CENTER FOR DRUG EVALUATION AND RESEARCH

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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

ALT associated with increased liver/gallbladder weight without corresponding histopathology changes in mice. In rats, minimal to slight random foci of hepatocyte necrosis and bile duct hyperplasia were noted. For these findings an 8-30 fold safety margin is available for the expected human exposure for LDV 90 mg once daily. In dogs, no clear clinically relevant findings were seen.

Additionally slight increases in cholesterol and triglycerides were noted in rats at 100 mg/kg/day.

LDV accumulates in the uveal tract of the eye in pigmented (but not albino) rats. LDV also absorbs ultraviolet light. An in vivo study with pigmented rats assessed potential ocular phototoxicity risk. Results of this study showed the phototoxicity risk was negative at up to the highest dose level tested (8 fold higher than the recommended LDV dose in humans)

- **Carcinogenicity and Mutagenesis**

LDV and SOF are not genotoxic following testing in bacterial mutagenicity, chromosome aberration and in vivo rat and mouse micronucleus assays.

Carcinogenicity studies of LDV in mice and rats are ongoing.

In mice and rats, no increases in the incidence of drug-related neoplasms were observed at the highest doses tested resulting in SOF metabolite GS-331007 exposures of approximately 4- and 18-fold (in mice) and 8- and 10 fold (rats) higher than those in humans at the recommended 400 mg once daily dose.

Additionally, no heart degeneration or inflammation was observed in rats following SOF doses of up to 750 mg/kg/day in the 2-year carcinogenicity study at GS-331007 AUC exposure approximately 9-fold the exposure in humans at the recommended 400 mg once daily dose.

- **Reproductive toxicology**

In rats, no effects on mating or fertility were seen with LDV at exposures approximately 5 and 2 fold higher, in males and females respectively than the exposure in humans at the recommended dose. The mean number of corpora lutea and implantation sites were slightly reduced at maternal exposures approximately 3 fold the exposure in humans at the 90mg once daily dose.

5. Clinical Pharmacology/Biopharmaceutics

Approval is recommended from the clinical pharmacology and pharmacometrics review team.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects**

The pharmacokinetic properties of LDV, SOF and the predominant circulating metabolite GS-331007 were evaluated in healthy and HCV infected subjects. Mean peak concentrations of LDV, SOF and GS-331007 were observed at 4-4.5 hours, 0.8-1 hour and 3.5-4 hours post-dose respectively. Following administration of LDV/SOF, the median terminal half-lives of LDV, SOF and GS-331007 were 47 hours, 0.5 hours and 27 hours, respectively.

Following a single dose of LDV/SOF FDC with a moderate fat meal and compared to fasting condition, SOF AUC was increased by approximately 2-fold (no significant effect on Cmax). LDV and GS-331007 were not affected by meal type. These data support dosing without regard to food. Phase 3 trials were conducted in this manner. In vitro, no detectable metabolism of LDV was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed.

SOF is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway.

Biliary excretion is the major route of elimination for LDV with renal excretion being a minor pathway (approximately 1%). Renal clearance is the major elimination pathway for GS-331007.

- **Dose Selection**

The dose selection for SOF 400 mg once daily is based on the safety and efficacy established during the review of NDA 204671. Section 2: Background provides a summary for the LDV 90 mg once daily dose selection. In sum, the LDV 90 mg once daily dose was selected based on results from a three day monotherapy trial and a phase 2 dose-ranging trial. Overall the 90 mg dose had numerically higher SVR rates and lower incidence of virologic breakthrough compared to a 30 mg once daily dose.

- **Drug-drug interactions**

LDV is an inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP); therefore, LDV may increase the intestinal absorption of coadministered substrates for these transporters. LDV also inhibits OATP1B1, OATP1B3 and BSEP but only at concentrations exceeding those achieved in humans. The drug-drug interaction potential of LDV is primarily limited to intestinal inhibition of P-gp and BCRP. Clinically relevant transporter inhibition by LDV in the systemic circulation is

not expected due to LDV high protein binding. SOF and GS-331007 are not inhibitors of drug transporters. LDV, SOF and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

LDV and SOF are substrates of P-gp and BCRP but GS-331007 is not. Therefore, P-gp inducers may decrease LDV and SOF exposures and affect efficacy. As a result coadministration of LDV/SOF with rifampin, rifapentine and St. John's wort is not recommended. SOF is not a substrate for CYP or UGT1A1 enzymes. Clinically significant drug interactions with LDV/SOF FDC mediated by CYP or UGT1A1 enzymes are not expected.

Drug interaction trials were conducted with LDV as a single agent, SOF as a single agent or LDV/SOF in combination with several antiretrovirals, H2 receptor antagonists, proton pump inhibitors, oral contraceptives, cyclosporine, rifampin and verapamil. Some potentially clinically significant interactions were noted. Please refer to Dr. Jenny Zheng's review for full details and rationale for recommendations despite changes in LDV, SOF or concomitant medication exposures. Below is the proposed table for the package insert and still under discussion. Two outstanding issues remain: use with acid reducing agents and tenofovir based regimens.

Acid-reducing agents:

LDV solubility decreases as pH increases; therefore drugs that increase gastric pH are expected to decrease LDV exposures. As a result separation of antacid intake and LDV/SOF by four hours is recommended. The data support simultaneous administration of proton-pump inhibitor doses comparable to omeprazole 20 mg or lower and LDV/SOF under fasted conditions. The Applicant recommends H2-receptor antagonists are administered simultaneously with or 12 hours apart from LDV/SOF at a dose that does not exceed doses comparable to famotidine 40 mg twice daily. We had concerns whether the results from the famotidine trials can be extended to all H2-receptor antagonists because some H2-receptor antagonists such as ranitidine may have a faster onset of action. The Applicant provided information from the Phase 2/3 trials, 231 out of 2120 HCV-infected patients on LDV/SOF reported the use of H2-RAs as concomitant medications with 10 subjects reporting the use of two agents within the H2-RA class. Thirteen subjects reported the use of cimetidine, 76 subjects reported the use of famotidine and 152 subjects reported the use of ranitidine. The Applicant evaluated the PK of LDV/SOF in subjects on H2 receptor antagonists and subjects not on H2 receptor antagonists using Phase 2/3 population PK analyses. The post-hoc comparison revealed comparable exposures for all analytes between the two groups. These findings are consistent with the results from the drug-drug interaction with famotidine. Similar high response rates were observed in subjects who received and did not receive H2 receptor antagonists in Phase 3 trials. The PK and efficacy data demonstrate that LDV/SOF may be administered with different agents within H2 receptor antagonist class and supports the proposed language in the package insert.

