroenterology 2010) because the epidemic began decades ago with 75% of those with HCV in the United States born between 1945-1965 (CDC).

Treatment regimens have improved over the years based on better tolerability and enhanced effectiveness. In 2013, two new direct-acting antivirals were approved from two different classes. SOF, an HCV nucleotide analog NS5B polymerase inhibitor was approved in combination with ribavirin, with and without pegylated interferon for treatment of chronic hepatitis C (CHC) GT 1- 4 infection. SVR12 rates increased to 89% with this new direct-acting antiviral in combination with pegylated interferon and ribavirin (P/R) for CHC GT 1 viral infection. Simeprevir (SIM), an NS3/4A protease inhibitor was also approved for use in

combination with P/R in 2013. Overall SVR12 rates were 80% for GT1a and GT1b patients naïve to treatment. Off-label use of the combination of SOF and SIM in the COSMOS trial was recently published. Overall SVR rates from the COSMOS trial were 93% for the populations enrolled (Lawitz, et al., Lancet, 2014).

Treatment of CHC infection allows for a chance of virologic cure. Virologic cure as measured by sustained virologic response (SVR) 12 weeks after completion of treatment is associated with histologic benefit, a decrease in all-cause and liver-related mortality, and decreases in rates of HCC and hepatic decompensation (van der Meer, et al. JAMA 2012). Regarding treatment for CHC, current standards are outlined in the 2014 American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) treatment guidelines that were recently revised as of August 11, 2014.

The NDA for the FDC was submitted on February 8, 2014 and reviewed under the PDUFA V program. As previously mentioned, SOF was approved in 2013. LDV is the first drug in its class and the FDC is recommended for use in HCV GT1 patients based on Phase 3 clinical trials that enrolled both treatment-naïve and treatment-experienced patients. Duration of treatment is dependent on whether cirrhosis is present and other baseline factors. For example, the FDC is recommended for use for 12 weeks duration for GT1 patients who are treatment-naïve. A treatment duration of 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL based on an analysis of baseline predictors of relapse. A 24-week treatment duration is recommended for treatment-experienced patients with cirrhosis; treatment-experienced is defined as those patients who have failed treatment with either P/R or an HCV protease inhibitor plus P/R. See Table 1 below that is excerpted from product labeling.

Table 1 Recommended Treatment Duration

Patient Population	Treatment Duration
Genotype 1 Treatment-naïve +/- cirrhosis	12 weeks*
Genotype 1 Treatment-experienced** without cirrhosis	12 weeks
Genotype 1 Treatment-experienced** With cirrhosis	24 weeks

The FDC for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA < 6 million IU/mL

The safety and efficacy of LDV/SOF in pediatric patients have not been studied.

The application was granted a priority review because CHC is a serious and life-threatening disease and the FDC appeared to provide improvement in safety and effectiveness. In addition, the FDC was designated as a Breakthrough Therapy under FDASIA,Title IX because preliminary clinical evidence indicated substantial improvement over available therapies in the treatment of CHC-infected adults including the first ribavirin-free regimen for GT1.

The original NDA submission contained clinical data from three Phase 3 trials in GT1 CHC viral infection and Phase 2 trials as well as other studies that supported dose selection. ION-1 and ION-3 trials were conducted in treatment-naïve patients and ION-2 was conducted in patients who had previously failed a P/R regimen including subjects who may have failed a PI-based regimen.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), six domestic Phase 3 clinical trial sites underwent inspection. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

The application was not presented before the Antiviral Drugs Advisory Committee because a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

3. Chemistry/Manufacturing/Controls (CMC): The CMC reviewers of the LDV/SOF NDA are: Drs. George Lunn, Sandra Suarez and Steven Donald. Dr. Rapti Madurawe supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity and quality of the FDC; complete SOF drug substance data was provided in approved NDA 204671 and was incorporated in this NDA by reference. The CMC team is in agreement with the Applicant that the FDC contains 90 mg of LDV and 400 mg SOF and concluded the following:

The composition, manufacturing process and specifications for the FDC tablets are appropriate. Specifically, for LDV, there are two isolated intermediates that have acceptable specifications. Per Dr. Lunn's review, a reasonable specification that includes tests for appearance, identity, acetone content, water, assay, impurities, residual solvents, and elemental impurities is also provided.

