CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205834Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL PRODUCTS

DATE: September 25, 2014
TO: NDA 205834 SDN 32, received August 7, 2014
FROM: Medical Officer, Division of Antiviral Products
SUBJECT: GS-US-337-0115 and NIAID-13-I-0159 Summary Interim Safety Data
GS-US-337-0115, *A Phase 3, Multicenter, Open-Label Study to Investigate the Safety and Efficacy 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 Infections*
NIAID-13-I-0159, *An Open Label Trial to Assess Safety, Tolerability, and Efficacy of the Fixed Dose Combination of GS-5885 and GS-7977 in HCV Genotype 1 Subjects Coinfected with HIV*

Summary interim safety data are available from approximately 175 subjects who received LDV/SOF plus Atripla (or its components) within the GS-US-337-0115 and NIAID-13-I-0159 trials, including approximately 94 subjects receiving a 12 week treatment duration. No subject discontinued LDV/SOF and a single subject changed their antiretroviral regimen from Atripla to EFV/RAL/FTC based upon laboratory evidence of renal dysfunction. Graded creatinine increases from GS-US-337-0115 were low (approximately 2.5%) and all were ≤Grade 2. One subject from the NIAID trial with baseline eGFR of 52.5 mL/min experienced treatment-emergent eGFR <50 and normoglycemic glycosuria. The eGFR improved to 52.2 mL/min by Week 12 and normoglycemic glucosuria was no longer detectable at post-treatment Week 2.

In summary, although LDV/SOF and Atripla coadministration increased tenofovir exposures by up to ~2-fold in the phase 1 DDI trial GS-US-337-0127, preliminary safety data from the GS-US-337-0115 and NIAID trials are determined to be adequate to support labeling for LDV/SOF and Atripla coadministration. (b) (4) Labeling regarding LDV/SOF and Atripla coadministration will refer to the respective tenofovir labels to inform providers of the need for close renal monitoring: please refer to Dr. Jenny Zheng's clinical pharmacology review for further details. Submission of the GS-US-337-0115 final clinical study report and datasets is an agreed upon postmarketing requirement.

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/s/

SARAH M CONNELLY
09/25/2014

KIMBERLY A STRUBLE
09/25/2014

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	205834
Priority or Standard	Priority
Submit Date(s)	February 8, 2014
Received Date(s)	February 10, 2014
PDUFA Goal Date	October 10, 2014
Division / Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Sarah M. Connelly, MD
Review Completion Date	July 10, 2014
Established Name	Ledipasvir (GS-5885) 90 mg/Sofosbuvir (GS-7977) 400 mg Fixed Dose Combination
(Proposed) Trade Name	
Therapeutic Class	Hepatitis C virus NS5A inhibitor/Hepatitis C virus NS5B polymerase inhibitor
Applicant	Gilead Sciences, Inc.
Formulation(s)	Tablets for oral use
Dosing Regimen	
Indication(s)	Treatment of chronic hepatitis C
Intended Population(s)	Adult patients (18 years and

older) with chronic hepatitis C

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of ledipasvir (LDV)/sofosbuvir (SOF) fixed dose combination (FDC) for use in adults with chronic genotype 1 (GT 1) hepatitis C virus (HCV) infection. This recommendation is based on data contained in the NDA submission 205834. The efficacy and safety of LDV/SOF is demonstrated in the three pivotal phase 3 trials, GS-US-337-0102 (ION-1), GS-US-337-0108 (ION-3), GS-US-337-0109 (ION-2). The currently available data supports a favorable risk benefit assessment for the use of LDV/SOF in treatment-naïve and treatment-experienced patients with chronic HCV GT 1 infection.

Efficacy

The efficacy of LDV/SOF in subjects with chronic HCV GT 1 infection is demonstrated in three pivotal phase 3 trials (ION-1, ION-2, ION-3). The primary efficacy endpoint is sustained virologic response, defined as HCV RNA less than the lower limit of quantification (LLOQ) 12 weeks after discontinuation of treatment (SVR12). Overall phase 3 efficacy results are summarized here and details are further discussed in Section 6 (Review of Efficacy).

- The efficacy and safety of LDV/SOF with or without (±) ribavirin (RBV) for 12 weeks was evaluated in HCV treatment-naïve subjects with HCV GT 1 infection, including 16% with compensated cirrhosis (ION-1). A statistically significant proportion of subjects ($p<0.001$) in each treatment group achieved SVR12 (99% LDV/SOF 12 Week, 97% LDV/SOF+RBV 12 Week) compared to a prespecified historical control rate of 60%. Relapse rates are 0.5% in the LDV/SOF 12 Week arm and 0% in the LDV/SOF+RBV 12 Week arm.

- The efficacy and safety of LDV/SOF±RBV for 8 or 12 weeks was evaluated in HCV treatment-naïve subjects with HCV GT 1 infection and without cirrhosis (ION-3). A statistically significant proportion of subjects ($p<0.001$) in each treatment group achieved SVR12 (94% LDV/SOF 8 Week, 93% LDV/SOF+RBV 8 Week, 96% LDV/SOF 12 Week) compared to a prespecified historical control rate of 60%. Relapse rates are 5.1% in the LDV/SOF 8 Week arm, 4.2% in the LDV/SOF+RBV 8 Week arm, and 1.4% in the LDV/SOF 24 Week arm.

- The efficacy and safety of LDV/SOF±RBV for 12 or 24 weeks was evaluated in HCV treatment-experienced subjects with HCV GT 1 infection, including 20% with compensated cirrhosis and 53% prior HCV NS3/4A protease inhibitor (PI)-containing treatment failures (ION-2). A statistically significant proportion of

subjects (p<0.001) in each treatment group achieved SVR12 (94% LDV/SOF 12 Week, 96% LDV/SOF+RBV 12 Week, 99% LDV/SOF 24 Week, 99% LDV/SOF+RBV 24 Week) compared to a prespecified historical control rate of 25%. Relapse rates are 6.5% in the LDV/SOF 12 Week arm, 3.6% in the LDV/SOF+RBV 12 Week arm and 0% in each of the LDV/SOF±RBV 24 Week arms.

In summary, two phase 3 trials demonstrate efficacy in HCV GT 1 treatment-naive subjects: ION-1 demonstrates the efficacy of LDV/SOF±RBV for 12 weeks, and ION-3 demonstrates the efficacy of LDV/SOF±RBV for 8 weeks and LDV/SOF for 12 weeks in non-cirrhotic subjects. One phase 3 trial (ION-2) demonstrates the efficacy of LDV/SOF±RBV for 12 or 24 weeks in HCV GT 1 treatment-experienced subjects. ION-1 and ION-2 include a subset of subjects with compensated cirrhosis which represents a harder to treat subgroup.

Safety

The observed safety profile of LDV/SOF-containing treatment is favorable. No safety event warrants Warnings and Precautions labeling consideration at this time. No on-treatment deaths occur in the phase 3 program. The overall percentage of serious adverse events (SAE) and discontinuations due to adverse events (AE) is low. A LDV/SOF regimen has an improved safety profile compared with a LDV/SOF+RBV regimen with a lower incidence of treatment-emergent AEs, Grade 3 or higher AEs, and AEs leading to dose modification or interruption. No safety signal is identified precluding administration of LDV/SOF treatment duration up to 24 weeks. LDV/SOF treatment durations of 8 and 12 weeks have similar safety profiles in treatment-naïve, non-cirrhotic subjects. LDV/SOF treatment durations of 12 and 24 weeks have similar safety profiles overall and in cirrhotic subjects. No unique safety concerns are identified based on analyses of sex, race and age.

In summary, LDV/SOF provides an all-oral treatment option for patients with chronic HCV GT 1 infection. A LDV/SOF regimen offers an improved safety profile compared to known toxicities associated with both interferon-based and RBV-based regimens, and provides a therapeutic option for patients who cannot take interferon and/or RBV, addressing an unmet need in this population.

No deficiencies in the submitted data preclude recommendation for approval of LDV/SOF at this time.

1.2 Risk Benefit Assessment

The overall risk benefit assessment is highly favorable for LDV/SOF. This assessment is based upon the demonstrated efficacy results, observed safety profile and interferon-

free, once daily, simpler treatment regimen compared to currently available therapeutic regimens for the treatment of chronic HCV GT 1 infection.

Benefit

LDV/SOF is a once daily tablet, interferon-free regimen for the treatment of HCV GT 1 infection. The addition of RBV does not significantly increase SVR12 rates, and is associated with greater treatment-emergent AEs compared with LDV/SOF regimens without RBV. Thus the availability of an interferon- and RBV-free regimen represents a notable improvement both in terms of convenience and, perhaps more importantly, in terms of safety compared to known toxicities associated with both interferon-based and RBV-based regimens. In addition, LDV/SOF treatment provides a therapeutic option for patients with chronic HCV GT 1 infection who cannot take interferon and/or RBV, addressing an unmet need in this population.

High SVR12 rates are observed across the three pivotal trials. Limited to the LDV/SOF alone regimens, in the treatment-naïve trial ION-1, a 12 week regimen achieves SVR12 of 99%. In the treatment-naïve non-cirrhotic trial ION-3, the 8 and 12 week regimens achieve SVR 12 of 94% and 96%, respectively. In the treatment-experienced trial ION-2, the 12 and 24 week regimens demonstrate SVR12 of 94% and 99%, respectively. Furthermore, high SVR12 rates are demonstrated in many subgroups with baseline factors traditionally associated with lower response to HCV treatment such as cirrhosis, high baseline viral load, IL28B non C/C genotype. Finally, LDV/SOF provides an HCV treatment option achieving high SVR12 rates for patients who have failed a prior PI-containing regimen, a population currently in need of effective therapy.

The overall safety profile of LDV/SOF is acceptable. Based upon the phase 3 data, no clinically meaningful safety differences are identified with extending LDV/SOF treatment duration from 8 to 12 weeks or 12 to 24 weeks.

Risks

Differences in relapse rates between LDV/SOF treatment durations are observed in the treatment-naïve, non-cirrhotic ION-3 trial and in the treatment-experienced ION-2 trial, with the respective longer 12 and 24 week durations having lower relapse rates. The consequences of relapse include the potential development of NS5A and/or NS5B resistance substitutions which may limit future HCV treatment options, particularly in patients who have already failed a prior PI-based regimen and in patients with underlying cirrhosis who risk progression of their liver disease to hepatic decompensation and/or hepatocellular carcinoma.

Balanced with the consideration of extending LDV/SOF treatment to minimize relapse is the consequence of exposing patients to additional LDV/SOF. As noted

above, high SVR12 rates are achieved with the 8 and 12 week regimens and thus many patients will not require extended LDV/SOF treatment to successfully achieve virologic response. No safety signal is identified precluding extending LDV/SOF treatment up to 24 weeks; however, the pivotal phase 3 trial robust safety monitoring and entry criteria may have mitigated potential safety concerns that may not be observed until use in a wider population.

In summary, high SVR12 rates following LDV/SOF treatment are observed in the phase 3 HCV GT 1 treatment-naive and treatment-experienced populations, including subjects with cirrhosis and with prior PI-failure. RBV is not identified as necessary to achieve these high response rates, and is associated with greater safety events compared with LDV/SOF alone regimens. LDV/SOF regimens provide an effective, all oral, once daily, interferon-free and RBV-free regimen option for the treatment of chronic HCV GT 1 infection, an advantage in convenience and in an improved safety profile compared with PEG/RBV-containing regimens. In addition, LDV/SOF regimens provide a treatment option for patients with chronic HCV GT 1 infection who cannot take interferon and/or RBV and for patients who have failed a prior PI-containing regimen, addressing an unmet need in these populations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this LDV/SOF FDC NDA submission at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The pediatric trials to assess safety and efficacy of sofosbuvir for the treatment of chronic hepatitis C in pediatric subjects will be required under Pediatric Research Equity Act (PREA). Postmarketing commitments regarding submission of trial data in the HCV population with advanced liver disease or who are post-liver transplantation, including those with decompensated cirrhosis (GS-US-337-0123, SOLAR-1 trial) and trial data in the HCV/HIV-1 coinfected population (GS-US-337-0115 trial) are recommended to obtain LDV/SOF safety data in a broader population. Specifically, SOLAR-1 will provide safety data in subjects with severe hepatic impairment and/or in subjects receiving concomitant immunosuppressive agents (e.g., cyclosporine). GS-US-337-0115 will provide safety data in HCV/HIV-1 subjects receiving concomitant antiretroviral agents (e.g., tenofovir-containing regimens). Please see Sections 7.4.5 Special Safety Studies/Clinical Trials, 7.5.4 Drug-Disease Interactions and 7.5.5 Drug-Drug Interactions for additional details supporting this recommendation. Additional postmarketing commitments or requirements may be proposed at a later time based on ongoing labeling and review discussions.