Tenofovir:

Based on results from a drug interaction trial with efavirenz/emtricitabine/tenofovir (Atripla) and LDV/SOF, LDV/SOF increases tenofovir AUC, Cmax and Ctau by 98%, 79% and 163%. The magnitude of the increase in tenofovir exposures is higher compared to other drug interaction trials with tenofovir and the concern is for tenofovir- associated toxicities, specifically renal events. Therefore, to support the safety of this magnitude of increase in tenofovir exposures, we requested the Applicant provide safety data for this combination. Currently data were only available for 15 subjects receiving efavirenz/tenofovir/emtricitabine and LDV/SOF from trial ERADICATE. All subjects completed 12 weeks of treatment and no discontinuations due to AEs were reported. No clinically significant changes in creatinine were observed. The review team is currently reviewing the summary safety data provided by the Applicant on August 7, 2014. The submission includes safety data from 175 subjects who received LDV/SOF + Atripla and includes safety data from 94 subjects receiving LDV/SOF for 12 weeks. These data will be reviewed to support LDV/SOF+ Atripla coadministration. Of note, the outstanding issue is use of LDV/SOF with an HIV protease inhibitor/ritonavir and tenofovir. The tenofovir exposures from a combination of LDV/SOF+ HIV protease inhibitor/ritonavir + tenofovir are higher than with LDV/SOF+ Atripla. To date, no safety data are available to support the increased tenofovir exposures from this combination. Currently the review team is considering a recommendation to avoid use with LDV/SOF + HIV protease inhibitor/ritonavir and tenofovir. However, if coadministration is necessary, monitor for tenofovir associated toxicities. Tenofovir associated toxicities are well characterized and could be managed with additional monitoring. Given the high SVR rates with LDV/SOF and the limited treatment duration (12-24 weeks), the opportunity to cure HCV in a co-infected patient is important. Additionally, there may be clinical circumstances where an alternative HIV treatment options that do not contain tenofovir with an HIV protease inhibitor/ritonavir is not possible and we wanted to provide an option. Therefore, if coadministration is necessary, we propose monitoring recommendations consistent with the tenofovir package insert.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir (b) (4)	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g. aluminum and magnesium hydroxide)		Separate antacid and [TRADENAME] administration by 4 hours
H_2-receptor antagonists		Recommendation pending
Proton-pump inhibitors		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with [TRADENAME] under fasted conditions.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration of [TRADENAME] with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with [TRADENAME].
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of [TRADENAME] with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of [TRADENAME]. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of [TRADENAME] with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of [TRADENAME]. Coadministration is not recommended. Coadministration of [TRADENAME] with rifampin (a P-gp inducer) is not recommended *[see Warnings and Precautions (5.1)].*
Antiretrovirals: elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate	(b) (4) ↑ tenofovir (b) (4)	There are insufficient data to make a dosing recommendation for coadministration of [TRADENAME] with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.
tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of [TRADENAME] with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of [TRADENAME]. Coadministration is not recommended.
HCV Products: simeprevir	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of [TRADENAME] with

		simeprevir is not recommended.
Herbal Supplements: St. John's wort (*Hypericum perforatum*)	↓ ledipasvir ↓ sofosbuvir ↓ GS-331007	Coadministration of [TRADENAME] with St. John's wort, a P-gp inducer is not recommended*[See Warnings and Precautions (5.1)].*
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of [TRADENAME] with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of [TRADENAME] with rosuvastatin is not recommended.

- **Critical intrinsic factors: age, gender, hepatic and renal impairment**

Based on population pharmacokinetic analyses, age, race, BMI, treatment status, presence of RBV, and cirrhosis status had no clinically relevant effects on the exposure of LDV, SOF or GS331007. LDV AUC, Cmax and Ctau were approximately 77%, 58%, and 75% higher in females compared to males. The relationship between sex and LDV exposures was not considered clinically relevant given the high response rates (>93%) and the lack of related safety issues in the clinical trials.

The effect of renal impairment was evaluated for LDV and SOF as individual agents. No clinically relevant differences in LDV pharmacokinetics were seen between healthy subjects and subjects with severe renal impairment, thus supporting that LDV can be given to patients with mild, moderate or severe renal impairment. However, the SOF component of the FDC cannot be given to patients with severe renal impairment. Higher exposures (up to 20 fold) for GS-331007 were seen in subjects with severe renal impairment. Safety and efficacy have not been established for GS-331007 exposures; therefore, dosing recommendations in patients with severe renal impairment cannot be made for LDV/SOF FDC.

No clinically relevant effect on the exposure of LDV, SOF and GS-331007 was seen in subjects with severe hepatic impairment. Therefore LDV/SOF FDC can be given to patients with mild, moderate and severe hepatic impairment. Data in subjects with decompensated cirrhosis are not available.

- **Thorough QT study or other QT assessment**

A thorough QT trial was not conducted for LDV/SOF FDC. The individual products were evaluated in a thorough QT trial. LDV or SOF did not prolong QTc to any clinically relevant extent compared to an active control (moxifloxacin 400 mg).

- **Exposure-response and Exposure-safety analyses**

A numeric trend of increased response with respect to increased LDV, SOF, and GS-331007 exposures was seen for the LDV/SOF +/- RBV-treated, treatment-naïve, non-

cirrhotic subjects in ION-3. SVR rates in subjects administered LDV/SOF +/- RBV for 8 weeks were numerically higher in subjects in the highest exposure quartile compared to the lowest exposure quartile. Dose adjustment or therapeutic drug monitoring is not recommended based on this finding because overall SVR12 rates were greater than 93%.

For treatment-naïve cirrhotic subjects and treatment-experienced cirrhotic and non-cirrhotic subjects no clinically relevant differences were observed in SVR12 between the highest and lowest exposure quartiles.

No exposure-response relationships were identified between LDV, SOF, GS-331007 AUC and the most commonly observed adverse events in Phase 3 trials.

6. Clinical Microbiology

Please refer to the reviews by Dr. Lisa Naeger and Dr. Eric Donaldson for a detailed assessment of the cell culture and in vivo clinical virology data. Dr. Naeger recommended an approval action.

The results from baseline NS5A resistance-associated polymorphism and outcome (SVR12 and relapse rate) are presented in section 7 Clinical/Statistical Efficacy. This section will focus on the virologic failures from the Phase 3 trials. Additionally a brief summary is presented from the next generation sequencing (NGS) analyses.

Overall 50 subjects experienced virologic failure from the Phase 2 and Phase 3 submitted trials. Two subjects experienced breakthrough and the remaining 48 were relapsers (41 genotype 1a subjects and 7 genotype 1b subjects). The comments below focus on the 37 virologic failures from the Phase 3 trials (29 with genotype 1a and 8 with genotype 1b; 35 relapsers and 2 breakthroughs due to documented non-adherence).

Overall 62% (23/37) of the failures in Phase 3 had emergent NS5A resistance substitutions. Notably more treatment-experienced subjects developed an NS5A substitution at failure (75%) compared to treatment-naïve subjects (56%).

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 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 resistance-associated substitutions.

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.

The SOF-associated resistance substitution S282T in NS5B was not detected in any failure isolate from the Phase 3 trials. However, the NS5B S282T substitution in combination with NS5A substitutions L31M, Y93H and Q30L was detected in one subject at failure following 8 weeks of treatment from a Phase 2 trial.