The stability data contained in the FDC NDA support an expiry date of 24 months when stored at or below 30 degrees centigrade. Further, the container-closure system and labeling are appropriate.

An inspectional report has been completed and the outcome is satisfactory.

4. Pharmacology/Toxicology: Please see review of submitted nonclinical toxicology studies by Dr. Christopher Ellis, supervised by Dr. Hanan Ghantous.

The nonclinical safety profile of SOF has been previously reviewed under NDA 204671 with the exception of two-year carcinogenicity studies that were reviewed with this application. Per Dr. Ellis' review, the nonclinical safety profile of LDV has been evaluated in: safety pharmacology studies in rats and dogs; repeat-dose toxicology studies in mice, rats and dogs for up to 1, 6 and 9 months duration, respectively; up to two-week repeat-dose toxicology studies to qualify impurities; phototoxicity studies in mice and rats; fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; and genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* rat micronucleus assays). In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of LDV have been conducted; rat and mouse carcinogenicity studies with LDV are currently in progress.

Myocardial inflammation and degeneration occurred in rats administered oral GS-9851 doses, a 1:1 mixture of SOF and its diasteriomer, of 2,000 mg/kg/day in a 7-day toxicology study. Cardiac toxicity was not observed in rats administered oral doses of SOF up to 750 mg/kg/day for approximately 20 months, or in dogs and mice administered SOF up to 500 and 1,000 mg/kg/day for 9 and 3 months respectively, with corresponding exposures approximately 9-fold (rat), 17-fold (dog) and 24-fold (mouse) that in humans at the recommended SOF dose of 400 mg once daily. Nonetheless, cardiac effects seen in nonclinical studies were further examined in clinical trials and are summarized in Dr. Sarah Connelly's clinical review.

As described in Dr. Ellis' review, no clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats and dogs administered LDV doses of up to 300, 100 and 30 mg/kg/day for 1, 6 and 9 months, respectively. Therefore, no specific overlapping toxicity of potential significant clinical concern was identified in animals administered LDV or SOF alone. However, a potential LDV-related mild hepatobiliary toxicity signal (not considered adverse and not clearly dose-dependent) was noted, with slight increases in ALP and/or ALT associated with increased liver/gall bladder weight (high-dose males only) without correlating histopathology changes observed in mice following oral administration of LDV at up to 300 mg/kg/day ($AUC_{0\text{-}24hr}$~164 & 271 μg.h/ml for LDV in females and males, respectively). In addition, minimal-to-slight random foci of hepatocyte necrosis (males) and bile duct hyperplasia (males and females) were noted in rats following oral administration of LDV at up to 100 mg/kg/day ($AUC_{0\text{-}24hr}$~56 μg.h/ml for LDV). These non-adverse hepatobiliary findings were observed at LDV AUC exposure ~8- and 30-fold higher, in rats and mice respectively, than in humans at the recommended LDV dose. In addition, slight increases in cholesterol and triglycerides were noted in rats at 100 mg/kg/day. In dogs, no clear clinically relevant LDV-related findings were

observed following oral administration of LDV at up to 30 mg/kg/day (AUC_{0-24hr}~41.3 & 80.3 μg.h/ml for LDV in males and females, respectively), resulting in LDV AUC exposure ~9-fold higher than in humans at the recommended LDV dose.

The FDC is pregnancy category B.

Ledipasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays. Carcinogenicity studies of ledipasvir in mice and rats are ongoing.

Two-year carcinogenicity studies of SOF were conducted in mice and rats and reviewed under this NDA. No increase in the incidence of drug-related neoplasms were observed at the highest doses tested in mice and rats, resulting in AUC exposure to the predominant circulating metabolite GS-331007 of approximately 4- and 18-fold (in mice) and 8- and 10-fold (in rats), in males and females respectively, compared to the exposure in humans at the 400 mg dose.

5. Clinical Pharmacology: The Office of Clinical Pharmacology reviewers were Drs. Jenny H. Zheng and Leslie Chinn with secondary review provided by Dr. Shirley Seo; Jeffry Florian and Yaning Wang provided primary and secondary pharmacometrics reviews of the NDA, respectively.