2 Introduction and Regulatory Background

Globally it is estimated that approximately 170 million people are infected with HCV, including approximately 3 million people in the United States (US) (http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/). The most common HCV GT in the US is GT 1 (70-75%), followed by GT 2 and GT 3. The natural history of chronic HCV infection (CHC) involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. In the US, CHC is currently the most common reason for liver transplantation and there are more yearly deaths related to HCV than human immunodeficiency virus (HIV) infection (Ly 2012). The ultimate goal of HCV treatment is to reduce the occurrence of end-stage liver disease and its related complications, and achieving sustained HCV viral eradication through successful HCV treatment is associated with improvements in clinical outcomes such as decreased development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (van der Meer 2012; Backus 2011; Singal 2010; Veldt 2007). Several host and viral baseline factors have been identified which are more likely to result in treatment failure in HCV GT 1 patients treated with pegylated interferon and ribavirin-containing regimens, including high baseline viral load, significant fibrosis (Metavir fibrosis score F3 or F4), older age and IL28B non-C/C genotype (Ge 2009; Ghany 2009; Jacobson 2011; Poordad 2012).

The current application requests approval of LDV/SOF for the proposed indication for the treatment of chronic hepatitis C GT 1 infection in adults.

2.1 Product Information

Generic (trade) Name:	Ledipasvir/Sofosbuvir (Harvoni) fixed-dose combination
Chemical Class:	New molecular entity
Pharmacological Class:	Sofosbuvir-Hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor; Ledipasvir-HCV NS5A inhibitor
Proposed Indication:	Treatment of chronic HCV genotype 1 infection
Dosing Regimens:	Ledipasvir 90 mg/Sofosbuvir 400 mg fixed-dose combination tablet once daily
Dosage Form:	Oral tablet
Age Group:	Adults

SOF is a nucleotide analog inhibitor of HCV nonstructural protein 5B (NS5B) polymerase, which is essential for viral replication, and has been approved for use in

combination with other agents for the treatment of chronic HCV infection in adults (tradename Sovaldi®; NDA 204671). LDV is an HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions.

The Applicant completed a clinical development program to assess the efficacy and safety of LDV/SOF in adult subjects with chronic hepatitis C GT 1 infection.

2.2 Tables of Currently Available Treatments for Proposed Indications

HCV is a small positive-strand ribonucleic acid (RNA) virus in the Flaviviridae family. At least six viral HCV GTs have been identified, numbered 1 to 6, and most GTs have been divided into multiple subtypes (e.g., GT 1 subtypes 1a and 1b). In the US, GT 1 is the most common, accounting for 70 to 80 percent of infections. The selection of treatment for chronic HCV GT 1 infection depends upon factors such as prior HCV treatment history and eligibility to receive interferon.

The currently approved drugs for the treatment of HCV infection are listed in Table 1.

Pegasys® (pegylated interferon alfa 2-a) and PegIntron® (pegylated interferon alfa-2-b), are immunostimulatory agents and are co-administered with RBV. RBV is a guanosine nucleoside analog. RBV is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form it interferes with RNA metabolism required for viral replication. The exact effects of RBV on viral replication are unclear; many mechanisms have been proposed but not established. RBV has shown an effect in decreasing post-treatment relapse following treatment and multiple mechanisms of action may be involved.

Telaprevir (Incivek®), boceprevir (Victrelis®) and simeprevir (Olysio™) are NS3/4A protease inhibitors and inhibit the HCV NS3/4A protease which is essential for viral replication. SOF (Sovaldi™) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase and is incorporated into the HCV RNA by the NS5B polymerase and disrupts the viral replication by chain termination. These direct acting antiviral agents (DAA) are currently indicated for co-administration with PEG and RBV for the treatment of chronic HCV GT 1 infection.

Table 1 Currently US Approved Agents for Treatment of Chronic HCV Genotype 1 Infection

Drug Class	Generic Name	Trade Name
Pegylated interferons	Peginterferon alfa-2a	Pegasys®
	Peginterferon alfa-2b	PegIntron®
Interferons	Interferon alfa-2a	Roferon-A®*
	Interferon alfa-2b	Intron-A®
Nucleoside Analogue	Ribavirin	Rebetol®, Copegus®
Protease Inhibitors	Boceprevir	Victrelis®
	Telaprevir	Incivek®
	Simeprevir	Olysio™
NS5B Inhibitor	Sofosbuvir	Sovaldi™

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns

2.3 Availability of Proposed Active Ingredient in the United States

SOF has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults (tradename Sovaldi™; NDA 204671), and is marketed in the US. Although not submitted for approval as a single agent, LDV is a new molecular entity. Therefore, as a component of the LDV/SOF FDC, the FDC is a new molecular entity. The LDV/SOF FDC is not currently marketed in the US or elsewhere.

2.4 Important Safety Issues With Consideration to Related Drugs

SOF is the only approved nucleotide analog HCV NS5B polymerase inhibitor. (b) (4)

[redacted]

Although SOF is structurally different, a detailed safety evaluation focused on cardiac disorders was done at the time of the original SOF NDA approval to identify any potential cardiac toxicity signal due to class effect. Based on the review of the submitted data, no obvious safety issue related to cardiac toxicity was identified at that time.

A detailed safety evaluation of cardiac disorders was conducted with this NDA review. No obvious safety issue related to cardiac toxicity is currently identified. Please refer to Section 7.2.6 for this analysis.

Currently, no pharmacologically related products to LDV have received FDA approval and LDV is the first drug in the pharmacologic class of HCV NS5A inhibitors filed for the marketing licensure in US.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This section will summarize and focus only on the notable events which had a direct relationship with the current LDV/SOF NDA.

An Investigational New Drug application (IND) for the LDV/SOF was submitted on May 31, 2012 by Gilead Sciences, Inc. After a 30-day safety review, it was determined the Sponsor may proceed with the proposed clinical investigation under IND 115268 in a letter signed July 2, 2012.

Clinical protocols and the development plan were reviewed by the Division throughout the LDV/SOF development program, with feedback provided regarding issues of dose selection, treatment duration and treatment regimen.

An End of Phase 2 meeting under the SOF IND (106739) was held June 5, 2012 and included discussion regarding initial LDV/SOF development and a proposed phase 2/3 trial design for ION-1 in treatment-naïve HCV GT 1 subjects. The final ION-1 protocol design submitted to the Division on August 31, 2012 was determined to be acceptable.

A Type C meeting (teleconference) was held June 3, 2013 to present the overall clinical, clinical pharmacology and nonclinical development plans for the LDV/SOF, to review key phase 2 data from the LDV/SOF development program in adults, and to seek agreement that the phase 3 trials (ION-1, ION-2, ION-3) will support an indication for use of LDV/SOF FDC for the treatment of chronic HCV GT 1 infection in adults.

- Agreement was reached that if the ION-1 SVR12 rate in Group 3 or 4 (LDV/SOF±RBV 12 weeks) is ≥90%, in both cirrhotic and non-cirrhotic subjects, the ION-1 trial results could be included in a new drug application package without waiting for SVR12 data in Group 1 or 2 (LDV/SOF±RBV 24 weeks), along with ION-2 and ION-3 SVR12 data.
- Agreement was reached on the ION-3 trial design, evaluating LDV/SOF±RBV 8 weeks versus LDV/SOF 12 weeks in treatment-naïve non-cirrhotic HCV GT 1 subjects. One of the comments conveyed to the Applicant is excerpted from the official meeting minutes which is relevant to the current submission:
    - ION-3 may support registration of an 8-week treatment duration in treatment-naïve non-cirrhotic HCV GT 1 infected subjects; however, no LDV/SOF-based regimen has been identified as optimal at the present

time and this trial may provide data, particularly in certain subpopulations (e.g., baseline NS5A resistance), which do not support an 8-week treatment duration.

A Pre-NDA meeting request occurred June 11, 2013 to seek agreement related to the NDA submission strategy, proposed indication, content and format of the application and approach for the NDA Safety Update. The planned meeting was cancelled by the Applicant because the preliminary comments provided by the Division were clear and further discussion was not necessary. The following issues relevant to the LDV/SOF NDA that were communicated to the Applicant include:

- Agreement sufficient data exist to submit an NDA for the proposed indication for LDV/SOF for the treatment of chronic HCV GT 1 infection in adults; however, the exact indication will be a review issue.
- The Division recommended the established names be ordered alphabetically, as have been recommending for HIV drugs. e.g., “Ledipasvir and Sofosbuvir”. A main consideration is the number of pharmacological mechanisms for HCV and HIV drugs, which makes mechanism-based ordering very complicated.

Type C meeting (teleconference) was held January 21, 2014 to discuss SVR12 results from the pivotal phase 3 trials, ION-1, ION-2 and ION-3 and to seek agreement on the data that will support an indication for use of LDV/SOF for the treatment of chronic HCV GT 1 infection in adults. The following issues relevant to the LDV/SOF NDA that were communicated to the Applicant and/or were discussed during the teleconference based upon the official meeting minutes include:

- Agreement sufficient data exist to submit an NDA for the proposed indication; however, the exact indication and dosage and administration will be review issues.
- Agreement the Applicant will provide data on 20 subjects who experienced virologic failure after prior treatment with a SOF-based therapy in the NDA.
- Agreement the FDC nomenclature will be updated according to the Agency guidance as stated in the pre-NDA meeting (LDV/SOF). Labeling will reflect the alphabetical order.

The following preliminary comments provided by the Division and the resulting discussion are excerpted from the official meeting minutes due to their relevance to the current submission.

FDA Additional Comment 1: We note relapse only occurred in the 12 week arms of ION-2, with numerically lower relapse rates in the 12 week ribavirin-containing arm. The Type C meeting backgrounder indicates cirrhosis is the only factor identified as a predictor of relapse in multivariate analysis. The NDA submission should contain sufficient information to support your rationale for a LDV/SOF 12 week duration, as this proposed regimen and duration will be a review issue.

FDA Additional Comment 2: Higher relapse rates are noted in the 8 week arms compared with the 12 week arm of ION-3. (b) (4) .

Discussion (1 and 2):
Gilead will provide rationales (b) (4) in the original NDA submission. Gilead noted that (b) (4) 12-week durations of the FDC will provide a short, simple, and effective therapy to patients without over treating and increasing additional issues related to longer duration (e.g. adherence, safety, and cost).

The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

Fast track designation for the LDV/SOF FDC was granted July 2, 2012, and Breakthrough Therapy Designation for the treatment of chronic HCV GT 1 infection was granted July 22, 2013.

2.6 Other Relevant Background Information

Ribavirin
LDV/SOF is coadministered with RBV in several arms within the phase 2 and 3 LDV/SOF clinical trials. The RBV safety profile includes hemolytic anemia and rash, and the RBV label contains a boxed warning that hemolytic anemia associated with RBV therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. RBV is embryocidal and teratogenic and is classified as Pregnancy Category X. Thus, the RBV label states RBV is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of treatment in both female patients and in female partners of male patients who are taking RBV therapy.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A consult request for clinical site inspections was submitted to the Division of Good Clinical Practice Compliance in the Office of Scientific Investigations (OSI), Office of Compliance/CDER on March 5, 2014 in response to the NME NDA submission under

the PDUFA timeline. The site selection process involved the NDA review team and Dr. Antoine El-Hage from OSI. Six domestic sites were inspected. The data submitted from these six sites are considered acceptable in support of Gilead's NDA application for the LDV/SOF FDC.

Please refer to OSI Consult Review (signed June 23, 2014 in DARRTS) for further details.

3.2 Compliance with Good Clinical Practices

The Applicant certified all Gilead-sponsored trials conducted under a US IND in the LDV/SOF development program met the requirements for International Conference on Harmonization (ICH) Good Clinical Practice guidelines, consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312. Protocols and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSI inspected selected clinical sites, and the submitted data from the site audits are considered acceptable (see Section 3.1). For a more detailed discussion of the OSI audit, please refer to the Clinical Inspection Summary, by Dr. Antoine El-Hage.

3.3 Financial Disclosures

Please refer to Attachment 1 for Financial Disclosure information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The significant efficacy and safety issues noted in other review disciplines are summarized in this section. Please refer to the Primary Review for the particular discipline for detailed assessments.

4.1 Chemistry Manufacturing and Controls

For a description of the clinical properties of SOF, please refer to the original SOF NDA 204671 review.

LDV has low aqueous solubility across the pH range 4.0-7.5 and is slightly soluble below pH 3.0. It is somewhat sensitive to light. The chemical name for LDV is methyl [(2S)-1-{(6S)-6-[5-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.

(b) (4)

The LDV/SOF (b) (4) tablet formulation was used in all three phase 3 trials, is used in all primary and registration stability batches and is the formulation proposed for the commercial drug product.

The proposed commercial LDV/SOF tablets for oral administration are orange colored, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7985" on the other side, containing 90 mg of LDV and 400 mg of SOF. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: FD&C yellow #6, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. (b) (4)

Inspections of the production facilities are ongoing at the time of this review. Please refer to the CMC Reviews for full details regarding chemistry, manufacturing and process controls, formulation specifications and the adequacy of data provided to assure drug stability, strength, purity and quality of drug substance and drug product.

4.2 Clinical Microbiology

Please refer to the Clinical Virology Review by Dr. Lisa Naeger and Dr. Eric Donaldson for detailed assessment.