Data on the retreatment strategy for subjects failing LDV/SOF is limited. Data from nine subjects who did not achieve SVR12 after receiving an LDV/SOF based regimen (LDV/SOF x 8 weeks or LDV/SOF+RBV x 6 weeks) were available for review. Only one subject from the Phase 2 trial LONESTAR was retreated with LDV/SOF+RBV for 24 weeks following virologic failure after receiving LDV/SOF for 8 weeks. This subject had multiple NS5A substitutions and an NS3 substitution (Q30L, L31M, Y93H and S282T). This subject achieved SVR12. The remaining eight subjects were all retreated with LDV/SOF+ RBV for 12 weeks. Of note only three of the eight subjects had NS5A resistance substitutions at relapse. All subjects achieved SVR12. In summary the optimal regimen (LDV/SOF, LDV/SOV+RBV or other DAA combination) or optimal duration (12 or 24 weeks) for retreatment for subjects failing LDV/SOF is unknown. Additional data are needed to make labeling recommendations for retreatment regimens; however, the limited data available appears encouraging for future retreatment options.

Dr. Donaldson concluded there was good agreement between his independent analysis of the NGS data and the analysis done by the Applicant despite different criteria used. Based on his review, LDV/SOF has a high barrier to resistance. Additional NS5B substitutions (A112T, E237G and S473T) should be evaluated to determine if these impact the efficacy of LDV/SOF.

7. Clinical/Statistical- Efficacy

This section summarizes the efficacy analyses conducted by the review team for the two Phase 3 trials in treatment-naïve subjects and one Phase 3 trial in treatment-experienced subjects. Additionally, the clinical virology data with respect to baseline NS5A polymorphism and outcome is presented in this section. Please refer to reviews by Dr. Sarah Connelly (clinical), Karen Qi (statistical) and Lisa Naeger (virology) for full details and discussion of efficacy. Each reviewer recommended approval for this NDA.

The results presented by the Applicant and FDA differ slightly; however, the overall efficacy findings were robust and the differences were minor and not clinically or statistically significant. FDA requested SVR12 data from three subjects in the ION-1 trial and two subjects in the ION-3 trial who did not have SVR12 data included in the

original NDA submission. FDA included these subjects in the SVR12 rate as presented in labeling. Additionally data from one genotype 4 subject was excluded from the FDA analyses.

The primary endpoint for the pivotal clinical trials was SVR (HCV RNA analyzed using Roche TaqMan assay with limit of quantitation < 25 IU/mL) measured 12 weeks after the end of therapy and deemed acceptable. SVR12 is the currently recommended primary endpoint in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013. Sustained virologic response (HCV RNA < LLOQ at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a cure for hepatitis C infection; and recent studies have shown that achievement of SVR is associated with halting the progression of liver disease and decreasing the frequency of chronic hepatitis C complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality.

ION-1 and ION-2 subjects were stratified by cirrhosis status. The method for determining cirrhosis (liver biopsy, Fibroscan and FibroTest +APRI) was acceptable. Liver biopsy accounted for the majority of cirrhosis determination (64% overall and 69-79% in the US).

Trial Design Attributes:

Treatment-naïve adults with and without cirrhosis:

The pivotal trials to support efficacy for the treatment-naïve genotype 1 population were two Phase 3 (ION-1 and ION-3) multicenter, randomized, open-label trials to evaluate the efficacy and safety of LDV/SOF FDC with or without RBV for 8, 12 or 24 weeks duration. The primary endpoint is the proportion of subjects achieving SVR12. The primary hypothesis was the SVR12 rate in each treatment arm is superior to the historical control rate of 60%.

An active or placebo control was not used in these trials. Per the Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Drugs for Treatment, an immediate versus deferred placebo-control trial design is preferable and in some situations, single-arm trials using a historical control may be appropriate. Alternatively duration comparison designs can be considered. Therefore, the choice of a duration comparison using a historical control was agreed upon by the Division. For both trials, the Division agreed with historical rate of 60% because this was close to the upper bound of the 95% CI of the highest SVR rate observed for PR between the historical trials ADVANCE and SPRINT2. Please refer to Dr. Qi's review for more details.

In ION-1 four treatment groups were evaluated, LDV/SOF +/- RBV for 12 weeks and LDV/SOF +/- RBV for 24 weeks. Efficacy from the 24 weeks arms were not included in the NDA because the Division agreed if the two 12 week arms achieved an SVR12

rate of ≥ 90% in subjects with and without cirrhosis separately the Applicant could submit an NDA and not wait for the 24 week arms to reach the SVR12 timepoint. Randomization was stratified by genotype (1a or 1b) and presence or absence of cirrhosis.

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

Treatment-experienced adults with and without cirrhosis:

The trial design for ION-2 was similar to ION-1 and ION-3. ION-2 was a randomized, multicenter, open-label trial to evaluate LDV/SOF +/- RBV for 12 and 24 weeks in subjects who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Randomization was stratified by the presence or absence of cirrhosis, HCV genotype (1a or 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse). The Division agreed with the primary efficacy hypothesis in that the SVR12 rate in each treatment group was superior to the historical SVR rate of 25%. Please refer to Dr. Karen Qi's review for details.

Results:

The Applicant proposed (b) (4) After extensive internal discussion, the review team concluded that collectively the results of the phase 3 trials support the use of LDV/SOF without RBV for the following recommended treatment durations and respective patient populations. The basis for our recommendations is outlined in the following subsections. Notably relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups. These differences led to our final treatment duration recommendations and are discussed in the subsections below.

Patient Population	Treatment Duration
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced without cirrhosis	12 weeks
Treatment-experienced with cirrhosis	24 weeks

* 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL

Treatment-naïve adults with and without cirrhosis:

In the two Phase 3 treatment-naïve trials, the representation of enrolled subjects for gender, race and baseline characteristics was reasonable. Of note, in ION-1 the Applicant targeted 20% cirrhotic subjects for enrollment but only enrolled approximately 16%. The majority of subjects were white, males and more than two-thirds had HCV genotype 1a infection and non-CC IL28B alleles.

Results from the Phase 3 treatment-naïve trials (ION-1 and ION-3) are robust and demonstrate the efficacy of LDV/SOF in this population. The SVR12 rates for the five treatment arms in ION-1 and ION-3 were at least 93%. These SVR12 rates were all superior to the 60% historical control. As shown in the tables below RBV use did not impact the SVR12 rates. Only one relapse was noted in ION-1. In ION-3 23 relapses were observed (20 in the 8 week arms and three in the 12 week arm). As shown in the statistical review, no statistically significant differences in SVR12 rates between any two groups were noted. However, clinical differences were noted for relapse rates in ION-3 and are further discussed below.

ION-1

A total of 865 subjects were randomized and treated and 97% of these subjects (863/865) completed treatment. The SVR12 rates are displayed in the table below. Additionally, SVR12 rates by the protocol-specified stratification factors are the following. Within the LDV/SOF 12 week arm, SVR12 rates for subjects with genotype 1a and 1b were 98% and 100%, respectively. Similarly, SVR12 rates were 99% and 94% in non-cirrhotic and cirrhotic subjects, respectively.