Multiple clinical studies were conducted to characterize the pharmacokinetics (PK) of LDV and SOF when administered either as single agents or as the FDC. Both intensive and sparse plasma concentration data from 391 healthy subjects and 2147 HCV-infected subjects who received LDV/SOF FDC, SOF and LDV administered together as single agents, or LDV as a single agent from 14 clinical studies (9 Phase 1, 2 Phase 2, and 3 Phase 3 studies) were used for population PK evaluation of SOF, its predominant circulating metabolite GS-331007, and LDV.

Dose selection rationale for SOF can be found in the review of NDA 204671. Dose selection rationale for LDV was based on an abbreviated monotherapy trial and a Phase 2 dose-ranging trial where the 90 mg dose of LDV had higher SVR rates and lower breakthrough rates than a 30 mg once daily dose.

Below, key PK characteristics for LDV as a single agent are summarized from Dr. Zheng's review:

- A high-fat meal reduced LDV AUC and Cmax by approximately 45%.
- LDV is >99.8% bound to human plasma proteins.
- The half-life of LDV is approximately 47 hours
- Following a single 90 mg oral dose of [^{14}C]-LDV, mean total recovery of the [^{14}C]-radioactivity in feces and urine was approximately 87%, with most of the radioactive dose recovered from feces (approximately 86%). Unchanged LDV excreted in feces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. The data

indicate that biliary excretion of unchanged LDV is a major route of elimination with renal excretion being a minor pathway.

- LDV exhibits dose linearity for AUCinf and Cmax over the 3- to 100-mg range.
- LDV PK is not affected by race (as determined by both popPK analysis of Phase 3 data as well as one dedicated Phase 1 study in Japanese subjects) or age (18-80 years)
- Relative to healthy subjects, LDV AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively, in HCV patients.
- AUC and C_{max} of LDV were 77% and 58% higher, respectively, in females than males. After correcting for body weight differences between genders, females still have approximately 40% higher exposure as compared to males. This observation has no clinical relevance because neither response rate nor rate or severity of adverse events was significantly different between genders.
- Renal impairment has no clinically significant effect on LDV PK and no dose adjustment of LDV is needed. The effect of hemodialysis on LDV PK was not evaluated; however, due to the high protein binding of LDV, hemodialysis is unlikely to have a significant impact.
- Hepatic impairment (including cirrhosis) has no clinically significant effect on LDV PK, and no dose adjustment of LDV is needed for any degree of hepatic impairment.
- LDV solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease systemic concentrations of LDV.
    - A substantial decrease in LDV plasma exposure (~ 42% to 48% lower AUC and Cmax) was observed upon administration of the proton pump inhibitor (PPI) omeprazole (20 mg) 2 hours prior to LDV administration.
    - LDV absorption was unaffected upon simultaneous or staggered (12 hours) administration of the H2-receptor antagonist (H2RA) famotidine (20 mg).
- LDV is a substrate of the drug transporters P-gp and BCRP.
- LDV is an inhibitor of P-gp and BCRP.
- LDV is not expected to inhibit OATP1B1, OATP1B3 and BSEP at concentrations achieved in vivo at the recommended dose
- LDV 30 mg once daily increased SIM Cmax and AUC by 161% and 169%, respectively, due to P-gp inhibition, which is a similar magnitude of the effect of DRV/RTV on (SIM) and DRV/RTV is not recommended to be coadministered with simeprevir. Thus, SIM is not recommended to be coadministered with LDV/SOF.
- At the supratherapeutic dose of 120 mg twice daily, LDV does not prolong QTc to a clinically relevant extent.

The PK characteristics of SOF and its major metabolite GS-331007are detailed in NDA 204671.

Below, key PK characteristics for SOF, GS-331007 and LDV following oral administration of LDV/SOF FDC are excerpted from Dr. Zheng's review; drug-drug interactions are depicted in Tables 3, 4 and 5 of product labeling:

- LDV/SOF FDC can be administered without regard to food (as instructed in Phase 3 studies).
- LDV/SOF FDC tablets have been studied with antiretrovirals as well as acid reducing agents. The following are the results from these studies:
    - No clinically significant effects on SOF and GS-331007 exposures were observed with any of the above agents, which was similar to what was observed for SOF administered as a single agent.
    - The effects of these drugs on LDV AUC or Cmax are in the range of a 34% decrease by Atripla to ~100% increase by ritonavir-boosted atazanivir. Safety data to support these shifts in plasma concentrations come from clinical trials where P-gp inhibitors were allowed; efficacy data come from a co-infected trial where all participants achieved SVR four weeks after the end of treatment (n=16).
    - LDV solubility decreases as pH increases. Consequently, drugs that increase gastric pH are expected to decrease the concentration of LDV. Dosing of antacids containing aluminum and magnesium hydroxide with the FDC should be separated by 4 hours. Famotidine (40 mg single dose) was administered either simultaneously with or 12 hours apart from LDV/SOF, while omeprazole (20 mg) was studied only with simultaneous administration with LDV/SOF. Since the onset of the antisecretory effect of H2RAs occurs within 1 hour, while the onset of antisecretory effect of PPIs may be delayed and prolonged, staggered administration of LDV/SOF with H2RAs or PPIs may result in lower LDV concentrations. As shown in Study GS-US-256-0110, a substantial decrease in LDV plasma exposure (~42% to 48% lower AUC and Cmax, respectively) was observed with administration of omeprazole 2 hours earlier than LDV as a single agent. Therefore, H2RAs should only be administered simultaneously or 12 hours apart with LDV/SOF, at doses comparable to famotidine 40 mg twice daily. PPIs should only be administered simultaneously with LDV/SOF under fasted conditions at doses comparable to omeprazole 20 mg once daily (or lower).
    - No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with ledipasvir or sofosbuvir: abacavir, cyclosporine, efavirenz, emtricitabine, lamivudine, methadone, or rilpivirine.
    - No effect on the pharmacokinetic parameters of ledipasvir, sofosbuvir and GS-331007 was observed with abacavir/ lamivudine, emtricitabine/rilpivirine/ tenofovir disoproxil fumarate or raltegravir.

Tenofovir concentrations are increased with concomitant use of a ritonavir-boosted protease inhibitor. There are no clinical safety data with LDV/SOF and regimens containing tenofovir plus ritonavir-boosted HIV protease inhibitors. Table 3 in product labeling recommends consideration of alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. However, if coadministration is necessary, labeling recommends monitoring for tenofovir-

associated adverse reactions. There are also no clinical data with LDV/SOF and elvitegravir/cobicistat/emtricitabine/tenofovir DF (Stribild, STR) and coadministration with STR is not recommended. The rationale for the different recommendations in Table 3 for these respective drug interactions is based upon benefit-risk considerations. Patients on regimens containing tenofovir and HIV protease inhibitors boosted with ritonavir may not have alternative HIV antiretroviral options, whereas patients receiving STR are generally treatment-naïve and have other options. Thus, the wording in Table 3 is intended to communicate the risk of increased tenofovir exposure with LDV/SOF coadministered with regimens containing tenofovir plus an HIV protease inhibitor/ritonavir, allow provider flexibility to determine the preferred treatment regimen for their patient and convey the need for renal monitoring for patients who receive these medications concomitantly.

Tenofovir concentrations are also increased with concomitant use of Atripla. Review of summary clinical trial safety data from approximately 175 subjects who received LDV/SOF plus Atripla is determined to be adequate to support labeling for LDV/SOF and Atripla coadministration. Wording in Table 3 conveys the need for renal monitoring for patients who receive these medications concomitantly. Obtaining additional safety data in subjects receiving concomitant LDV/SOF and Atripla (or its components) from the ongoing trial GS-US-337-0115 is a recommended postmarketing requirement.

No dose adjustment of LDV/SOF is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C).

No dose adjustment of LDV/SOF is required for patients with mild or moderate renal impairment. However, no dose recommendation can be given for patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or with end stage renal disease due to higher exposures of the predominant SOF metabolite. Further, the use of P-gp inducers is not recommended (e.g., rifampin) as they may lead to a reduced therapeutic effect of the FDC.

6. Clinical Virology: Please see extensive reviews by Drs. Lisa Naeger and Eric Donaldson who conducted the review of virology and resistance data, including next generation sequencing (NGS) data with supervisory concurrence by Dr. Jules O'Rear. Our virology review staff concluded that this FDC NDA for LDV and SOF is approvable with respect to virology for the treatment of GT1 HCV infection. They recommend the 12-week duration of LDV/SOF for treatment-naive and treatment-experienced patients without cirrhosis. For subjects with cirrhosis, a 24-week duration of LDV/SOF is recommended.