SOF has EC_{50} values ranging from 14-110 nM in stable full-length replicon cells of GT1a, 1b, 2a, 3a and 4a; and chimeric GT1b Con-1 replicons carrying NS5B coding sequences from GT2b, 5a, or 6a. NS5B substitutions identified in SOF clinical trials include S282T, L159F, V321A and C316N. LDV has antiviral activity against HCV GT1a and 1b, with EC_{50} values of 0.031 nM and 0.004 nM, respectively. Evaluation of SOF in combination with LDV showed no antagonistic effect in reducing HCV RNA levels in replicon cells. LDV is fully active against the SOF resistance-associated substitution S282T in NS5B while all LDV resistance-associated substitutions in NS5A are fully susceptible to SOF.

Data from the three LDV/SOF phase 3 trials, ION-1, ION-2 and ION-3, and two phase 2 trials, P7977-0523 (ELECTRON) and GS-US-337-0118 (LONESTAR), were submitted for resistance analyses.

In the pooled phase 3 analysis, 23% (370/1615) subjects' virus had baseline NS5A resistance-associated polymorphisms (any change at NS5A amino acid positions K24, M28, Q30, L31, H58, A92 or Y93) identified by population or deep sequencing. Relapse rates for subjects whose virus had one baseline NS5A polymorphism was 3.6%. Relapse rates were higher for subjects whose virus had 2 or more baseline NS5A resistance-associated polymorphisms; 9.5% and 9% for subjects whose virus had 2 and 3 baseline NS5A resistance polymorphisms, respectively.

In ION-3, in treatment-naïve subjects with baseline NS5A resistance-associated polymorphisms, relapse rates were 6.3% (3/48 subjects) after 8 weeks and 0% (0/56 subjects) after 12 weeks of LDV/SOF treatment. In ION-2, in treatment-experienced subjects whose virus had baseline NS5A resistance-associated polymorphisms, relapse rates were 22% (5/23 subjects) after 12 weeks and 0% (9/19 subjects) after 24 weeks of LDV/SOF treatment.

SVR12 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 SOF resistance-associated substitution S282T was not detected in the baseline NS5B sequence of any subject in phase 3 trials by population or deep sequencing.

There were 37 virologic failures (GT1a n=29; GT1b =8) in total from the phase 3 trials. One ION-1 and one ION-2 subject experienced breakthrough due to documented non-adherence. All remaining virologic failures (n=35) were relapsers. Overall, 63% (23/37 subjects) of the failures had emergent NS5A resistance substitutions, and 38% (14/37 subjects) of virologic failure subjects had 2 or more NS5A resistance-associated substitutions emerge at failure.

- Of the 29 GT1a virologic failure subjects, 55% (16/29 subjects) of subjects' viruses had emergent NS5A resistance-associated substitutions at failure. The most common variants were Q30R, Y93H or N, and L31M.
- Of the 8 GT1b virologic failure subjects, 88% (7/8 subjects) had virus with emergent NS5A resistance-associated substitutions at failure. The most common variant was Y93H.

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

NS5A resistance-associated substitutions also emerged in viruses with NS5A resistance polymorphisms present at baseline. Twenty-seven percent (4/15 subjects) of the virologic failure subjects with baseline NS5A polymorphisms had additional NS5A resistance substitutions emerge at failure.

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 were detected in one subject at failure following LDV/SOF 8 week treatment the phase 2 trial LONESTAR.

Twenty subjects who failed on SOF-containing regimens in phase 2 trials, LONESTAR and ELECTRON, were retreated with LDV/SOF+RBV for either 12 (n=19) or 24 weeks (n=1). All 20 subjects achieved SVR12 upon retreatment; however, only 4 of these subjects had NS5A resistance-associated substitutions before retreatment. Three subjects each had a single NS5A resistance substitution (Q30R, M28T or L31M) and received LDV/SOF+RBV 12 weeks. The fourth subject, from LONESTAR mentioned above, had three NS5A substitutions (L31M, Y93H and Q30L) in addition to NS5B substitutions, S282T, L320I and V after relapsing following LDV/SOF 12 weeks, and subsequently achieved SVR12 after receiving LDV/SOF+RBV 24 weeks.

Pertinent data pertaining to NS5A and NS5B substitutions and the individual trials are integrated into Sections 5 and 6 where deemed appropriate.

Reviewer Comment: While retreatment of prior LDV/SOF relapse subjects who have NS5A substitutions is demonstrated, the data are limited and issues of optimal retreatment duration, contribution of RBV and impact of the number or certain types of NS5A resistance substitutions remain unclear at the present time.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology Review by Dr. Christopher Ellis for complete details. In addition, please refer to the SOF NDA 204671 Pharmacology/Toxicology Review for a detailed summary of SOF nonclinical data. Rodent 2-year SOF carcinogenicity studies were reviewed with this application. Notable findings are summarized in this section.

SOF: The major target organs identified in the SOF nonclinical studies include the heart and gastrointestinal tract. Heart degeneration and inflammation were observed in rats following GS-9851 (a stereoisomeric mixture containing approximately 50% SOF) doses of 2000 mg/kg/day for up to 5 days. At this dose, AUC exposure to the predominant circulating metabolite GS-331007 is approximately 17-fold higher than human exposure at the recommended clinical dose. No heart degeneration or inflammation was observed in mice, rats or dogs in studies up to 3 months, 6 months or 9 months at GS-331007 AUC exposures approximately 24-, 5- or 17-fold higher, respectively, than human exposure at the recommended clinical dose. 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 exposures approximately 9-fold the exposure in humans at the recommended clinical dose.

Gastrointestinal (GI) hemorrhage occurred in male dogs administered oral SOF doses, corresponding to AUC exposures at least ~17-fold that in humans. Hemorrhage

occurred in the lamina propria of the pyloric stomach or jejunum in some animals. Increased frequency and incidence of emesis and diarrhea also occurred. The NOEL for GI toxicity is 100 mg/kg/day in dogs administered oral SOF doses for up to 9 months, corresponding to AUC exposure ~7-fold that in humans. GI hemorrhage has not been observed in rats or mice.

SOF was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays. No increase in the incidence of drug-related neoplasms were observed at the highest SOF doses tested in 2-year carcinogenicity studies 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, the exposure in humans at the recommended clinical dose.

LDV: 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 2-week repeat-dose toxicology studies to qualify impurities; phototoxicity studies in mice and rats; fertility and pre- and post-natal developmental (PPND) 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.

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. No specific overlapping toxicity of potential significant clinical concern was identified in animals administered LDV or SOF alone. A potential LDV-related mild hepatobiliary toxicity signal in mice (not considered adverse and not clearly dose dependent) was noted, with slight increases in alkaline phosphatase and/or ALT associated with increased liver/gallbladder weight (high-dose males only) without correlating histopathology changes. Minimal to slight random foci of hepatocyte necrosis (males) and bile duct hyperplasia (males and females) were noted in rats. These non-adverse hepatobiliary findings were observed at LDV AUC exposure ~8- and 30-fold higher, in rats and mice respectively, than that in humans at the recommended LDV dose. In dogs, no clear clinically relevant LDV-related findings were observed, resulting in LDV AUC exposure ~9-fold higher than that in humans at the recommended LDV dose. Preclinical studies demonstrate LDV, which absorbs ultraviolet (UV) light, accumulates in the uveal tract of the eye in pigmented (but not albino) rats. An in vivo study in pigmented rats to assess potential ocular phototoxicity risk was negative at up to the highest dose level tested, resulting in LDV AUC exposure ~8-fold higher than that in humans at the recommended LDV dose.

The average number of corpora lutea, implantations and viable embryos were reduced slightly in rats following LDV administration and were associated with non-adverse maternal toxicity findings. The NOEL for female fertility and early embryonic development is considered to be 30 mg/kg/day. At 30 and 100 mg/kg/day, LDV AUC exposure is estimated to be ~2 and 3.4-fold higher, respectively, than that in humans at the recommended LDV dose. A slight trend for reduced rat pup body weight (F1 generation) associated with adverse maternal toxicity was observed in pregnant rats following oral LDV administration at 100 mg/kg/day. The NOAEL for maternal toxicity and NOEL for PPND is estimated conservatively to be 30 mg/kg/day. At 30 and 100 mg/kg/day, LDV AUC exposure is ~1.6- and 5-fold higher, respectively, than that in humans at the recommended LDV dose.

LDV was not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo rat micronucleus assays. Carcinogenicity studies of LDV in mice and rats are ongoing.

4.4 Clinical Pharmacology

This section provides a brief summary of the clinical pharmacology of LDV/SOF. The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA to support a recommendation of approval of LDV/SOF. Please refer to the Clinical Pharmacology Review by Dr. Jenny Zheng and Dr. Jeffry Florian for additional information.

4.4.1 Mechanism of Action

LDV is an HCV inhibitor targeting the HCV NS5A protein, which is essential for RNA replication. Resistance selection in cell culture and cross-resistance studies indicate LDV targets NS5A as its mode of action.

SOF is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. SOF is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV GT1b, 2a, 3a and 4a with IC_{50} values ranging from 0.7 to 2.6 μM. GS-461203 is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

4.4.2 Pharmacodynamics

LDV is both a substrate and inhibitor of the drug transporters P-gp and BCRP. LDV is not expected to inhibit OATP1B1, OATP1B3 and BSEP at concentrations achieved in

vivo at the recommended dose. SOF is a substrate of the drug transporters P-gp and BCRP. Please see Section 7.5.5 Drug-Drug Interactions for additional details.

Please refer to the Clinical Pharmacology Review for detailed assessment of exposure-response. Regarding safety, exposure-response analyses were conducted based on pooled phase 3 data for common AEs and included headaches, nausea, insomnia, and fatigue. In each of these analyses, exposure-response relationships could not be identified between LDV, SOF, or GS-331007 AUC_{tau} and these most common AEs.

4.4.3 Pharmacokinetics

A comprehensive program of phase 1 trials characterized the pharmacokinetics (PK) of LDV and SOF, administered as single agents or as the LDV/SOF FDC. In addition, intensive and sparse plasma concentration data from phase 1, 2 and 3 trials were used for population PK evaluation.

The PK of SOF and its predominant circulating metabolite GS-331007 are characterized in the SOF NDA 204671 and reflected in the currently approved label. This section summarizes the LDV and SOF absorption, distribution, metabolism, elimination, food effect and PK assessment between healthy and HCV-infected subjects. Drug exposure in renal impairment and hepatic impairment is also discussed. Note, LDV causes a 2.3 and 2.2-fold increase in SOF AUC_{inf} and C_{max}, respectively, due to P-gp and BCRP inhibition by LDV. Therefore, results of SOF PK as a single agent should be interpreted within this context.

Absorption:

- LDV median peak concentrations are observed 4.0 to 4.5 hours post-dose.
- SOF median peak plasma concentrations are observed ~0.8 to 1 hour post-dose. GS-331007 median peak plasma concentrations are observed 3.5 to 4 hours post-dose.

Distribution:

- LDV is >99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-LDV in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66.
- SOF is ~61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-SOF in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was ~0.7.

Metabolism:

- In vitro, no detectable LDV metabolism is observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6 and CYP3A4. Evidence of slow

oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90mg [^{14}C]-LDV, systemic exposure is almost exclusively attributed to the parent drug (>98%). Unchanged LDV is the major species present in feces.

- 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. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [^{14}C]-SOF, GS-331007 accounted for approximately >90% of total systemic exposure.

Elimination:

- For LDV, mean total recovery of [^{14}C]-LDV radioactivity in feces and urine is approximately 87%, with most of the radioactive dose recovered from feces (~86%). Unchanged LDV excreted in feces accounts for a mean of 70% of the administered dose and the oxidative metabolite M19 accounts for 2.2% of the dose. These data indicate that biliary excretion of unchanged LDV is a major route of elimination with renal excretion being a minor pathway (~1%). The LDV median terminal half-life is 47 hours.
- For SOF, mean total recovery of [^{14}C]-SOF is >92%, consisting of ~80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the SOF dose recovered in urine is GS-331007 (78%) while 3.5% is recovered as SOF. These data indicate that renal clearance is the major elimination pathway for GS-331007. The SOF and GS-331007 median terminal half-lives are 0.5 and 27 hours, respectively.

Food Effect: Relative to fasting conditions, a single LDV/SOF dose with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal increases SOF $AUC_{0\text{-}inf}$ by ~2-fold, but do not significantly affect SOF C_{max}. The exposures of GS-331007 are not altered in the presence of either meal type. The response rates in the phase 3 trials are similar in HCV-infected subjects who received LDV/SOF with food or without food. Based on these data, it will be recommended that LDV/SOF can be administered without regard to food.

Healthy and HCV-Infected Subjects:

- Relative to healthy subjects, LDV $AUC_{0\text{-}24}$ and C_{max} are 24% lower and 32% lower, respectively, in HCV-infected subjects.
- SOF and GS-331007 $AUC_{0\text{-}24}$ and C_{max} are similar in healthy and HCV-infected subjects.