Response Rates in Study ION-1

	LDV/SOF 12 Week (N=214)	**LDV/SOF+RBV 12 Week (N=217)**
SVR12 rate[a] (# of responders/N) [95% CI]	99% (210/213) [95.9% to 99.7%]	97% (211/217) [94.1% to 99.0%]
Not achieving SVR12 On-treatment virologic failure Relapse[a,b] Other[a,c]	 0/213 0.5% (1/212) 0.9% (2/213)	 0/217 0/217 2.8% (6/217)

a. Excluding one subject with genotype 4 infection
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).
Source: Dr. Karen Qi, Statistical Reviewer

ION-3

A total of 647 subjects were randomized and treated and 99% (639/647) completed treatment. The SVR12 rates are displayed in the table below. The treatment difference between the 8-week treatment of LDV/SOF and 12-week treatment of LDV/SOF is -2.3% (97.5% confidence interval -7.2% to 2.5%).

Response Rates in ION-3

	LDV/SOF 8 Week (N=215)	LDV/SOF+RBV 8 Week (N=216)	LDV/SOF 12 Week (N=216)
SVR12 rate (# of responders/N) [95% CI]	94% (202/215) [89.9%, 96.7%]	93% (201/216) [88.8%, 96.1%]	96% (208/216) [92.8%, 98.4%]
Not achieving SVR12 On-treatment virologic failure Relapse[a] Other[b]	 0% (0/215) 5.1% (11/215) 0.9% (2/215)	 0% (0/216) 4.2% (9/214) 2.8% (6/216)	 0% (0/216) 1.4% (3/216) 2.3% (5/216)

a. The denominator for relapse is the number of subjects with HCA 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).
Source: Dr. Karen Qi, Statistical Reviewer

SVR12 rates for the protocol specified stratification factor (genotype 1a and 1b) by treatment duration is summarized in the table below.

Response Rates in Study ION-3

	LDV/SOF 8 Weeks (N = 215)	LDV/SOF 12 Weeks (N = 216)
Genotype		
Genotype 1a	93% (159/171)	96% (165/172)
Genotype 1b	98% (42/43)	98% (43/44)

In the two 8 week treatment arms, relapse was the main reason for not achieving SVR12. A statistically significant lower relapse rate in the 12 week arm compared to the pooled and unpooled 8 week arms was observed.

As a result the statistical, clinical and virology reviewers developed a review plan to evaluate the characteristics of those subjects who relapsed to determine if certain subjects could benefit from the longer treatment duration (12 weeks) or receive an 8 week duration while minimizing the consequence of relapse. The following baseline factors were considered in a post hoc exploratory subgroup analyses for relapse: age (< 50, ≥ 50 years), gender, race, weight (≤ 82 [median weight], > 82 kg), BMI (< 30, ≥

30 kg/m^2), HCV genotype (1a or 1b), IL28B (CC, non-CC), baseline HCV RNA, baseline ALT (≤1.5 x ULN, > 1.5 x ULN), baseline NS5A polymorphisms and viral kinetics (HCV RNA target not detected or detected at Weeks 1 or 2). As shown in Dr. Qi and Connelly's reviews, the 12 week treatment duration showed numerically lower relapse rates for almost all subgroups compared to the pooled 8 week arms. The differences in relapse rates were more apparent in age ≥ 50 years, male subjects and subjects with genotype 1a. A 4% difference in relapse rates between the 8 week and 12 week arms was seen for both the CC and non-CC IL28B subgroups. No relationship between early viral kinetics and relapse was seen. Additionally in subjects with baseline NS5A resistance-associated polymorphisms the relapse rate was 6.3% (3/48) for the 8 week group compared to 0% (0/56) for the 12 week group. Dr. Qi noted no statistically significant interactions between treatment duration and these subgroups.

Because baseline HCV RNA is historically an important prognostic factor for HCV treatment, a comparison of relapse rates for the pooled 8 week arms and 12 week arm using 13 baseline HCV RNA cut-offs was conducted (details shown on pages 27 and 28 of the statistical review). Two important findings were noted. No relapse occurred in any treatment arm among subjects with baseline HCV RNA < 1.5 million IU/mL compared to 4.4% difference in relapse rates between the two durations for subjects with baseline HCV RNA ≥ 1.5 million IU/mL. Additionally an HCV RNA 6 million IU/mL cut off value was an important predictor of relapse. The 6 million IU/mL cut off was the largest proportion difference between the 8 and 12 week durations as shown below.

	8-Week LDV/SOF & LDV/SOF+RBV	12-Week LDV/SOF	Proportion Difference (95% Exact CI[1])	P-value for Interaction Based on Zelen's Test
< 1.5 million	0% (0/114)	0% (0/60)	0% (-3.3%, 6.7%)	not significant
≥ 1.5 million	6.4% (20/315)	1.9% (3/156)	4.4% (0.3%, 8.1%)	
< 6 million	1.9% (5/260)	1.5% (2/131)	0.4% (-3.7%, 3.2%)	0.20
≥ 6 million	8.9% (15/169)	1.2% (1/85)	7.7% (1.9%, 13.3%)	

Source: Adapted from Dr. Karen Qi's review

Initially the review team proposed a table for relapse rates for selected subgroups for inclusion in the label, section 14, Clinical Studies. The subgroups included genotype 1a and 1b, presence or absence of baseline NS5A resistance-associated substitutions, IL28B status (CC or non-CC) and baseline HCV RNA (< 1.5 million, ≥ 1.5 million and < 6 million, ≥ 6 million). Gilead responded that an exact logistic regression analyses was performed for the above mentioned variables and HCV RNA ≥ 6 million IU/mL was the only significant baseline factor associated with relapse. Based on this and other factors the review team concluded a table displaying relapse rates based only on baseline HCV RNA of 6 million IU/mL was reasonable.

In summary, our review goal was to optimize treatment success with the first LDV/SOF regimen and minimize relapse and development of NS5A and/or NS5B resistance associated substitutions which could negatively impact future retreatment options. Based on the collective analyses, we concluded a 12 week regimen is recommended for treatment-naïve subjects without cirrhosis. However, an 8 week duration could be considered for treatment-naïve, non-cirrhotic subjects with baseline HCV RNA < 6 million IU/mL. HCV RNA is performed prior to starting treatment, therefore, a treatment duration decision based on pretreatment HCV RNA is not a burden to clinicians or patients.

For treatment-naïve subjects with cirrhosis, the review team considered including a duration of 24 weeks for patients with multiple baseline factors traditionally associated with a lower response to HCV treatment. Our concern was related to wider use of LDV/SOF for 12 weeks post-marketing that may result in lower response rates than observed in ION-1;a longer duration may also minimize relapse rates. Further, the consequences of treatment failure in patients with cirrhosis include risk of progression to decompensation and hepatocellular carcinoma. However, only one subject relapsed in ION-1. The data submitted demonstrate a high SVR12 rate and low relapse rate for treatment-naïve cirrhotic subjects; thereby supporting the 12 week treatment duration.