Per Drs. Naeger and Donaldson's reviews and product labeling, the following wording describes resistance in cell culture: Reduced susceptibility to LDV was associated with the primary NS5A amino acid substitution Y93H in both genotypes 1a and 1b. Additionally, a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotypes 1a and 1b,

as well as the Q30E substitution in genotype 1a, conferred high levels of reduced susceptibility to LDV (fold change in EC_{50} greater than 1000-fold).

HCV replicons with reduced susceptibility to SOF have been selected in cell culture. Reduced susceptibility to SOF was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to SOF.

Virology reviews and resultant product labeling contain the following wording related to resistance in clinical trials: In (b) (4) a pooled analysis of subjects who received the FDC, 37 subjects (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure (35 with virologic relapse and 2 with breakthrough on-treatment due to documented non-adherence). Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 subjects' viruses, respectively.

Of the 29 genotype 1a virologic failure subjects, 55% (16/29) of subjects had virus with emergent NS5A resistance-associated substitutions K24R, M28T/V, Q30R/H/K/L, L31M, or Y93H/N at failure. Five of these 16 subjects also had baseline NS5A polymorphisms at resistance-associated amino acid positions. The most common substitutions detected at failure were Q30R, Y93H or N, and L31M.

Of the 8 genotype 1b virologic failure subjects, 88% (7/8) had virus with emergent NS5A resistance-associated substitutions L31V/M/I or Y93H at failure. Three of these 7 subjects also had baseline NS5A polymorphisms at resistance-associated positions. The most common substitution detected at failure was Y93H.

At failure, 38% (14/37) of virologic failure subjects had 2 or more NS5A substitutions at resistance-associated positions.

In phenotypic analyses, post-baseline isolates from subjects who harbored NS5A resistance-associated substitutions at failure showed 20- to >243-fold reduced susceptibility to LDV.

Treatment-emergent NS5B substitutions L159 (n=1) and V321 (n=2) previously associated with SOF failure were detected in the Phase 3 trials. In addition, NS5B substitutions at highly conserved positions D61G (n=3), A112T (n=2), E237G (n=2), and S473T (n=1) were detected at low frequency by next generation sequencing in treatment failure subjects infected with HCV GT1a. The D61G substitution was previously described in subjects infected with HCV GT1a in a liver pre-transplant trial. The clinical significance of these substitutions is currently unknown.

The SOF-associated resistance substitution S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. NS5B substitutions S282T, L320V/I, and V321I in combination with NS5A substitutions L31M, Y93H, and Q30L were

detected in one subject at failure following 8 weeks of treatment in a Phase 2 trial.

Not surprisingly, LDV was fully active against the SOF resistance-associated substitution S282T in NS5B while all LDV resistance-associated substitutions in NS5A were fully susceptible to SOF. Both LDV and SOF were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of actions, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. NS5A substitutions conferring resistance to LDV may reduce the antiviral activity of other NS5A inhibitors. Importantly, the efficacy of the FDC has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

No data are available on the persistence of LDV or SOF resistance-associated substitutions. NS5A resistance-associated substitutions for other NS5A inhibitors have been found to persist for more than one year in some patients.

Critical analyses were conducted to explore the association between pre-existing baseline NS5A polymorphisms at resistance-associated positions and relapse rates. In the pooled analysis of the Phase 3 trials, 23% (370/1589) of subjects' virus had baseline NS5A polymorphisms at resistance-associated positions (any change from reference at NS5A amino acid positions 24, 28, 30, 31, 58, 92 or 93 identified by population or deep sequencing).

In treatment-naïve patients whose virus had baseline NS5A polymorphisms at resistance-associated positions in Studies ION-1 and ION-3, relapse rates were low and comparable to subjects without baseline polymorphisms: 6% (3/48) after 8 weeks and 1% (1/113) after 12 weeks of treatment with baseline polymorphisms versus 5% (8/167) after 8 weeks and 1% (3/306) after 12 weeks treatment without baseline polymorphisms.

In treatment-experienced patients whose virus had baseline NS5A polymorphisms at resistance-associated positions, relapse rates were 22% (5/23) after 12 weeks and 0% (0/19) after 24 weeks of treatment with the FDC. Patients with multiple NS5A polymorphisms at resistance-associated positions appeared to have higher relapse rates. SVR was achieved in all 24 subjects (N=20 with L159F+C316N; N=1 with L159F; and N=3 with N142T) who had baseline polymorphisms associated with resistance to NS5B nucleoside inhibitors. The S282T SOF resistance-associated substitution was not detected in the baseline NS5B sequence of any subject in Phase 3 trials by population or deep sequencing.