Renal Impairment:

- LDV PK was studied with a single LDV 90 mg dose in HCV-negative subjects with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault). No clinically relevant differences in LDV PK were observed between healthy subjects and subjects with severe renal impairment. No LDV dose adjustment is required for patients with mild, moderate or severe renal impairment. Although not clinically evaluated, hemodialysis is unlikely to have an impact with LDV elimination due to high LDV protein binding.
- As described in the SOF label, following a single SOF 400 mg dose in HCV-negative subjects, the SOF $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively, relative to subjects with normal renal function (eGFR >80 mL/min/1.73m^2). In subjects with ESRD, relative to subjects with normal renal function, SOF and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when SOF was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when SOF was dosed 1 hour after hemodialysis, respectively. A 4 hour hemodialysis session removed ~18% of administered dose. No SOF dose adjustment is required for patients with mild or moderate renal impairment. The safety and efficacy of SOF have not been established in patients with severe renal impairment or ESRD. No dose recommendation can be given for patients with severe renal impairment or ESRD at this time.
- LDV/SOF was not specifically studied in subjects with renal impairment. Since LDV increases SOF AUC by ~2.3-fold, SOF AUC could be up to 4.5-fold higher in patients with mild or moderate renal impairment receiving LDV/SOF if the effects on SOF AUC are additive. Phase 3 population PK analysis found subjects with baseline mild renal impairment had ~17% higher SOF AUC_{tau} compared to subjects with baseline normal renal function. This SOF AUC increase is lower than observed in non-HCV-infected subjects, suggesting the impact of LDV/SOF on SOF exposure in patients with mild and moderate renal impairment may be lower in HCV-infected patients. Based on these data, currently it will be recommended that LDV/SOF can be administered to patients with mild or moderate renal impairment. Please refer to Section 7.5.4 Drug-Disease Interactions for additional details.

Hepatic Impairment:

- LDV PK was studied with a single LDV 90 mg dose in HCV-negative subjects with severe hepatic impairment (Child-Pugh Class C). LDV plasma exposure (AUC_{inf}) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Population PK analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on LDV exposure. No LDV dose adjustment is recommended for patients with mild, moderate and severe hepatic impairment.
- SOF PK was studied following 7-day dosing of 400 mg SOF in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and

C). Relative to subjects with normal hepatic function, the SOF AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population PK analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on SOF and GS-331007 exposure. No dose adjustment of SOF is recommended for patients with mild, moderate and severe hepatic impairment.

- LDV/SOF PK data
  - In the LDV/SOF phase 2 and 3 program, subjects with compensated cirrhosis (Child-Pugh Class A) and noncirrhotic subjects achieved similar mean SOF, GS-331007, and LDV exposures. Cirrhosis was not identified as a relevant covariate based on population PK analyses.
  - In the ongoing GS-US-337-0122 and GS-US-337-0123 (SOLAR-1) trials, enrolling HCV-infected subjects with moderate and severe hepatic impairment, PK data are available from 33 subjects, including 8 post-liver transplant subjects. Compared to 1845 non-cirrhotic subjects enrolled in phase 2 and 3 trials: (1) subjects with Child-Pugh Class B demonstrate ~2.7-fold and ~3.2-fold increase in SOF AUC_{tau} and C_{max}, respectively, (2) subjects with Child-Pugh Class C demonstrate ~2.8-fold increase in SOF AUC_{tau} and C_{max}. Please see Section 7.4.5 Special Safety Studies/Clinical Trials for safety information in SOLAR-1, an ongoing trial enrolling subjects with decompensated cirrhosis and/or who are post-liver transplantation.
- Based on the combined PK and available safety information, currently it is recommended LDV/SOF can be administered to patients with mild, moderate or severe hepatic impairment, noting the safety and efficacy of LDV/SOF have not been established in patients with decompensated cirrhosis.

5 Sources of Clinical Data

This application includes 18 SOF single-agent trials, 19 LDV single-agent trials, and 10 LDV/SOF FDC trials. LDV/SOF has been evaluated by the Applicant in three phase 2 trials [GS-US-337-0118 (LONESTAR), P7977-0523 (ELECTRON), GS-US-337-0122 (ELECTRON-2)] and three pivotal phase 3 trials (ION-1, ION-2, ION-3). The data from the three pivotal trials form the principal basis for characterizing the LDV/SOF safety and efficacy in patients with chronic HCV GT 1 infection.

The primary safety population is represented by the integrated data from the three pivotal phase 3 trials. Supportive safety data from phase 2 LDV/SOF trials, phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV, phase 1/2 short-term dose-ranging trials, the Safety Update Report (SUR) and the SOF-development program are integrated into safety assessments where deemed appropriate.

5.1 Tables of Studies/Clinical Trials

Three pivotal phase 3 trials form the primary basis of the LDV/SOF Clinical Review. Three single-center phase 2 LDV/SOF trials provide supportive evidence. In addition, a large number of phase 1 clinical pharmacology trials have been submitted by the Applicant. Please refer to the Clinical Pharmacology review for further details on these trials. The LDV-containing phase 2 trials were targeted for a focused safety review and are summarized in Table 2. Please refer to the SOF NDA 204671 for the pivotal phase 3 and other trials supporting the original SOF approval.

Phase 2 LDV-Containing Trials

Six phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV are submitted with the NDA (Table 2).

Table 2 Phase 2 LDV-Containing Trials

Trial Number	Trial Design	Population	Regimen and Duration	Number Enrolled
GS-US-248-0120	Randomized, open-label LDV 90 mg group: (+) vRVR and HCV RNA <LLOQ maintained through Week 10 re-randomized at Week 12 to stop treatment or continue to Week 24	HCV GT1, TN	**LDV 30 mg group:** LDV 30 mg QD + VDV + TGV + RBV: 24 weeks **LDV 90 mg group:** LDV 90 mg QD +VDV + TGV+RBV:12-24 weeks	LDV 30 mg: 46 treated 23 completed LDV 90 mg: 94 treated 62 completed
GS-US-248-0121	Randomized, open-label, multicenter LDV+VDV+PEG/RBV group: (+)vRVR and maintained HCV RNA <LLOQ through Week 4 re-randomized (1:1) at Week 6 to stop all therapy or continue through Week 12.	HCV GT 1, TN, IL28B C/C	**LDV+VDV + PEG/RBV:** 6 or 12 weeks **PEG/RBV:** 24 weeks	LDV+VDV + PEG/RBV: 123 treated 104 completed PEG/RBV: 121 treated 46 completed
GS-US-248-0131	Randomized, double-blind, placebo-controlled, multicenter	HCV GT 1, TE	**LDV+VDV+TGV+RBV:** 24 weeks **LDV+VDV+TGV:** 24 weeks **LDV+VDV+RBV:** 24 weeks	Overall: 169 treated 41 completed
GS-US-248-0132	Randomized, double-blind, placebo-controlled, multicenter	HCV GT 1 IFN-ineligible or intolerant	**LDV+VDV+TGV+RBV:** 24 weeks **LDV+VDV+TGV:** 24 weeks	Overall: 160 treated 62 completed

			LDV+VDV+RBV: 24 weeks	
GS-US-256-0124	Randomized, double-blind, placebo-controlled (+) eRVR [HCV RNA< LLOQ at Week 4 and maintained through Week 20] stopped all therapy at Week 24. (-) eRVR received all study drugs to Week 24, continued PEG/RBV through Week 48.	HCV GT 1 TE	**VDV+TGV+PEG/RBV:** 24-48 weeks **LDV+VDV+ PEG/RBV:** LDV 30 mg QD + VDV + PEG/RBV: 24-48 weeks **LDV+TGV+ PEG/RBV:** LDV 30 mg QD+ TGV + PEG/RBV: 24-48 weeks	Overall: 163 treated 119 completed VDV+TGV+PEG/RBV 6 treated, 5 completed LDV+VDV+PEG/RBV 151 treated, 112 completed LDV+TGV+PEG/RBV 6 treated, 2 completed
GS-US-256-0148	Randomized, double-blind, placebo-controlled LDV+VDV+ PEG/RBV: (+) vRVR and HCV RNA <LLOQ through Week 8 received 12 or 24 weeks [re-randomized 1:1]. (-)vRVR, but with eRVR received all study drugs for 24 weeks. All other subjects stopped LDV+VDV after 24 weeks, but continued PEG/RBV through 48 weeks. LDV+PEG/RBV: (+)eRVR stopped treatment at Week 24. (-)eRVR stopped LDV at Week 24 and continued PEG/RBV through Week 48	HCV GT 1 TN	**LDV+VDV+PEG/RBV group:** LDV 30 mg QD + VDV + PEG/RBV: 12, 24 or 48 weeks **LDV+PEG/RBV group:** LDV 30 mg QD + PEG/RBV: 24 or 48 weeks	Overall: 348 treated 278 completed LDV+VDV+PEG/RBV 232 treated, 196 completed LDV+PEG/RBV 116 treated, 82 completed

VDV – vedroprevir, 200 mg QD; TGV – tegobuvir, 30 mg BID; vRVR – very rapid virologic response; eRVR – extended rapid virologic response; TN – treatment-naïve; TE – treatment-experienced
Source: Adapted from NDA 205834 Applicant Clinical Summary of Safety, Table 34 and Synopses of Individual Studies

Phase 2 and Pivotal Phase 3 LDV/SOF Trials

The primary clinical trials analyzed for the assessment of the clinical efficacy and safety are the three pivotal phase 3 trials: ION-1, ION-2 and ION-3. These trials are summarized in Table 3.

Table 3 Overview of Phase 2 and Pivotal Phase 3 LDV/SOF Trials

Trial Number	Trial Design	Population	Regimen and Duration	Number Enrolled	Primary Efficacy Endpoint
Pivotal Phase 3 LDV/SOF Trials					
GS-US-337-0102 (ION-1)	Randomized, open-label, international, multicenter trial	GT 1 Treatment-naïve ≤20% may have had cirrhosis at screening	**LDV/SOF:** 12 or 24 weeks **LDV/SOF+RBV**: 12 or 24 weeks	865	SVR12
GS-US-337-0109 (ION-2)	Randomized, open-label, multicenter trial	GT 1 Treatment-experienced, including prior PI-failures ≤ 20% may have had cirrhosis at screening	**LDV/SOF:** 12 or 24 weeks **LDV/SOF+RBV**: 12 or 24 weeks	440	SVR12
GS-US-337-0108 (ION-3)	Randomized, open-label, multicenter trial	GT 1 Treatment-naïve, non-cirrhotic	**LDV/SOF:** 8 or 12 weeks **LDV/SOF+RBV**: 8 weeks	647	SVR12
Phase 2 LDV/SOF Trials					
GS-US-337-0118 (LONESTAR)	Open-label Single center trial	GT 1 Treatment-naïve and Treatment-experienced, including prior PI-failures; ≤50% of treatment-experienced subjects may have had cirrhosis at screening	**LDV/SOF:** 8 or 12 weeks **LDV/SOF+RBV:** 8 or 12 weeks	100	SVR12
GS-US-337-0122 (ELECTRON-2; Cohort 2, Groups 3 and 4)	Open-label Two center trial (New Zealand)	GT 3 Treatment-naïve Subjects may have had cirrhosis	**LDV/SOF:** 12 weeks **LDV/SOF+RBV**: 12 weeks	51	SVR12
P7977-0523 (ELECTRON; Part 4, Groups 12 and 13; Part 6, Groups 16-18, 20, and 21)	Open-label Two center trial (New Zealand)	GT 1, 2 or 3 Treatment-naïve and Treatment-experienced Subjects may have had cirrhosis at screening	**LDV+SOF:** 12 weeks **LDV/SOF:** 12 weeks **LDV/SOF+RBV**: 6 or 12 weeks	102	SVR12

The dose for LDV/SOF was 90 mg/400 mg QD and the dose for RBV was RBV 1000 or 1200 mg/day divided BID (for subjects who weighed < 75 kg, the dose of RBV was 1000 mg/day divided BID and for subjects who weighed ≥ 75 kg, the RBV dose was 1200 mg/day divided BID).
Source: Adapted from NDA 205834 Applicant Clinical Summary of Efficacy, Table 1

Cirrhosis determination in the LDV/SOF phase 3 trials was done using the following criteria:

a) Cirrhosis is defined as any one of the following:
- Liver biopsy showing cirrhosis
- Fibroscan (in countries where locally approved) showing cirrhosis or results >12.5 kPa (*Note: This criterion was not part of the ION-2 protocol definition*)
- FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2 performed during screening

b) Absence of cirrhosis is defined as any one of the following:
- Liver biopsy within 2 years of Screening showing absence of cirrhosis
- Fibroscan (in countries where locally approved) with a result of ≤12.5 kPa within ≤ 6 months of Baseline/Day 1 (*Note: This criterion was not part of the ION-2 protocol definition*)
- FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 performed during Screening

In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above noninvasive criteria, a liver biopsy was required. Biopsy results were considered to be definitive and superseded results obtained by other detection methods.

Table 4 presents the methods of cirrhosis determination in the phase 3 trials. Liver biopsy accounts for the majority of cirrhosis determination methods, 64% overall, with higher percentages in the US population (69-79%) compared with the European population (16%) as expected due to earlier Fibroscan approval in Europe.