Treatment-experienced adults with and without cirrhosis:

ION-2

A total of 440 subjects were randomized and treated and 99% (437/440) completed treatment. The median age is 57 years, and the majority of subjects were white (81%) and male (65%). A higher percentage of HCV genotype 1a (79%) and IL28B non-CC subjects (88%) were enrolled in ION-2 compared to ION-1 and ION-3. Twenty percent of subjects had cirrhosis. Approximately 56% subjects had prior relapse/breakthrough, 44% had prior nonresponse to PR treatment and 53% failed prior HCV protease inhibitor + PR treatment. The SVR12 rates across the four treatment arms range from 94-99% and are displayed in the table below. All treatment arms were superior to the historical control SVR12 rate of 25%. Ribavirin use did not impact the SVR12 rates. Response rates were similar and ranged from 92-100% in subjects who received prior PR or HCV protease + PR based treatment and in subjects who were prior relapse/breakthrough or non-responders.

Response Rates in ION-2

	LDV/SOF 12 Week (N=109)	LDV/SOF +RBV 12 Week (N=111)	LDV/SOF 24 Week (N=109)	LDV/SOF +RBV 24 Week (N=111)
SVR12 rate (# of responders/N) [95% CI]	94% (102/109) [87.2%, 97.4%]	96% (107/111) [91.0%, 99.0%]	99% (108/109) [95.0%, 100%]	99% (110/111) [95.1%, 100%]
Not achieving SVR12				
On-treatment virologic failure	0% (0/109)	0% (0/111)	0% (0/109)	0.9% (1/111)
Relapse	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/111)
Other	0% (0/109)	0% (0/111)	0.9% (1/109)	0% (0/111)

Source: Adapted from Dr. Karen Qi

The SVR12 rates for the protocol specified stratification factors were the following for the LDV/SOF 12 and 24 week treatment arms.

SVR Rates for Selected Subgroups in Study ION-2

	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.

Of note, no relapse occurred in the two 24 week treatment arms whereas 11 subjects relapsed across the two 12 week treatment regimens. Similar to ION-3 the review team conducted several post-hoc exploratory analyses to determine if certain patients would benefit from a longer treatment duration. Of note, the Applicant proposed a 12 week treatment duration for treatment-experienced patients (b) (4) without cirrhosis. No apparent interaction between treatment duration and the following subgroups were identified: age, sex, race, HCV genotype, IL28B status, prior HCV therapy and prior response to HCV therapy. We did note the presence of cirrhosis was an important

baseline factor predictive of treatment-response. Seven of the 11 subjects experiencing relapse had cirrhosis. As shown below, compared to the pooled 12 week arms, the relapse rate for the pooled 24 week arms is 15.9% lower (95% CI 6.5%, 29.8%) in the cirrhotic subjects versus only 2% lower (95% CI 0.1%, 6.0%) in the non-cirrhotic subjects. Note the two 95% CI do not overlap.

Response and Relapse Rates in Subjects with Cirrhosis, ION-2

	LDV/SOF 12 Week	LDV/SOF+RBV 12 Week	LDV/SOF 24 Week	LDV/SOF+RBV 24 Week
N	109	111	109	111
Cirrhosis - Yes				
SVR12	86% (19/22)	82% (18/22)	100% (22/22)	100% (22/22)
Relapse	13.6% (3/22)	18.2% (4/22)	0% (0/22)	0% (0/22)
Cirrhosis - No				
SVR12	95% (83/87)	100% (88/88)	99% (85/86)	99% (88/89)
Relapse	4.7% (4/86)	0% (0/88)	0% (0/86)	0% (0/88)

Source: Dr. Karen Qi, Statistical Reviewer

In addition to the presence of baseline cirrhosis, other important baseline characteristics were found to affect relapse rates although no significant treatment interaction was seen. Notably of the non-cirrhotic subjects who relapsed, all four had baseline NS5A resistance associated polymorphisms.

Relapse Rates for Selected Subgroups in ION-2

	LDV/SOF 12 Weeks (N=109)	LDV/SOF 24 Weeks (N=109)
Number of responders at end of treatment	108	109
Cirrhosis		
No	5% (4/86)[a]	0% (0/86)
Yes	14% (3/22)	0% (0/22)
Presence of Baseline NS5A Resistance-Associated Polymorphisms[b]		
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. These 4 non-cirrhotic relapsers all had baseline NS5A resistance associated polymorphisms.
b. NS5A Resistance Associated Polymorphisms include any change at NS5A positions K24, M28, Q30, L31, H58, A92 or Y93.

Based on the results presented above, the review team concluded LDV/SOF for 24 weeks was the appropriate duration for treatment-experienced subjects with cirrhosis. LDV/SOF for 12 weeks is recommended for treatment-experienced noncirrhotic subjects. The SVR rate in treatment-experienced non-cirrhotic population with

LDV/SOF for 12 weeks was 95% compared to 99% for LDV/SOF for 24 weeks. The difference was not statistically significant. Based on the exploratory analyses to identify a subset of treatment-experienced non-cirrhotic patients who could benefit from a 24 week regimen, no baseline factors were predictive of treatment response. The only common feature among the non-cirrhotic subgroup of patients who relapsed was the presence of baseline NS5A resistance associated polymorphisms. This information is displayed as a footnote in the label. We are not recommending screening for presence of baseline NS5A resistance associated polymorphisms to make clinical decisions regarding duration of treatment. Presently a commercial assay is not available. These data could be considered in the future by clinicians to make individual patient recommendations.

Concordance between SVR12 and SVR24 was assessed for each trial. FDA has shown concordance between SVR12 and SVR24 for PR based regimens (hence supporting the change in the primary endpoint from SVR24 to SVR12) and this assessment was done to confirm if similar findings for non-PR based regimens are seen. Based on the available data submitted concordance between SVR12 and SVR24 was >99% and similar to observations seen for PR based regimens.

In ION-2 206 of the 219 subjects had both SVR12 and SVR24 data available and 205 subjects achieved SVR12 and SVR24 (99.5% concordance). In ION-1 SVR12 and SVR24 data were available for Part A (first 96 subjects enrolled). Concordance between SVR12 and SVR24 was 100%. SVR24 data were not available from ION-3.

8. Safety

This section focuses on the safety data from the Phase 3 trials. Pertinent data from Phase 2 and the safety update report is also briefly referenced. Overall Dr. Sarah Connelly's independent analyses of the safety data confirmed the Applicant's findings with few exceptions and did not affect the overall safety assessment.

Adequacy of Safety Database:

The safety database for LDV/SOF for 8-24 weeks is adequate and consistent with the safety considerations as outlined in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment . A total of 2462 subjects received LDV/SOF at the to be marketed doses, including 1952 subjects in Phase 3 trials, 253 subjects in Phase 2 trials and 257 subjects in the Phase 1 trials. Approximately 2180 subjects received LDV/SOF+/-RBV for ≥ 8 weeks; 1708 subjects received LDV/SOF+/-RBV for ≥ 12 weeks and 654 subjects received LDV/SOF +/- RBV for ≥ 24 weeks, of whom 630 completed treatment. The primary safety population includes 1952 subjects from Phase 3.