7. Efficacy and Safety: Clinical reviews were conducted by Dr. Sarah Connelly with secondary review provided by Dr. Kim Struble. The Biometrics review was conducted by Dr. Karen Qi with secondary review provided by Dr. Fraser Smith and supervisory review provided by Dr. Daphne Lin.

The Phase 3 program encompasses treatment-naïve and treatment experienced patient populations with GT1 who enrolled in three principal clinical trials, ION-1, ION-2 and ION-3. Results from ION-1 and ION-3 supported an indication for treatment-naïve patients with and without cirrhosis. ION-1 was a randomized, multicenter, four-arm, open-label trial that examined LDV/SOF for 12 or 24 weeks with and without ribavirin. The primary endpoint was SVR12 and the primary hypothesis was that each treatment arm had to be superior to a historical control rate of 60%, derived from the upper bound of the 95% confidence interval of the highest SVR rate for pegylated interferon and ribavirin from historical trials ADVANCE and SPRINT2. Per Dr. Struble's CDTL review and Dr. Qi's statistical review, efficacy from the 24 week arms were not included in the NDA because the Division agreed that if the two 12-week arms achieved an SVR12 rate of $\geq$ 90% in subjects with and without cirrhosis, separately, then the Applicant could submit an NDA and not wait for the 24 week arms to reach the SVR12 timepoint. Randomization was stratified by genotype subtype (1a or 1b) and presence or absence of cirrhosis. Of note, ION-1 was conducted in the United States and Europe.

ION-3 evaluated LDV/SOF in three treatment groups: LDV/SOF +/- RBV for 8 weeks and LDV/SOF for 12 weeks. Only non-cirrhotic subjects were enrolled and randomization was stratified by genotype subtype (1a or 1b). Of note, ION-3 was only conducted in the United States.

Demographics and baseline characteristics were balanced across treatment groups in the individual trials. Results from ION-1 and ION-3 were robust. SVR12 rates exceeded 90% for all treatment arms. The following table describing results from ION-1 appears in product labeling. As ribavirin did not alter treatment outcomes, only the LDV/SOF 12-week arm is displayed in Table 9 in product labeling.

Table 9

ION-1: SVR Rates for Selected Treatment Naïve Subgroups after 12 Weeks Treatment

	LDV/SOF 12 Weeks (N = 214)
Genotype[a]	
Genotype 1a	98% (142/145)
Genotype 1b	100% (67/67)
Cirrhosis[b]	
No	99% (176/177)
Yes	94% (32/34)

a. One subject without a confirmed subtype for genotype 1 infection and one subject with genotype 4 infection were excluded from this subgroup analysis.
b. Subjects with missing cirrhosis status were excluded from this subgroup analysis.

Table 6 in product labeling presents the response rates for the FDC treatment groups in the ION-3 trial. Ribavirin was not shown to increase the response rates, therefore the 8-week FDC plus ribavirin arm is not presented in Table 6.

Table 6

ION-3: Response Rates in Treatment Naïve Patients after 8 and 12 Weeks Treatment

	LDV/SOF 8 Weeks (N = 215)	LDV/SOF 12 Weeks (N = 216)
SVR	94% (202/215)	96% (208/216)
Outcome for subjects without SVR		
On-Treatment Virologic Failure	0/215	0/216
Relapse[a]	5% (11/215)	1% (3/216)
Other[b]	<1% (2/215)	2% (5/216)
Genotype[c]		
Genotype 1a	93% (159/171)	96% (165/172)
Genotype 1b	98% (42/43)	98% (43/44)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).
c. One subject without a confirmed subtype for genotype 1 infection was excluded from this subgroup analysis.

The review team recommended 12 weeks of treatment with LDV/SOF based on relapse rates, 5% compared to 1% for 8 weeks versus 12 weeks. It was felt that to be able to give patients the best outcome with a first regimen it was appropriate to treat longer to attempt to overcome relapse. However, in those patients with more favorable baseline characteristics, a shorter treatment regimen could be considered. Relapse rates based on baseline viral load by treatment duration are depicted in Table 7 of product labeling.