Table 4 Methods of Cirrhosis Determination in Phase 3 Trials

Trial	Liver Biopsy	FibroTest + APRI	Fibroscan	Missing
ION-1, % (n/N)	53% (462/865)	13% (116/865)	33% (284/865)	0.3% (3/865)
US	79% (405/512)	19% (96/512)	2% (10/512)	0.2% (1/512)
Europe	16% (57/353)	6% (20/353)	78% (274/353)	0.6% (2/353)
ION-2, % (n/N)	78% (342/440)	22% (96/440)	0	0.5% (2/440)
ION-3, % (n/N)	69% (448/647)	30% (197/647)	0.3% (2/647)	0

Source: Integrated Datasets, ADSL (ION-1, ION-2, ION-3)

5.2 Review Strategy

This reviewer, Sarah Connelly, is the primary clinical reviewer for this NDA. The clinical and statistical reviewer collaborated extensively throughout the review process, and a

number of analyses included in this review were performed by the FDA Statistical Reviewer (Statistical Review by Dr. Karen Qi/Division of Biometrics). In addition, there were significant interactions with the FDA clinical virology, clinical pharmacology, pharmacology/toxicology and chemistry/product evaluation groups. Their assessments are summarized in this review in the relevant sections. Please refer to their respective reviews for complete descriptions of their findings.

This NDA submission was part of the JumpStart program performed by the Computational Science Center (CSC) at the Center for Drug Evaluation and Research (CDER). Assessment of the NDA data quality fitness was performed by the JumpStart project team and CSC staff.

5.3 Discussion of Individual Studies/Clinical Trials

This section describes the individual LDV/SOF phase 2 and pivotal phase 3 trials. The pertinent efficacy and safety results from the LDV dose-ranging trial, GS-US-248-0120, are also included. Safety data from the individual phase 3 trials with event onset dates on or after the start of treatment and up to 30 days after the discontinuation of all the study drugs are discussed in this section. Efficacy results from the phase 3 trials are discussed in Section 6 (Review of Efficacy). Integrated phase 3 safety data are presented in Section 7 (Review of Safety).

The SOF dose for SOF-containing trials is the approved 400 mg QD dose. The LDV dose used for the phase 2 trials is 90 mg QD unless otherwise stated. The LDV/SOF dose is LDV 90mg/SOF 400 mg QD. Finally, the RBV dose used in RBV-containing regimens is 1000 or 1200 mg/day, based on weight, divided into twice daily dosing (for subjects <75 kg, the RBV dose is 1000 mg/day divided BID and for subjects ≥75 kg, the RBV dose is 1200 mg/day divided BID).

Phase 2 LDV Dose Ranging Trial

GS-US-248-0120

Title: A Phase 2 Randomized, Open-Label Study of GS-5885 Administered Concomitantly with GS-9451 (vedroprevir, VDV), Tegobuvir and Ribavirin (RBV) to Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

Trial Design
This phase 2, randomized, open-label, multicenter trial evaluated the safety, tolerability, and efficacy of LDV 30 mg or 90 mg when given with TGV+VDV+RBV for 12 or 24 weeks in subjects with chronic GT1a or 1b HCV infection. Eligible subjects were to be initially randomized in a 1:2 ratio to one of the following treatment groups:

- Group 1 (n=40): LDV 30 mg+TGV+VDV+RBV, which consisted of LDV 30 mg QD + TGV 30 mg twice daily (BID) + VDV 200 mg QD + RBV for 24 weeks.

- Group 2 (n=80): LDV 90 mg+TGV+VDV+RBV, which consisted of LDV 90 mg QD + TGV 30 mg BID + VDV 200 mg QD + RBV for 12 or 24 weeks. Subjects with very rapid virologic response (vRVR; HCV RNA< LLOQ at Week 2) and HCV RNA <LLOQ maintained through Week 10 were re-randomized (1:1) at Week 12 to stop initial treatment or continue therapy to Week 24.

TGV is an investigational non-nucleoside NS5B inhibitor. VDV is an investigational NS3 protease inhibitor.

Randomization and re-randomization stratified by HCV RNA viral load (< or ≥800,000 IU/mL) and HCV GT (1a or 1b). The primary objectives were to evaluate the antiviral efficacy as measured by SVR24 of LDV 30 mg or 90 mg when given with VDV, TGV, and RBV for 12 or 24 weeks, and to evaluate the safety and tolerability of LDV 30 mg or 90 mg when given with TGV, VDV, and RBV for 12 or 24 weeks. For this review, only data from the original trial are summarized here: Rescue Therapy Substudy (LDV+VDV+PEG/RBV) data are not presented.

A total of 140 HCV TN subjects with GT1a or 1b infection (73.6% or 26.4%, respectively) received study drug (46 subjects received LDV 30 mg+TGV+VDV+RBV and 94 subjects received LDV 90 mg+TGV+VDV+RBV). Approximately one-third of subjects had the IL28B C/C allele (37.9%), and 81.4% of subjects had HCV RNA >800,000 IU/mL. In Group 2, 2 subjects who were re-randomized to continue the initial treatment through Week 24 were included in the 12-week subgroup because they discontinued treatment at Week 12. Therefore, 33 subjects were analyzed in the Group 2 12-week subgroup and 31 subjects were analyzed in the Group 2 24-week subgroup.

Treatment with LDV 30 mg+TGV+VDV+RBV for 24 weeks resulted in an SVR24 rate that was lower, though not statistically different (p value=0.18), compared with LDV 90 mg+TGV+VDV+RBV for 12 or 24 weeks (47.8% and 58.5% of subjects, respectively). However, more subjects experienced virologic breakthrough in the LDV 30 mg +TGV+ VDV+RBV group than in the LDV 90 mg +TGV+VDV+RBV group (19.6% and 10.6%, respectively). Viral breakthrough and relapse were associated with the detection of VDV-, LDV-, and/or TGV-associated resistance-associated substitutions.

Reviewer Comment: These data supported advancing the LDV 90 mg dose into phase 3 trials. Please see Section 7.2.2 for additional details.

Safety
No deaths and no Grade 4 events occurred. The most common AEs in both treatment groups were fatigue and headache. One subject had SAEs of viral gastroenteritis followed by pancreatitis. The event of pancreatitis was considered related to study drug; however, the event did not lead to study drug discontinuation and the subject completed therapy (Subject #1225-6268, please see Section 7.3.4 Lipase Elevations/Pancreatitis Events for additional details). Three subjects had AEs leading to discontinuation of

study drug (one subject LDV 30 mg group, two subjects LDV 90 mg group); no AEs leading to discontinuation of study drug were reported in >1 subject. As noted in Table 5, the safety profile for common AEs is similar between the 30 and 90 mg LDV arms.

Table 5 GS-US-248-0120: Adverse Events in at Least 10% of Subjects in Any Treatment Group

Preferred Term	Group 1	Group 2
	LDV 30 mg + VDV+TGV+RBV 24 weeks (N = 46)	LDV 90 mg + VDV+TGV+RBV 12 or 24 weeks (N = 94)
Number of Subjects (%) Experiencing Any AE	40 (87.0%)	83 (88.3%)
Fatigue	16 (34.8%)	17 (18.1%)
Headache	9 (19.6%)	20 (21.3%)
Nausea	8 (17.4%)	13 (13.8%)
Diarrhea	5 (10.9%)	14 (14.9%)
Pruritus	5 (10.9%)	11 (11.7%)
Rash	6 (13.0%)	10 (10.6%)
Anemia	6 (13.0%)	6 (6.4%)

Source: NDA 205834 Applicant Clinical Summary of Safety, Table 35.

Three subjects (2.1%) had a Grade 4 laboratory abnormality (increased creatine kinase, increased urate, and increased lipase); all Grade 4 laboratory abnormalities were reported to be transient and returned towards baseline levels before or by the Week 24 visit. Two subjects in Group 2 (12 week subgroup) had AST or ALT >3x ULN and total bilirubin >2x ULN. Please refer to Section 7.3.5 Hepatic Events for further details of these two subjects (Subject #2761-6380, Subject #5664-6364).

Phase 2 LDV/SOF Trials

LDV/SOF duration regimens were explored in three phase 2 clinical trials: P7977-0523 (ELECTRON), GS-US-337-0118 (LONESTAR), GS-US-337-0122 (ELECTRON-2). Trial results have been summarized from the review of clinical study reports provided in the NDA submission. No independent safety or efficacy data analyses were done from LDV/SOF phase 2 trials; however, pertinent safety information is integrated into Section 7 where applicable.

P7977-0523 (ELECTRON)

Title: A Multi-center, Open-Labeled Exploratory Study to Investigate the Safety,

Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of SOF 400 mg and Ribavirin for 12 Weeks With and Without Pegylated Interferon in Treatment-Naive Patients with Chronic HCV Infection Genotype 2 or Genotype 3

This summary presents the trial design and results from LDV+SOF- and LDV/SOF-containing treatment groups only. Note, Group 20 does not have SVR12 data included in this submission and therefore will not be included in the efficacy summary. The primary objectives of the relevant trial groups are:

- Safety and tolerability of SOF for 8 or 12 weeks, administered ± RBV, in HCV GT 1, 2 or 3 subjects, ± LDV in HCV GT 1 subjects, and also of LDV/SOF for 6 or 12 weeks ±RBV in HCV GT 1, 2 or 3 subjects

Trial Design

Part 4 (Groups 12 and 13) enrolled HCV GT 1 subjects who had documented null response following previous PEG/RBV treatment for ≥12 weeks and HCV GT 1 treatment-naive subjects into the following 2 treatment groups:

- LDV+SOF+RBV 12 Weeks: HCV GT 1 null-responder subjects (Group 12, N=9)
- LDV+SOF+RBV 12 Weeks: HCV GT 1 TN subjects (Group 13, N=25)

Part 6

HCV GT 1 subjects who were prior PEG null responders with a fibrosis score of F4, were randomized in equal proportions into:

- LDV/SOF 12 Weeks: HCV GT 1 null-responder subjects (Group 16, N=10)
- LDV/SOF+RBV 12 Weeks: HCV GT 1 null-responder subjects (Group 17, N=9))

HCV GT 2 or 3 noncirrhotic TN subjects were enrolled into:

- LDV/SOF 12 Weeks: HCV GT 2 or 3 TN subjects (Group 18, N=10)

HCV GT 1 subjects with hemophilia were enrolled into:

- LDV/SOF+RBV 12 Weeks: HCV GT 1 subjects with hemophilia (Group 20, N=14)

HCV GT 1 TN noncirrhotic subjects were enrolled into:

- LDV/SOF +RBV 6 Weeks: HCV GT 1 TN subjects (Group 21, N=25)

All treated subjects were enrolled at two study sites in New Zealand.

All Group 12 and 13 enrolled subjects received at least one dose of study drug. One subject in Group 13 (Subject #1030-5205) discontinued treatment due to an SAE of diverticular perforation/diverticulitis. Across groups, the mean subject age was 48 years, with a range of 25 to 61 years. In Group 12 most subjects were male (7 of 9 subjects [78%]), and in Group 13 most subjects were female (17 of 25 subjects [68%]). The most subjects were white (32 of 34 subjects [94%]), and none of the subjects was of Hispanic or Latino ethnicity; BMI values ranged from 19.8 to 37.3 kg/m^2.

A total of 68 subjects were randomized to Groups 16 to 18, 20, and 21 and completed study treatment. Across groups, the mean subject age was 52 years, with a range of 26 to 74 years. Most subjects were male (46 of 68 subjects [68%]), white (58 of 68 subjects [85%]), and not of Hispanic or Latino ethnicity (66 of 68 subjects [97%]); BMI values ranged from 19.2 to 42.8 kg/m^2.

Table 6 summarizes SVR12 data from the pertinent ELECTRON HCV GT 1 groups. Note, this non-IND trial was not designed to evaluate formal statistical hypotheses. No statistical inference was performed.

Table 6 Response Rates in Selected ELECTRON HCV Genotype 1 LDV+SOF- and LDV/SOF-Containing Treatment Groups

	Treatment Naïve	Null Responder	Null Responder with Cirrhosis		Treatment Naive
Group	13	12	16	17	21
Regimen (N)	LDV+SOF +RBV 12 Weeks (N=25)	LDV+SOF +RBV 12 Weeks (N=9)	LDV/SOF 12 Weeks (N=10)	LDV/SOF +RBV 12 Weeks (N=9)	LDV/SOF +RBV 6 Weeks (N=25)
SVR12, % (n/N)	100% (25/25)	100% (9/9)	70% (7/10)	100% (9/9)	68% (17/25)
95% CI	86.3-100	66.4-100	34.8-93.3	66.4-100	46.5-85.1

Source: Adapted from NDA 205834 Applicant Clinical Summary of Efficacy, Tables 7 and 8

HCV GT 2 or 3 (Group 18)
Treatment-naïve HCV GT 2/3 subjects treated with LDV/SOF 12 weeks had 80% SVR12 (8/10 subjects) with a 95% CI of 44.4-97.5. Relapse was the reason for virologic failure in both subjects. These subjects each had HCV GT3a infection.

Safety
In Groups 12 and 13, the most common study drug-related AEs were fatigue, headache, and insomnia. Two subjects experienced SAEs: one subject had one SAE each of diverticular perforation, colovesical fistula, and diverticulitis (all Grade 3) which led to study drug discontinuation. Please see Section 7.3.5 Gastrointestinal Events for further details. One subject had an SAE of pyelonephritis (Grade 3), which resolved without sequelae. There were no study drug-related SAEs. No other subjects discontinued study drug due to AEs. Six subjects had AEs leading to RBV interruption or dose modification. No Grade 4 laboratory abnormalities were reported. No Grade 3 or 4 laboratory abnormalities in ALT, AST, or total bilirubin were reported.