General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

No on-treatment deaths were reported in Phase 2 or 3 LDV/SOF trials. In ION-1, one death (hepatic failure secondary to HCV infection and alcohol use in a cirrhotic subject) occurred post-treatment and not related to study treatment.

Nine deaths were reported in the safety update report and occurred in subjects enrolled in ongoing trials (Japanese trial GS-US-337-0113 and SOLAR-1 in subjects with advanced liver disease or who are post-liver transplantation). I agree with Dr. Connelly's assessments of the reported deaths. Of the eight deaths in SOLAR-1 no clustering of events were seen and cause of death is likely attributed to comorbidities in this advanced liver disease/post-transplant population. Two deaths occurred in Phase 2 trials with LDV in combination with other investigational DAAs with and without PR. These deaths (respiratory failure following hemorrhagic stroke with associated elevated blood pressure and cause of death unknown) were not considered related.

Overall the incidence of nonfatal SAE was low (51 subjects: 2.6%) in the Phase 3 trials and comparable across treatment groups. The LDV/SOF 24 week arm had a higher rate of nonfatal SAEs (7%) compared to the other groups (<1%); however many of the nonfatal SAEs were reported within the first 12 weeks of treatment. Only five subjects experienced drug related SAE (headache, salpingitis, mesenteric vein thrombosis and Factor VIII inhibition). Headache is a labeled event and the other cases suggest an alternative etiology.

The discontinuation rate due to adverse events in Phase 3 was low and occurred in <1% (13/1952) of subjects receiving LDV/SOF +/- RBV. The only event leading to discontinuation in more than one subject was palpitations and anxiety (two subjects each and all Grade 2 or less).

The safety assessment for commonly reported events focused on the LDV/SOF arms without ribavirin. Dr. Connelly's assessment was in agreement with the Applicant in that the addition of RBV to LDV/SOF resulted in an increased incidence of AEs and increased need for dose modification or interruption. Given RBV did not increase SVR12 rates, we concluded the benefit/risk assessment was not favorable for the addition of RBV to LDV/SOF. Therefore, the commonly reported safety analyses focused on the LDV/SOF without RBV for 8, 12 and 24 week arms.

The most commonly reported adverse reactions (all grade, related) in subjects receiving 8, 12 or 24 weeks of LDV/SOF treatment were fatigue (13-18%), headache (11-17%), nausea (6-9%), diarrhea (3-7%) and insomnia (3-6%). Overall 46 subjects (4%) experienced a Grade 3 or 4 adverse event. For the pooled LDV/SOF treatment groups no notable differences were seen between subjects ages $\geq$ 65 years with AEs compared to subjects < 65 years. Similar findings were seen for race. Black African American subjects have similar/lower percentage of AEs compared with non-

black/African-Americans. As noted previously noted females have higher LDV exposures compared to men; however no clinically significant safety differences were noted between men and women.

Additionally, as noted above, our recommended treatment duration was extended for certain patient populations, specifically extending the duration from 8 to12 weeks in treatment-naïve non-cirrhotic patients and extending the duration from 12 to 24 weeks in treatment-experienced cirrhotic patients. As a result Dr. Connelly conducted analyses to determine if the safety profile differs for LDV/SOF 8 vs 12 weeks in treatment-naïve non-cirrhotic subjects and 12 vs 24 weeks in treatment-experienced cirrhotic subjects by determining if new AEs occur beyond Week 8 or greater than Week 12 for the respective analyses. I agree with Dr. Connelly's conclusions in that these analyses did not identify a negative safety consequence for extending LDV/SOF treatment from 8 to 12 weeks for treatment-naïve non-cirrhotic patients or extending the duration from 12 to 24 week for treatment-experienced cirrhotic patients. The majority of events occurred in the less than 8 or less than 12 week window for the respective analyses. Of the events occurring greater than 8 weeks or greater than 12 weeks in the respective analyses, the events were manageable and Grade 2 or less in severity. For example, events occurring outside the Week12 window include memory impairment, malaise, rash and edema/depression with no event occurring in more than one subject.

Focusing on the LDV/SOF without RBV treatment arms, the incidence of overall laboratory abnormalities was low. Only three laboratory abnormalities are proposed for labeling and include bilirubin, lipase and creatine kinase.

Lipase elevations were seen during the SOF NDA review and are a labeled laboratory abnormality. Overall the incidence of lipase elevations > 1 x ULN ranged from 9-17% for the LDV/SOF 8,12 and 24 treatment arms with a numerical trend of increased incidence with longer duration. The incidence of asymptomatic lipase increases of greater than 3 x ULN was <1%, 2% and 3% of subjects treated with LDV/SOF for 8, 12 and 24 weeks respectively. This finding is consistent with the experience with SOF in combination with RBV or PR. No cases of pancreatitis were reported in Phase 3. One case of pancreatitis was reported post treatment and not related to study drug. Two cases of pancreatitis in the LDV+investigational DAA trials were reported and confounded by underlying comorbidities and/or concomitant medication use. Events of pancreatitis will be monitored postmarketing.

Although creatine kinase was not assessed in the Phase 3 trials, isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) were reported with SOF in combination with RBV or PR; therefore, this laboratory abnormality is mentioned in product labeling. Of note, one case of non-drug related rhabdomyolysis was observed in the LDV/SOF group on post-treatment day 12 following a motor vehicle accident. Events of rhabdomyolysis/myopathy will be monitored during postmarketing.

We recommended inclusion of bilirubin data in the label because biliary excretion of unchanged LDV is a major route of elimination which is supportive of a potential causal relationship. Grade 1 bilirubin elevations (>1 to 1.5x ULN) were seen in 4%,

4% and 5% of subjects treated with LDV/SOF for 8, 12 and 24 weeks, respectively Bilirubin elevations of greater than 1.5xULN were observed in 3%, <1% and 2% of subjects treated with LDV/SOF for 8, 12 and 24 weeks, respectively. See discussion below regarding gallbladder events.

Special safety concerns

Dr. Connelly conducted detailed reviews of adverse events of interest based upon SOF labeling (rhabdomyolysis/myopathy, lipase elevations/pancreatitis, depression and suicidal events) and primary safety concerns based upon LDV preclinical data, selected designated medical events or SAEs. The primary safety concerns included ocular events, Factor VIII inhibition, gastrointestinal events, hepatic events, gallbladder events, rash, myocardial ischemia events, fall and fracture events, dizziness events, hypersensitivity/analphylaxis/angioedema/swollen tongue events and chest pain events. This review will not discuss Factor VIII inhibition, rash, fall and fracture, dizziness or hypersensitivity/anaphylaxis/angioedema/swollen tongue events. A causal relationship was not found for these events and therefore labeling of these events is not supported. Of note, the Division of Hematology Products consulted on the Factor VIII inhibition cases. Please refer to Dr. Connelly's review for details.