Table 7

ION-3: Relapse Rates in Treatment Naïve Patients by Baseline Viral Load after 8 and 12 Weeks of Treatment

	LDV/SOF 8 Weeks (N = 215)	LDV/SOF 12 Weeks (N = 216)
Number of responders at end of treatment	215	216
Baseline HCV RNA[a]		
HCV RNA < 6 million IU/mL	2% (2/123)	2% (2/131)
HCV RNA ≥ 6 million IU/mL	10% (9/92)	1% (1/85)

a. HCV RNA values were determined using the Roche TaqMan Assay; a subject's HCV RNA may vary from visit to visit.

Previously treated GT1 HCV-infected adults with and without cirrhosis and who had failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor enrolled in ION-2 which was a randomized, open-label trial that evaluated 12 and 24 weeks of treatment with LDV/SOF, with or without ribavirin. Randomization was stratified by the presence or absence of cirrhosis, HCV genotype subtype (1a vs 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse).

Demographics and baseline characteristics were balanced across the treatment groups.

Response rates and relapse rates for selected subgroups in ION-2 are presented below and in Tables 11 and 12 in product labeling.

Table 11

ION-2: SVR Rates for Selected Treatment-Experienced Subgroups after 12 and 24 Weeks of Treatment

	LDV/SOF 12 Weeks (N=109)	**LDV/SOF 24 Weeks (N=109)**
Genotype		
Genotype 1a	95% (82/86)	99% (84/85)
Genotype 1b	87% (20/23)	100% (24/24)
Cirrhosis[a]		
No	95% (83/87)	99% (85/86)
Yes	86% (19/22)	100% (22/22)
Prior HCV Therapy		
Peg-IFN+RBV	93% (40/43)	100% (58/58)
HCV protease inhibitor+Peg-IFN+RBV	94% (62/66)	98% (49/50)
Response to prior HCV Therapy		
Relapse/Breakthrough	95% (57/60)	100% (60/60)
Nonresponder	92% (45/49)	98% (48/49)

a. Subjects with missing cirrhosis status were excluded from this subgroup analysis.

Table 12

ION-2: Relapse Rates for Selected Treatment-Experienced Subgroups after 12 and 24 Weeks of Treatment

	LDV/SOF 12 Weeks (N=109)	LDV/SOF 24 Weeks (N=109)
Number of responders at end of treatment	108	109
Cirrhosis[a]		
No	5% (4/86)[b]	0% (0/86)
Yes	14% (3/22)	0% (0/22)
Presence of Baseline NS5A Resistance-Associated Polymorphisms[c]		
No	2% (2/85)	0% (0/90)
Yes	22% (5/23)	0% (0/19)
IL28B Status		
C/C	0% (0/10)	0% (0/16)
Non-C/C	7% (7/98)	0% (0/93)

a. Subjects with missing cirrhosis status were excluded from this subgroup analysis.
b. These 4 non-cirrhotic relapsers all had baseline NS5A resistance-associated polymorphisms.
c. NS5A resistance-associated polymorphisms include any change at NS5A positions 24, 28, 30, 31, 58, 92 or 93.

Based on the results of ION-2, 12 weeks of treatment with LDV/SOF is recommended for treatment-experienced patients without cirrhosis and a 24-week treatment duration is recommended for patients with cirrhosis based on SVR rates. Treatment-experienced patients whose virus had resistance-associated baseline NS5A polymorphisms had relapse rates of 22% after 12 weeks compared to 0% after 24 weeks of treatment.

8. Safety

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety assessment is based on pooled data from the Phase 3 trials and includes data from a total of 1080 subjects receiving the FDC for 8, 12 or 24 weeks. The proportion of subjects who permanently discontinued treatment due to an adverse event was $\leq$1%. The most common adverse reactions $\geq$ 10% were fatigue and headache.

Regarding laboratory abnormalities, bilirubin elevations of greater than 1.5xULN were observed in <1% - 3% of subjects treated with LDV/SOF. Transient, asymptomatic lipase elevations of greater than 3xULN were observed in <1% - 3% of subjects treated with the FDC for 8-24 weeks. Creatine kinase (CK) was not assessed in Phase 3 trials, however isolated, asymptomatic CK elevations

(Grade 3 or 4) have been previously reported and reviewed in NDA 204671 in subjects treated with SOF with ribavirin or peginterferon/ribavirin in other clinical trials.