In Groups 16-18, 20, 21, the most common study drug-related AEs were headache, fatigue, insomnia, and nausea. Two subjects experienced SAEs: one subject with a history of atrial fibrillation, cerebrovascular accident/transient ischemic attacks had Grade 3 syncope, and one subject had Grade 2 cholelithiasis. Each of the SAEs

resolved. There were no study drug-related SAEs. One subject in Group 20 permanently discontinued RBV treatment due to anemia. Two Grade 4 laboratory abnormalities were reported (increased INR, increased PTT), both in subjects with hemophilia. No Grade 3 or 4 laboratory abnormalities in ALT, AST, or total bilirubin were reported.

GS-US-337-0118 (LONESTAR)

Title: A Phase 2, Randomized, Open-Label Study of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin in Subjects with Chronic Genotype 1 HCV Infection

Trial Design
This phase 2, randomized, open-label trial assessed the safety, tolerability, and antiviral efficacy of LDV/SOF administered ±RBV for 8 or 12 weeks. The trial had 2 parallel cohorts. In Cohort 1, HCV GT 1 TN noncirrhotic subjects were randomized 1:1:1 to:

- LDV/SOF 8 Week (Group 1)
- LDV/SOF+RBV 8 Week Group 2)
- LDV/SOF 12 Week (Group 3)

In Cohort 2, HCV GT 1 TE cirrhotic and noncirrhotic subjects were randomized 1:1 to:

- LDV/SOF 12 Week (Group 4)
- LDV/SOF+RBV 12 Week (Group 5)

Randomization was stratified by GT (1a or 1b) in Cohort 1, and by GT (1a or 1b) and the presence or absence of cirrhosis in Cohort 2. Subjects randomized to the 8-week groups who experienced post-treatment virology failure were offered LDV/SOF+RBV for 24 weeks as rescue retreatment within the trial.

A total of 100 subjects were randomized: 60 HCV GT 1 TN subjects (n=20 LDV/SOF 8 Week group, n=21 LDV/SOF+RBV 8 Week group, n=19 LDV/SOF 12 Week group) and 40 HCV GT 1 TE subjects (n=19 LDV/SOF 12 Week group, n=21 LDV/SOF+RBV 12 Week group). All randomized and treated subjects were enrolled at a single US site. One subject withdrew consent and discontinued from the trial.

Most subjects were male (66.0%) and white (88.0%) with a mean age of 50 years (ranging 21 to 73 years). Approximately 40% of subjects were Hispanic or Latino. Higher percentages of HCV GT 1 TE subjects had BMI ≥ 30 kg/m^2 (range 61.9% to 73.7%) than HCV GT 1 TN subjects (range 31.6% to 40.0%). Most subjects (87.0%) had HCV GT1a infection. Higher percentages of HCV GT 1 TE subjects had baseline HCV RNA >800,000 IU/mL (range 76.2% to 78.9%) than TN subjects (range 55.0% to 66.7%). Most subjects (85.0%) had non-C/C IL28B alleles. In HCV GT 1 TE subjects, prior treatment failure with a PI-based regimen was predominantly due to nonresponse (67.5%); relapse/breakthrough was reported in 32.5% of subjects. Approximately equal proportions of HCV GT 1 TE subjects received prior treatment with boceprevir (55%) or

telaprevir (45%). Per enrollment criteria, approximately half (55%, 22 of 40) of HCV GT 1 TE subjects had cirrhosis.

SVR12 rates ranged approximately 95-100% across treatment groups (Table 7).

Table 7 GS-US-337-0118: Sustained Virologic Response Rate at Posttreatment Follow-Up Week 12 (Full Analysis Set)

	Treatment-Naive			Treatment-Experienced	
	Group 1	Group 2	Group 3	Group 4	Group 5
	LDV/SOF 8 Weeks (N = 20)	LDV/SOF+RBV 8 Weeks (N = 21)	LDV/SOF 12 Weeks (N = 19)	LDV/SOF 12 Weeks (N = 19)	LDV/SOF+RBV 12 Weeks (N = 21)
SVR12	19/20 (95.0%)	21/21 (100.0%)	18/19 (94.7%)	18/19 (94.7%)	21/21 (100.0%)
95% CI	75.1% to 99.9%	83.9% to 100.0%	74.0% to 99.9%	74.0% to 99.9%	83.9% to 100.0%

Source: NDA 205834 Applicant Clinical Summary of Efficacy, Table 16

One subject had baseline NS5A resistance associated polymorphism, L31M; following relapse, other NS5A substitutions (Y93H and Q30L) and the NS5B S282T were detected in addition to L31M. Subsequently, the levels of S282T decreased 11-fold in 5 days. The Applicant reports the subject subsequently achieved SVR12 following rescue treatment with LDV/SOF+RBV for 24 weeks.

Safety
The most frequently reported overall AEs were nausea, anemia, and upper respiratory tract infection. Five treatment-emergent SAEs were reported in four subjects and were considered unrelated to study drug (delirium, peptic ulcer, spinal compression fracture, suicidal ideation/anemia), with the exception of anemia reported in one subject in the LDV/SOF+RBV 12 Week TE group. No individual SAE was experienced by more than one subject. No subjects discontinued study drug due to AEs. Regarding the LDV/SOF+RBV groups, four subjects had a Grade 3 (3 subjects) or Grade 4 (1 subject) decrease in hemoglobin, and 8 subjects had post-baseline hemoglobin values <10 g/dL, of whom two had hemoglobin values <8.5 g/dL; no subjects in the RBV-free groups met these criteria. No subject in any group had Grade 3 or 4 ALT or total bilirubin changes (increases) from baseline.

GS-US-337-0122 (ELECTRON-2)

Title: A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection

This summary presents the trial design and preliminary safety and efficacy results for HCV GT 3 TN subjects who received LDV/SOF ± RBV for 12 weeks (Cohort 2, Groups 3 and 4).

The primary objectives of the relevant groups were as follows:

- To evaluate the antiviral efficacy of combination therapy with SOF-containing regimens for the treatment of chronic HCV infection as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of SOF-containing regimens administered for up to 12 weeks

Trial Design

This phase 2 ongoing, open-label, non-IND trial evaluates the safety, tolerability, and antiviral efficacy of SOF-containing regimens administered for up to 12 weeks in subjects with chronic HCV infection. The trial design for Cohort 2, Groups 3 and 4 in HCV GT 3 TN subjects with or without cirrhosis are as follows:

- LDV/SOF 12 weeks (Group 3)
- LDV/SOF+RBV 12 weeks (Group 4)

A total of 51 subjects enrolled: 25 subjects in the LDV/SOF treatment-group and 26 subjects in the LDV/SOF+RBV treatment group. All treated subjects were enrolled at two study sites in New Zealand.

Table 8 presents SVR12 rates in the HCV GT 3 TN population.

Table 8 GS-US-337-0122: Proportion of Subjects with HCV Genotype 3 Infection Achieving SVR12 (Full Analysis Set)

	Treatment Group	
	Cohort 2, Group 3 LDV/SOF 12 Weeks (N = 25)	Cohort 2, Group 4 LDV/SOF+RBV 12 Weeks (N = 26)
Overall Number (%) of Subjects with HCV RNA < LLOQ 12 Weeks Posttreatment		
SVR12	16/25 (64.0%)	26/26 (100.0%)
95% CI	42.5% to 82.0%	86.8% to 100.0%
Number (%) of Noncirrhotic Subjects with HCV RNA < LLOQ 12 Weeks Posttreatment		
SVR12	15/22 (68.2%)	21/21 (100%)
95% CI	45.1% to 86.1%	83.9% to 100.0%
Number (%) of Cirrhotic Subjects with HCV RNA < LLOQ 12 Weeks Posttreatment		
SVR12	1/3 (33.3%)	5/5 (100%)
95% CI	0.8% to 90.6%	47.8% to 100.0%

Source: NDA 205834 Applicant Clinical Summary of Efficacy Table 18

Safety

The most common AEs reported across treatment groups were headache, upper respiratory tract infection, and nausea. Four subjects, all in the LDV/SOF treatment group, experienced SAEs including the three subjects with Grade 3 SAEs (abdominal

pain, upper abdominal pain, and diverticular perforation), one subject with a Grade 1 SAE of choroidal effusion and a Grade 2 SAE of lens dislocation. The events of abdominal pain and upper abdominal pain were considered related to study drug. Constipation was considered a potential cause of both events of abdominal pain, and each resolved without modifications in study drug dosing. The subject with the Grade 3 SAE of diverticular perforation accounted for the only discontinuation of study drug due to an AE. Please see Section 7.3.5 Gastrointestinal Events for additional details. There were no Grade 4 laboratory abnormalities.

Reviewer Comment: These LDV/SOF phase 2 trials are generally supportive of the pivotal phase 3 efficacy and safety findings. One LDV/SOF-treated subject in the LONESTAR trial relapsed with the presence of multiple NS5A resistance associated substitutions and also the NS5B 282T substitution, and subsequently achieved SVR12 after retreatment with LDV/SOF+RBV 24 weeks. Available efficacy data in HCV GT 3 subjects are limited, derived from 1 or 2 non-US sites and are not considered sufficient to base a labeling conclusion at the present time.

Phase 2 Additional LDV-Containing Trials

Six phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV are submitted with the NDA (Table 2). Only pertinent high-level safety data and LDV dose-ranging data from GS-US-248-0120 are integrated into this review where deemed appropriate.

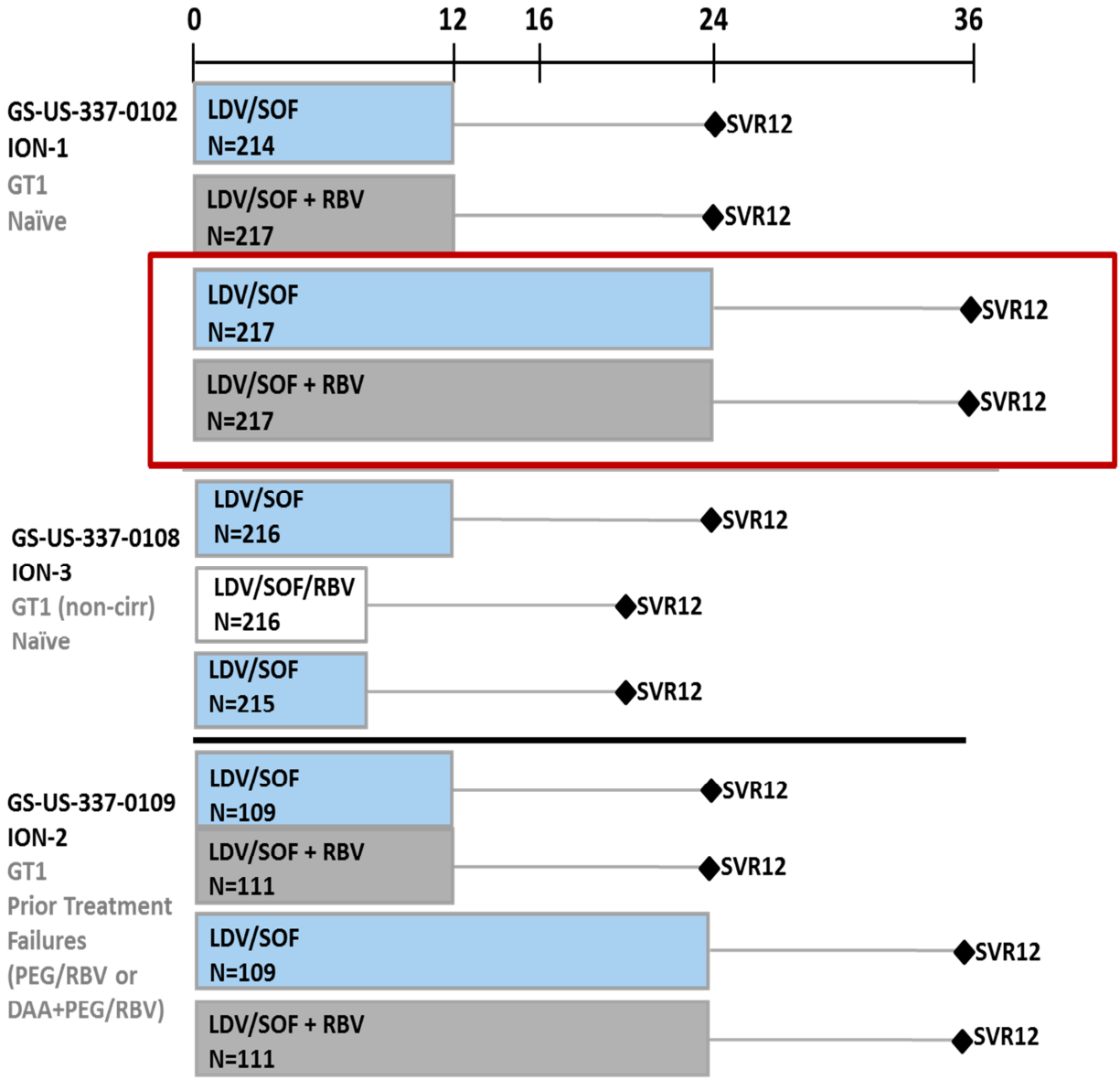
Phase 2 and 3 SOF-Containing Trials

Please refer to the SOF NDA 204671 for comprehensive reviews of phase 2 and 3 SOF-containing trials. Pertinent information is integrated into this review where deemed appropriate.