Events of interest based upon SOF labeling:

Cases of rhabdomyolysis and pancreatitis are discussed above. Severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide is listed as a less common adverse reaction in the SOF label. The overall incidence of depression and suicidal events was 3.9% (2.7% with LDV/SOF and 5.4% for LDV/SOF/RBV). Sixty percent of subjects reported a psychiatric disorder history. All events were Grade 2 or less and none led to discontinuation of LDV/SOF. Three events of suicidal ideation occurred in the Phase 3 trials, all continued study mediation and all had pre-existing psychiatric history. The Phase 2 events are confounded by concomitant RBV or PR use and the majority of events occurred in subjects with underlying psychiatric history. Although depression and suicidal ideation are labeled events for SOF, we concluded inclusion of these events in the LDV/SOF label is not warranted at this time. The observed events during the SOF NDA review were confounded by RBV or PR use, both of which have known neuropsychiatric effects. Cases of drug related depression or suicidal ideation with LDV/SOF were neither serious nor resulted in treatment interruption.

Primary events of interest:

Ocular events

As previously noted preclinical studies demonstrated LDV absorbs UV light and accumulates in the uveal tract of the eye in pigmented rates. Ocular-related events range 3-6% across the LDV/SOF treatment arms, with no trend with increased duration. No SAEs were reported and all events were Grade 1-2 in severity. The most

common events were blurred vision and dry eye (1% each). Two ocular-related SAEs were observed in Phase 2 trials (iritis/vitritis (possibly related) and uveal suffusion syndrome (not related)). Dr. Bill Boyd from the Division of Transplant and Ophthalmology Products reviewed the SAEs and Phase 3 ocular-related trial data. He concluded LDV has a low potential for ocular toxicities, no significant ocular events were seen and additional clinical monitoring or labeling is not warranted. Additionally, results of the in vivo study in pigmented rats to assess potential ocular phototoxicity was negative (See Dr. Chris Ellis' review for details).

Gastrointestinal Events

Gastrointestinal events related SAEs were observed during SOF NDA review. Dr. Connelly concluded no obvious safety signal for serious gastrointestinal toxicity was seen with LDV/SOF use. All grade, related nausea and diarrhea are proposed for labeling and range from 3-9%. Six gastrointestinal SAEs were reported in Phase 3 trials and none were considered related. Review of Phase 2 LDV/SOF did not reveal any safety concerns. Overall a low frequency of serious or grade 3/4 gastrointestinal events was seen. Additionally a preclinical signal for gastrointestinal events with LDV was not evident; although a preclinical signal with SOF was seen (gastrointestional hemorrhage and increased frequency and incidence of emesis and diarrhea in male dogs). Further labeling is not warranted.

Hepatic events

LDV/SOF is recommended for subjects with underlying liver disease; therefore, a comprehensive hepatic safety evaluation was conducted. Additionally, as previously noted, slight increases in ALT associated with increased liver/gallbladder weight without corresponding histopathology was seen in mice. No hepatotoxicity signal was observed in humans. Overall 16 subjects experienced an adverse event within the hepatic and hepatobiliary disorder group, of which only three cases (acute hepatitis, hepatomegaly and jaundice) were observed with LDV/SOF without RBV (all in the 12 week arm). No on-treatment cases of serious hepatotoxicity or Hy's Law cases were identified in Phase 2 and 3. No subject in Phase 3 trials met the liver related protocol-specified stopping rules. One case of acute hepatitis four weeks after LDV/SOF discontinuation was reported and considered not likely related to LDV/SOF use with another casual etiology likely probable. Cases reported in Phase 2 were all confounded by use with other investigational DAA's that were known to increase bilirubin due to OATP1B1 hepatic transporters and had known preclinical findings of increased liver enzymes. The proportion of subjects with ALT/AST > 5 x ULN was <0.5% in the Phase 3 trials. Bilirubin elevations are observed with LDV/SOF as noted above. Based on these data no specific labeling aside from bilirubin increases is warranted at this time.

Gallbladder Disorders

An assessment of cholecystitis and cholelithiasis was done given the biliary excretion mechanism and potential LDV-related mild hepatobiliary toxicity signal noted in mice and rats. These events were infrequent with only three cases in the Phase 3 trials (0.2%). A possible causal relationship between LDV/SOF and gallbladder related events exist based on the biliary excretion mechanism. I agree with Dr. Connelly's assessment in that the cases presented in the NDA more likely are consistent with background rates. The literature suggests a higher incidence of gallstones in HCV infected population and cirrhosis, female sex, obesity and older age are identified risk factors.
Aside from inclusion of bilirubin elevations in the label, additional labeling for hepatotoxicity and gallbladder disorders is not warranted at this time. These events will be monitored postmarketing.

Cardiac Disorders

During the SOF review, a detailed analysis of cardiac disorders including cardiac failure, cardiomyopathy and congestive heart failure cases was conducted. This targeted review was done because during the development of an investigational NS5B, BMS-986094, nine patients were hospitalized and one died due to heart failure. Although SOF is structurally different than BMS-986094, a detailed review of cardiac disorders was done. Based on the SOF review, no obvious safety signal was noted for cardiac toxicity. Nevertheless, another review was undertaken with this NDA. In Phase 3, approximately 1% (28 subjects) reported a cardiac disorder. Most were Grade 1 (79%). Palpitations was the most common event within this system organ class and occurred more in the RBV-containing arms (1.5%) compared to non RBV-containing arms (<1%). In the LDV/SOF development program, six subjects experienced cardiac failure or cardiomyopathy, of which five cases had significant underlying heart disease. The sixth case was in a liver transplant patient in the setting of decompensated cirrhosis, hepatopulmonary syndrome and Clostridium perfringens bacteremia. Based on the totality of the data no obvious evidence for LDV/SOF cardiotoxicity is seen.

Additionally cases of MI and chest pain were reviewed due to several events noted during ongoing trials or SAE reports in Phase 3.

Several MI events were seen during development; therefore FDA requested a summary and evaluation by the Applicant. A causal relationship was not seen for LDV/SOF use and MI. Of the 3264 subjects evaluated nine (0.3%) experienced an MI. Two were considered related; however, both had alternative causalities (infection or preexisting condition). The majority of other cases had known risk factors for preexisting coronary artery disease. Most subjects did not discontinue treatment.

Chest pain was assessed due to five SAEs seen in the Phase 3 trials. Overall 2.3% of subjects reported chest pain events, more events seen with LDV/SOF +RBV use.

None of the SAEs were considered related. No obvious safety signal was noted by Dr. Connelly.

In summary LDV/SOF has a favorable safety profile. No safety related Warnings and Precautions are recommended and no safety related REMS are needed. Extending the duration from 8 to 12 weeks for treatment naïve non-cirrhotic subjects or extending the duration from 12 to 24 weeks for treatment-experienced cirrhotic subjects did not have a negative impact on the overall safety profile. In fact the majority of events seen in the 12 or 24 week treatment arms were seen within the first 8 or 12 weeks. Adverse events and laboratory abnormalities seen in Phase 3 are manageable and easily monitored.