A detailed safety evaluation of cardiac toxicity was done with the FDC in light of the fact that another investigational drug in the NS5B class had significant cardiac issues. Per Dr. Connelly's review, no potential safety concerns were identified related to cardiac toxicity with the FDC at this time. Potential nonclinical signals for ocular toxicity and gastrointestinal toxicity were identified and evaluated clinically; no clinical concerns were observed in the safety data base. Nausea and diarrhea are labeled events. A detailed hepatic review was also performed. As LDV is primarily eliminated by biliary excretion, a potential causal relationship exists with bilirubin elevations, therefore bilirubin information is included in product labeling. A separate analysis of gallbladder events did not identify a causal association between LDV/SOF use and cholelithiasis and/or cholecystitis.

Deaths

In the completed and ongoing Phase 2 and 3 trials of LDV/SOF, no on-treatment deaths occurred. One death occurred in the post-treatment period in ION-1 which was not considered related to study treatment by the investigator.

9. Postmarketing Requirements and Commitments:

Recommended Postmarketing Requirements and Commitments include the following to which the Applicant agreed on August 7, 2014 during the late cycle meeting. Final dates for protocol and data submissions will be forthcoming from the Applicant.

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of LDV/SOF in pediatric subjects 3 through 17 years of age with chronic hepatitis C.
- Collect and analyze long-term safety data for subjects enrolled in the pediatric LDV/SOF safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety including growth assessment, sexual maturation and characterization of LDV/SOF resistance associated substitutions in viral isolates from subjects failing therapy.
- Submit the final report and datasets for the ongoing trial GS-US-337-0115, entitled "A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co-infection", in order to obtain additional safety data in subjects receiving concomitant LDV/SOF and Atripla (or its

components) and to provide dosing recommendations for co-infected subjects.

- Submit the final report and datasets for the ongoing trial GS-US-337-0123, entitled “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant”, in order to provide safety data and dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g., cyclosporine).
- Submit the final report for the LDV 2-year carcinogenicity study in rats.
- Submit the final report for the LDV 26-week carcinogenicity study in rasH2 mice.
- Conduct a study to assess the impact of NS5B substitutions A112T, E237G, and S473T on the phenotypic susceptibility of sofosbuvir in the GT1a HCV replicon system.
- Submit the longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.

Conclusions and Recommendations: This comprehensive NDA contained multiple clinical trials examining the use of the FDC, LDV/SOF, in treatment naïve and treatment-experienced patients with GT1 CHC infection. The FDC was both efficacious and well-tolerated with a manageable safety profile.

SVR rates in ION-1 ranged from 94-99% for cirrhotic and non-cirrhotic patients, respectively, in treatment-naïve patients receiving the FDC for 12 weeks. Despite high SVR rates in ION-3, relapse rates were higher in the 8-week versus the 12-week arm, 5% versus 1%, respectively. Since it is anticipated that clinical trials results may not fully translate to the post-marketing situation and because retreatment of patients who relapse may be more difficult, given persistence of resistance-associated substitutions for other NS5A inhibitors, a 12-week treatment duration is recommended for the treatment-naïve population, which is consistent with ION-3. An 8-week treatment duration may be considered for patients with more favorable baseline factors such as a low viral load.

In patients who previously failed prior therapy, overall SVR rates also ranged from 94-99% based on a treatment duration of 12-24 weeks. Treatment for 24 weeks will be recommended for cirrhotic patients who previously failed therapy because SVR rates increased with longer treatment. SVR was achieved in all subjects who had baseline polymorphisms associated with resistance to NS5B nucleoside inhibitors.

Drug-drug interactions are manageable in monoinfected and HIV co-infected patients. Adequate guidance appears in product labeling.

In sum, I am in agreement with the conclusions of the multidisciplinary review team that the benefit-risk assessment favors approval of the breakthrough therapy, LDV/SOF for treatment of adult patients with GT 1 CHC. This potent regimen consisting of one pill, once a day will address unmet medical needs such as use in populations intolerant or unable to take interferon and ribavirin and populations who have failed prior therapy with a protease inhibitor. With use of LDV/SOF leading to high SVR rates approaching 100% in some populations, we are getting closer to eradication of chronic hepatitis C infection.

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/s/

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09/23/2014