Pivotal Phase 3 LDV/SOF Trials

The trial designs and the safety results for the three pivotal phase 3 LDV/SOF trials are described in this section. The notable safety events and the integrated safety analyses are discussed in detail in Section 7.3. The efficacy results of these trials are discussed in Section 6. Figure 1 shows the schematic trial designs for the phase 3 trials: ION-1, ION-2, ION-3. The red box highlights the ION-1 trials arms not included in the NDA efficacy review, as agreed upon between the Applicant and the Division; however, these 24 week arms are included in the safety review.

Figure 1 Trial Schematic of Pivotal Phase 3 Trials



N=Number of subjects; SVR12=Sustained virologic response at week 12; LDV=Ledipasvir; SOF=Sofosbuvir; RBV=Ribavirin; GT1=Genotype 1

Source: Dr. Jeffry Florian, Pharmacometrics Reviewer

GS-US-337-0102 (ION-1)

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

The primary objectives of this trial as noted by the Applicant are the following:

- To determine the antiviral efficacy of combination treatment with LDV/SOF±RBV as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data

Trial Design

This phase 3 randomized, open-label, multicenter trial evaluated the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in HCV GT 1 TN subjects. Eligible subjects were randomized 1:1:1:1 to one of the following treatment groups:

- LDV/SOF 24 Week (Group 1)
- LDV/SOF+RBV 24 Week (Group 2)
- LDV/SOF 12 Week (Group 3)
- LDV/SOF+RBV 12 Week (Group 4)

Randomization was stratified by GT (1a, 1b, or mixed 1a/1b) and the presence or absence of cirrhosis at screening. Approximately 20% of the subjects enrolled may have had evidence of compensated cirrhosis at screening. Post-treatment HCV RNA results were blinded to the investigator and Sponsor.

After approximately 200 subjects were enrolled (Part A), an interim analysis was conducted to assess futility of the LDV/SOF±RBV 12-week treatment groups. Stopping for futility would have been triggered if the conditional power had been ≥ 5% (equivalent to an observed response rate of 60% or less), but it was not. Subsequently, approximately 600 additional subjects were randomized 1:1:1:1 across the four groups (Part B). After completing this trial, eligible subjects could enroll into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123).

This submission includes complete data through the SVR12 time point from the 12-week treatment groups. The Division agreed that if 12 weeks of LDV/SOF ± RBV had SVR12 ≥ 90% in subjects with and without cirrhosis separately, complete efficacy data from the 24-week treatment groups would not be necessary for the initial LDV/SOF NDA filing. Therefore, for this submission, results from the primary efficacy analysis for Groups 3 and 4 (12-week treatment groups) and results from all subjects in Part A are included.

A total of 870 subjects were randomized, and 865 subjects received at least one study drug dose. All randomized and treated subjects were enrolled at 100 sites: 62 in the US (512 subjects, 59%) and 38 in Europe (353 subjects, 41%): 10 in Germany (84 subjects), 7 in France (63 subjects), 7 in the United Kingdom (55 subjects), 6 in Spain (55 subjects), and 8 in Italy (96 subjects).

The majority of subjects experienced at least one AE. The overall summary of the AE profile in ION-1 is shown in Table 9.

Table 9 Overall Summary of Adverse Events in ION-1 (GS-US-337-0102: Safety Analysis Set)

	LDV/SOF 12 week N=214	LDV/SOF+RBV 12 week N=217	LDV/SOF 24 week N=217	LDV/SOF+RBV 24 week N=217
Number (%) of Subjects Experiencing Any:				
Adverse Event (AE)	168 (79%)	184 (85%)	177 (82%)	200 (92%)
Treatment-Related AE	106 (50%)	152 (70%)	115 (53%)	170 (78%)
Serious Adverse Event (SAE)	1 (<1%)	7 (3%)	18 (8%)	6 (3%)
Treatment-Related SAE	0	1 (<1%)	4 (2%)	0
Grade 3 and 4 AE	4 (2%)	14 (6%)	21 (10%)	12 (6%)
Treatment-Related Grade 3 and 4 AE	1 (<1%)	7 (3%)	7 (3%)	6 (3%)
AE Leading to Permanent Discontinuation of Any Study Drug	0	1 (<1%)	4 (2%)	8 (4%)
AE Leading to Permanent Discontinuation of LDV/SOF	0	0	4 (2%)	6 (3%)
AE Leading to Modification or Interruption of Any Study Drug	1 (<1%)	35 (16%)	4 (2%)	38 (18%)
AE Leading to Interruption of LDV/SOF	1 (<1%)	1 (<1%)	4 (2%)	3 (1%)

Source: Integrated Datasets, ADSL, ADAE (ION-1)

There are an increased number of treatment-emergent and treatment-related AEs observed in the RBV-containing arms compared to the non-RBV-containing arms (85-92% vs. 79-82% and 70-78% vs. 50-53%, respectively). In addition, more subjects in the RBV-containing arms modified/interrupted any study drug. The most common reason for study drug modification/interruption was anemia (23 subjects in 12 week arm, 15 subjects in 24 week arm) followed by fatigue (6 subjects in 12 week arm, 10 subjects in 24 week arm), occurring only in the RBV-containing arms and consistent with the known RBV safety profile.

Increasing the LDV/SOF treatment duration from 12 to 24 weeks resulted in a generally similar occurrence of treatment-emergent AEs and treatment-related AEs. Grade 3-4 AEs, SAEs and discontinuations due to AEs are numerically increased in either or both of the 24 week duration arms. As will be discussed in Section 7.4.1, despite a higher occurrence in the longer duration arms, most treatment-emergent AEs occurred within the first 12 weeks of treatment.

The overall percentage of SAEs, Grade 3-4 AEs, and AEs leading to LDV/SOF discontinuation is low across all arms. Ten subjects discontinued LDV/SOF, all in the 24 week arms. There is no pattern to the types of AEs leading to discontinuation. The only AEs leading to LDV/SOF discontinuation reported in >1 subject are anxiety (2 subjects in the LDV/SOF+RBV 24 Week group) and palpitations (1 subject each in the LDV/SOF 24 Week and the LDV/SOF+RBV 24 Week groups). Although all events occurred in the 24 week arm, Table 10 demonstrates the range of AE onset with several events occurring within the first 12 weeks.

Table 10 Discontinuation of LDV/SOF due to Adverse Events, ION-1 (GS-US-337-0102: Safety Analysis Set)

Treatment Arm Subject ID	Dictionary-Derived Term	Study Day, AE Onset	Study Day, DC LDV/SOF	SAE
LDV/SOF 24 Weeks				
0446-71357	Palpitations*	95	113	No
1039-71100	Chest Pain*	57, 59	58	Yes
1302-71477	Dizziness, Throat Tightness*	71, 87	157	No
5295-71745	Hemorrhage, Factor VIII Inhibition*	154, 155	154	No, Yes
LDV/SOF+RBV 24 Weeks				
0330-71316	Eyelid Edema, Headache*	86	87	No
0331-71383	Fatigue	4	126	No
0334-71335	Ear Pain, Sensory Disturbance	147	147	No
1081-71454	Gastrointestinal Viral Infection, Vertigo, Anxiety	135, 137(2)	137	No
2493-71034	Palpitations, Dyspnea*	63, 69	92	No
5667-71249	Anxiety	4	112	No

*Discussed in further detail in Section 7
Source: Integrated Datasets, ADSL, ADAE, ADEFF (ION-1)

The observed SAEs are shown in Table 9 and range <1% to 8% across treatment arms. There is no consistent pattern to the types of SAEs reported. The only SAEs reported in >1 subject are chest pain (2), gastroenteritis (2), hand fracture (2), non-cardiac chest pain (2) and pneumonia (2). Five subjects experience SAEs assessed as treatment-related by the investigator: salpingitis, headache, anemia, Factor VIII inhibition, mesenteric vein thrombosis. Investigator causality assessments of anemia in setting of RBV use and headache appear reasonable. The case of mesenteric vein thrombosis may be related to underlying cirrhosis and portal hypertension. The case of salpingitis occurs in the setting of intrauterine device use which confounds causal assessment. These cases are discussed further in Section 7.3.2. Please see Section 7.3.5 Factor VIII Inhibition for further details regarding the Factor VIII event. The 24 week treatment durations numerically have more SAEs; however, the shaded areas in Table 11 demonstrate a number of SAEs occurred within the first 12 weeks of LDV/SOF-containing treatment.

Table 11 Serious Adverse Events in ION-1 (GS-US-337-0102: Safety Analysis Set)

Treatment Arm Subject ID	Dictionary-Derived Term	Study Day, Start of AE	Study Day, End of AE
LDV/SOF x 12 weeks			
2760-71126	Chest Pain*	79	80
LDV/SOF+RBV x 12 weeks			
0380-71016	Intervertebral Disc Protrusion	18	93
4264-71467	Pneumonia	25	31
2053-71601	Anemia	30, 60	31, 86
3996-71002	Migraine	39	41
1082-71608	Tibia Fracture*	52	54
1516-71863	Non-Cardiac Chest Pain*	80	81
7751-71496	Hypertension*	61	62
LDV/SOF x 24 weeks			
2012-71373	Salpingitis*	4	103
4435-71138	Lumbar Spinal Stenosis	28	41
4488-71159	Lower Limb Fracture*	49	52
5667-71227	Mesenteric Vein Thrombosis, Abdominal Discomfort*	49, 160	160, 161
1039-71100	Chest Pain*	59	60
4488-71174	Non-Cardiac Chest Pain*	79	80
3974-71621	Fall*	83	-
0773-71425	Colitis*	98	101
1305-71819	Gastroenteritis	99	101
0472-71556	Foot, Hand Fracture*	102	190,-
0481-71667	Progressive Multifocal Leukoencephalopathy (Restaging)	113	120
4238-71644	Cellulitis	152	156
1305-71820	Gastroenteritis	155	157
5295-71745	Factor VIII Inhibition*	155	-
6819-71615	Breast Mass-Benign	156	156
4323-71465	Urinary Tract Infection	162	-
7751-71491	Hand Fracture*	169	180
2024-71789	Headache*	174	-
LDV/SOF+RBV x 24 weeks			
1081-71416	Alcohol Poisoning, Concussion, Rib Fracture, Depression*	72	72, 75, 102, 131
6819-71617	Carotid Artery Stenosis	85	88
0330-71316	Squamous Cell Carcinoma*	102	-
4435-71808	Calculus Ureteric	103	121
5300-71545	Alcohol Withdrawal Syndrome, Substance Abuse	171	178
0367-71530	Pneumonia	183	188

*Discussed in further detail in Section 7
Source: Integrated Datasets, ADAE, ADSL (ION-1)

There was no life-threatening AE reported, and no treatment-emergent deaths. One subject (Subject #5871-71038, LDV/SOF x 12 week) died due to hepatic failure on post-treatment Day 121. Further details are provided in Section 7.3.1.

GS-US-337-0108 (ION-3)

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection

The primary objectives of this trial as noted by the Applicant are the following:

- To determine the antiviral efficacy of combination treatment with LDV/SOF±RBV as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data

Trial Design
This phase 3 randomized, open-label, multicenter trial evaluated the antiviral efficacy, safety, and tolerability of LDV/SOF+RBV for 8 weeks and LDV/SOF (without RBV) for 8 and 12 weeks in HCV GT 1 TN subjects. Eligible subjects were randomized 1:1:1 to one of the following treatment groups:

- LDV/SOF 12 Week (Group 1)
- LDV/SOF+RBV 8 Week (Group 2)
- LDV/SOF 8 Week (Group 3)

Randomization was stratified by GT (1a or 1b; subjects with mixed GT1a/1b were stratified as 1a). Eligible subjects were to have documentation of the absence of cirrhosis. Investigators and the Sponsor were blinded to post-treatment HCV RNA results. After completing this trial, eligible subjects could enroll into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123).

A total of 647 subjects were randomized and received at least one dose of study drug. All randomized and treated subjects were enrolled across 59 sites in the US.

The majority of subjects experienced at least one AE. The overall summary of the ION-3 AE profile is shown in Table 12.