9. Advisory Committee Meeting

No meeting was held. See section 2 for rationale.

10. Pediatrics

To date, no trials in subjects < 18 years of age were conducted or are ongoing. The Applicant submitted a waiver for less than three years of age and a deferral for greater than or equal to three years of age. The requested waiver and deferral are consistent with other DAA NDAs. The Division has waived all trials in HCV infected children less than three years of age because infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection. Based on these data, the small number of patients in these age groups, and current practice guidelines, a waiver for children less than 3 years of age is deemed appropriate. The waiver and deferral were accepted by the PeRC.

The Applicant plans to conduct three trials as part of their LDV/SOF pediatric development plan for subjects with genotype 1, 2, 4, 5, and 6 HCV infection. Trials GS-US-337-1116 (b) (4) will be PMRs. The Division is in agreement with the pediatric study plans.

BP-US-337-1115 – Phase 1 Bioavailability Study of Pediatric Formulation of SOF/LDV in Healthy Adult Subjects
Protocol submission: May, 2015
Trial completion: September, 2015
Final report submission: May, 2016

GS-US-337-1116 – Phase 2, Two Part Open-Label, Single Arm Study of SOF/LDV in GT 1, 2, 5, 4, 6 Chronic HCV-Infected Adolescents and Children
Protocol submission: July, 2014
Trial completion: June, 2018
Final report submission: February, 2019

(b) (4)

11. Other Relevant Regulatory Issues

Office of Scientific Investigation Inspections

Six domestic sites were inspected. The data submitted are considered acceptable. Please refer to the OSI Consult Review for further details.

Good Clinical Practice

The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines. No GCP issues were identified.

Financial Disclosures

Financial disclosures were reviewed for all investigators involved in Phase 3 trials used for assessment of efficacy and safety in the Division's review. See Dr. Connelly's review for full details. Dr. Connelly concluded the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

12. Labeling

The proprietary name Harvoni was found acceptable. Several labeling discussion with respect to treatment duration and patient population based on SVR12 rates and relapse rates are described in section 7 above. Additional label discussions are summarized in section 5.

At the August 7, 2014 Late Cycle meeting, all labeling changes were agreed to by the Applicant with one exception. As mentioned in section 5, we are currently reviewing safety data to make recommendations for use with tenofovir-containing regimens. Additionally, the Applicant will propose text to discuss the concordance between SVR12 and SVR24 data from ION-2.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** I agree with the review team's assessment and recommend approval of LDV/SOF FDC for the treatment of chronic hepatitis C genotype 1 infection pending satisfactory outcome from CMC inspections.

- **Risk Benefit Assessment:**

  LDV/SOF was effective and safe in a broad population of HCV infected genotype 1 subjects (treatment-naïve and treatment-experienced with and without cirrhosis). The data submitted provide sufficient evidence to recommend LDV/SOF FDC once daily for the treatment of chronic hepatitis C genotype 1 infection. Sufficient data were provided to assess the contribution of each component, LDV and SOF, to the FDC regimen. Across the three Phase 3 trials, all treatment arms were superior to the pre-specified historical control rate. The addition of RBV did not improve SVR12 rates and given the increased rate of RBV-associated adverse events and dose reduction/interruption, the benefit/risk assessment did not support an RBV-containing regimen for any patient population studied. High SVR12 rates (94-99%) were seen across all LDV/SOF treatment arms. In ION-1, the 12 week LDV/SOF achieves SVR12 of 99% with only one subject experiencing relapse. In ION-3, the SVR12 rate for treatment-naïve non-cirrhotic subjects was 94% and 96% for the LDV/SOF 8 and 12 week treatment arms, respectively. In the treatment-experienced ION-2 trial, the SVR12 rates for the LDV/SOF 12 and 24 week arms were 94% and 99%, respectively. High SVR12 rates were seen in subgroups who traditionally have lower response rates during treatment, including cirrhosis, high baseline HCV RNA, and non-CC IL28B status. Importantly SVR12 rates of 94-98% were seen in prior HCV protease inhibitor + PR failures, currently a population of unmet medical need.

  Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups. The consequences of relapse include potential development of NS5A or NS5B resistance substitution which could affect future HCV treatment options. This is especially a concern for patients with cirrhosis who risk progression of their liver disease to hepatic decompensation or hepatocellular carcinoma. As a result the treatment duration was extended from 12 to 24 weeks in treatment-experienced patients with cirrhosis. Relapse was not observed in the 24 week LDV/SOF containing arms. In comparison relapse was seen in a total of 11 subjects (9%) in the pooled 12 week treatment arms, of which 7 subjects had cirrhosis. No safety signal was evident to preclude extending the duration to 24 weeks for treatment-experienced cirrhotic patients.

Additionally, the treatment duration was extended from 8 weeks to 12 weeks in non-cirrhotic treatment-naïve patients. An 8 week regimen for patients with baseline HCV RNA < 6 million IU/mL can be considered. Again, no safety signal was evident to preclude extending the duration to 12 weeks for this population.

The overall safety profile was favorable. I echo Dr. Connelly's conclusion, "although no safety signal is identified for LDV/SOF treatment up to 24 weeks, the Phase 3 trials included robust safety monitoring and entry criteria which may have mitigated potential safety concerns that may not be observed until use in a wider population." Grade 3 or 4 adverse events were infrequent and the proportion of subjects who permanently discontinued treatment due to adverse events was 0%, <1% and 1% for subjects receiving LDV/SOF for 8, 12 and 24 weeks, respectively. No adverse event or laboratory related Warnings or Precautions are warranted.

LDV/SOF appears to provide a number of advantages, including improved tolerability as this represents the first non-PR containing regimen, manageable safety profile, ease of administration, one pill once a day, and high SVR12 rates across various patient populations including those with cirrhosis and prior HCV protease inhibitor failures. The overall benefit/risk assessment is favorable.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Based on the safety profile of LDV/SOF FDC, the Division does not recommend a Risk Evaluation and Management Strategy (REMS).

- Recommendation for other Postmarketing Requirements and Commitments

Below is a recommended list of PMR/PMCs. The Applicant agreed to these during the August 7, 2014 late cycle meeting. Final dates for protocol and data submissions are forthcoming from the Applicant. Seven PMRs are recommended. We are waiting a recommendation from SRT to determine if the request for longitudinal data on persistence of NS5A resistance substitutions is a PMR or PMC.

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir 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 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.

- 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 ledipasvir/sofosbuvir 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", (b) (4) in order to provide dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents (e.g., cyclosporine).
- Submit the final report for the ledipasvir 2-year carcinogenicity study in rats.
- Submit the final report for the ledipasvir 26-week carcinogenicity study in rasH2 mice.
- Determine the phenotypic assessment of sofosbuvir against: A112T, E237G, and NS5B_S473T in the HCV GT1a replicon.
- 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.

- **Recommended Comments to Applicant**

No additional comments for the Applicant at this time

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A STRUBLE
08/08/2014