Table 12 Overall Summary of Adverse Events in ION-3 (GS-US-337-0108: Safety Analysis Set)

	LDV/SOF 8 Week (N=215)	LDV/SOF+RBV 8 Week (N=216)	LDV/SOF 12 Week (N=216)
Number (%) of Subjects Experiencing Any:			
Adverse Event	145 (67%)	165 (76%)	149 (69%)
Treatment-Related Adverse Event	82 (38%)	133 (62%)	93 (43%)
Serious Adverse Event (SAE)	4 (2%)	1 (<1%)	5 (2%)
Treatment-Related SAE	0	0	0
Grade 3 or 4 Adverse Event (AE)	2 (1%)	8 (4%)	7 (3%)
Grade 3 or 4 Treatment-Related AE	0	6 (3%)	0
AE Leading to Permanent Discontinuation from Any Study Drug	0	2 (1%)	2 (1%)
AE Leading to Permanent Discontinuation from LDV/SOF	0	1 (<1%)	2 (1%)
AE Leading to Modification or Interruption of Any Study Drug	0	17 (8%)	1 (<1%)
AE Leading to Interruption of LDV/SOF	0	1 (<1%)	1 (<1%)

Source: Integrated Datasets, ADAE, ADSL (ION-3)

There are an increased number of treatment-emergent and treatment-related AEs observed in the RBV-containing arm compared to the non-RBV-containing arms (76% vs. 67-69% and 62% vs. 38-43%, respectively). In addition, more subjects in the RBV-containing arm modified/interrupted any study drug. The most common reason for study drug modification/interruption was anemia (10 subjects), occurring only in the RBV-containing arm and consistent with the known RBV safety profile.

Increasing the LDV/SOF treatment duration from 8 to 12 weeks resulted in a generally similar treatment-emergent AEs (67% vs 69%), treatment-related AEs (38% vs 43%), SAEs (2% in each group) and AEs leading to LDV/SOF discontinuation (0 vs <1%).

The overall percentage of SAEs, Grade 3-4 AEs, and AEs leading to LDV/SOF discontinuation is low across all arms. Three subjects discontinued LDV/SOF, one subject in the LDV/SOF+RBV 8 week arm and two subjects in the LDV/SOF 12 week arm (Table 13). There is no pattern to the types of AEs leading to discontinuation. The two events in the 12 week arm occurred within the first 8 weeks.

Table 13 Discontinuation of LDV/SOF due to Adverse Event, ION-3 (GS-US-337-0108: Safety Analysis Set)

Treatment Arm Subject ID	Dictionary-Derived Term	Study Day, AE Onset	Study Day, DC LDV/SOF	SAE
LDV/SOF+RBV 8 Weeks				
5847-73029	Road Traffic Accident*	2	2	No
LDV/SOF 12 Weeks				
0331-73239	Squamous Cell Carcinoma Of Lung*	43	57	Yes
0380-73346	Arthralgia*	9	22	No

*Discussed in further detail in Section 7
Source: Integrated Datasets, ADAE, ADSL, ADEFF (ION-3)

The observed SAEs are shown in Table 14 and ranged <1% to 2% across the treatment arms. There is no pattern to the types of reported SAEs. No SAE was reported in >1 subject, and no SAE was assessed as treatment-related by the investigator. The investigators' causality assessments for these events appear reasonable.

Table 14 Serious Adverse Events in ION-3 (GS-US-337-0108: Safety Analysis Set)

Treatment Arm Subject ID	Dictionary-Derived Term	Study Day, Start of AE	Study Day, End of AE
LDV/SOF 8 Weeks			
4326-73477	Hypertension*	12	15
2140-73157	Lower Gastrointestinal Hemorrhage; Colitis*	34, 35	52, 53
4078-73488	Anaphylactic Reaction*	66	66
4326-73128	Diabetes Mellitus Inadequate Control	82	83
LDV/SOF+RBV 8 Weeks			
0380-73282	Pituitary Tumor*	75	95
LDV/SOF 12 Weeks			
2130-73381	Bile Duct Stone; Abdominal Pain; Jaundice*	2	3, 8, 11
3054-73011	Hypoglycemia	13	13
0331-73239	Squamous Cell Carcinoma Of Lung*	43	185
4308-73109	Road Traffic Accident, Hemothorax, Mental Status Changes, Respiratory Failure, Rhabdomyolysis; Skeletal Injury*	97	156; -
4488-73366	Intestinal Perforation*	115	-

*Discussed in further detail in Section 7
Source: Integrated Datasets, ADAE, ADSL (ION-3)

Three subjects experienced life-threatening AEs (anaphylaxis, hypoglycemia, road traffic accident with resultant complications), all were SAEs. There were no treatment-emergent deaths.

GS-US-337-0109 (ION-2)

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection

The primary objectives of this trial as noted by the Applicant are the following:

- To determine the antiviral efficacy of combination treatment with LDV/SOF±RBV as measured by the proportion of subjects with SVR12.
- To evaluate the safety and tolerability of each treatment regimen as assessed by review of the accumulated safety data.

Trial Design

This phase 3 randomized, open-label, multicenter trial evaluated the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in HCV GT 1 TE subjects who were virologic failures to prior treatment with a PEG/RBV regimen. Eligible subjects were randomized 1:1:1:1 to one of the following treatment groups:

- LDV/SOF 24 Week (Group 1)
- LDV/SOF+RBV 24 Week (Group 2)
- LDV/SOF 12 Week (Group 3)
- LDV/SOF+RBV 12 Week (Group 4)

Originally the Applicant proposed 12 weeks for Group 3. Discussions with the Division led to amending Group 3 to a LDV/SOF 24 week duration until availability of LONESTAR SVR4 data in HCV GT 1 TE PI-failure subjects receiving LDV/SOF for 12 weeks (LONESTAR Group 4). If ≥75% subjects in the LONESTAR Group 4 achieved SVR4, then the ION-2 Group 3 would be changed to 12 weeks.

Randomization was stratified by HCV GT (1a or 1b; subjects with mixed GT1a/1b were stratified as 1a), the presence or absence of cirrhosis at screening, and response to prior HCV therapy (relapse/breakthrough or nonresponse) at screening. Enrollment was managed so that approximately 20% of randomized subjects had cirrhosis and approximately 50% of randomized subjects had failed prior treatment with a PI+PEG/RBV regimen. The treatment duration for all subjects randomized to Group 3 was shortened from 24 weeks to 12 weeks when the protocol pre-specified criterion was met. Post-treatment HCV RNA results were blinded to the investigator and Sponsor. After completing the current study, eligible subjects could enroll into 1 of 2 follow-on studies: the SVR Registry Study (GS-US-248-0122) or the Sequence Registry Study (GS-US-248-0123).

A total of 441 subjects were randomized, and 440 subjects received at least one study drug dose. All randomized and treated subjects were enrolled across 64 sites in the US.

The majority of subjects experienced at least one AE. The overall summary of the AE profile in ION-2 is shown in Table 15.

Table 15 Overall Summary of Adverse Events in ION-2 (GS-US-337-0109: Safety Analysis Set)

	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
Number (%) of Subjects Experiencing Any:				
Adverse Event (AE)	73 (67%)	96 (86%)	88 (81%)	100 (90%)
Treatment-Related AE	38 (35%)	77 (69%)	50 (46%)	85 (77%)
Serious Adverse Event (SAE)	0	0	6 (6%)	3 (3%)
Treatment-Related SAE	0	0	0	0
Grade 3 and 4 AE	2 (2%)	3 (3%)	10 (9%)	8 (7%)
Treatment-Related Grade 3 and 4 AE	1 (1%)	3 (3%)	2 (2%)	5 (5%)
AE Leading to Permanent Discontinuation of Any Study Drug	0	0	0	0
AE Leading to Permanent Discontinuation of LDV/SOF	0	0	0	0
AE Leading to Modification or Interruption of Any Study Drug	0	11 (10%)	0	17 (15%)
AE Leading to Interruption of LDV/SOF	0	0	0	2 (2%)

Source: Integrated Datasets, ADAE, ADSL (ION-2)

There are an increased number of treatment-emergent and treatment-related AEs observed in the RBV-containing arms compared to the non-RBV-containing arms (86-90% vs. 67-81% and 69-77% vs. 35-46%, respectively). In addition, only subjects in the RBV-containing arms modified/interrupted any study drug. The most common reason for study drug modification/interruption was anemia (3 subjects in 12 week arm, 10 subjects in 24 week arm), occurring only in the RBV-containing arms and consistent with the known RBV safety profile.

Increasing the LDV/SOF treatment duration from 12 to 24 weeks resulted in a generally increased occurrence of treatment-emergent AEs, treatment-related AEs, Grade 3-4 AEs and SAEs. As will be discussed in Section 7.4.1, despite a higher occurrence in the longer duration arms, most treatment-emergent AEs occurred within the first 12 weeks of treatment.

The overall percentage of SAEs and Grade 3-4 AEs is low across all arms. No subjects discontinued study drug treatment.

The observed SAEs are shown in Table 16 and ranged 0 to 6% across the treatment arms, occurring only in the 24 week groups. There is no consistent pattern to the types of SAEs reported. No SAE was reported in >1 subject, and no SAE was assessed as treatment-related by the investigator. The investigators' causality assessments for these events appear reasonable. Although all SAEs occurred in the 24 week treatment durations, the shaded areas in Table 16 demonstrate three of the SAEs occurred within the first 12 weeks of LDV/SOF-containing treatment.

Table 16 Serious Adverse Events in ION-2 (GS-US-337-0109: Safety Analysis Set)

Treatment Arm Subject ID	Dictionary-Derived Term	Study Day, Start of AE	Study Day, End of AE
LDV/SOF 24 Weeks			
2760-79165	Non-Cardiac Chest Pain*	35	36
2111-79260	Convulsion*	47	47
2760-79085	Upper Gastrointestinal Hemorrhage*	55	59
2493-79305	Hepatic Encephalopathy	104	105
2493-79317	Angina Unstable*	152	154
6840-79431	Intervertebral Disc Protrusion, Spondylolisthesis	183	185
LDV/SOF+RBV 24 Weeks			
4007-79145	Cholecystitis Acute*	129	130
3055-79333	Vaginal Prolapse	142	144
0529-79110	Wound Infection	153	155

*Discussed in further detail in Section 7
Source: Integrated Datasets, ADAE, ADSL (ION-2)

One subject in the LDV/SOF 24 week arm experienced a life-threatening AE of unstable angina which was also reported as an SAE. There were no treatment-emergent deaths.

6 Review of Efficacy

Efficacy Summary

The ION-1, ION-2 and ION-3 pivotal phase 3 trials evaluated the efficacy of LDV/SOF-containing regimens in subjects with chronic HCV GT 1 infection. High SVR12 rates ≥93% were achieved across these trials which included HCV GT 1 treatment-naïve and prior PEG/RBV treatment-experienced populations with and without cirrhosis, LDV/SOF-containing treatment durations ranging 8 to 24 weeks, and RBV-containing and RBV-free regimens. All treatment arms met the primary efficacy endpoint of SVR12 superiority to a prespecified historical control SVR rate (60% SVR in ION-1 and ION-3, 25% SVR in ION-2).

- The efficacy and safety of LDV/SOF±RBV for 12 weeks was evaluated in HCV treatment-naïve subjects with HCV GT 1 infection, including 16% with compensated cirrhosis (ION-1). A statistically significant proportion of subjects

(p<0.001) in each treatment group achieved SVR12 (99% LDV/SOF 12 Week, 97% LDV/SOF+RBV 12 Week) compared to a prespecified historical control rate of 60%. Relapse rates are 0.5% in the LDV/SOF 12 Week arm and 0% in the LDV/SOF+RBV 12 Week arm.

- The efficacy and safety of LDV/SOF±RBV for 8 or 12 weeks was evaluated in HCV treatment-naïve subjects with HCV GT 1 infection and without cirrhosis (ION-3). A statistically significant proportion of subjects (p<0.001) in each treatment group achieved SVR12 (94% LDV/SOF 8 Week, 93% LDV/SOF+RBV 8 Week, 96% LDV/SOF 12 Week) compared to a prespecified historical control rate of 60%. Relapse rates are 5.1% in the LDV/SOF 8 Week arm, 4.2% in the LDV/SOF+RBV 8 Week arm, and 1.4% in the LDV/SOF 24 Week arm.

- The efficacy and safety of LDV/SOF±RBV for 12 or 24 weeks was evaluated in HCV treatment-experienced subjects with HCV GT 1 infection, including 20% with compensated cirrhosis and 53% prior PI-containing treatment failures (ION-2). A statistically significant proportion of subjects (p<0.001) in each treatment group achieved SVR12 (94% LDV/SOF 12 Week, 96% LDV/SOF+RBV 12 Week, 99% LDV/SOF 24 Week, 99% LDV/SOF+RBV 24 Week) compared to a prespecified historical control rate of 25%. Relapse rates are 6.5% in the LDV/SOF 12 Week arm, 3.6% in the LDV/SOF+RBV 12 Week arm and 0% in each of the LDV/SOF±RBV 24 Week arms.

Within the trials, the differences in SVR12 rates were not statistically significant between the ION-1 LDV/SOF±RBV 12 week arms and the ION-3 LDV/SOF±RBV 8 week and LDV/SOF 12 week arms.

ION-3 and ION-2 have numerically higher SVR12 rates and lower relapse rates in the respective longer treatment duration arms. In ION-3, relapse rates are 4.2-5.1% in the LDV/SOF±RBV 8 week arms versus 1.4% in the LDV/SOF 12 week arm. In ION-2, relapse rates are 3.6-6.5% in the LDV/SOF±RBV 12 week arms versus 0% in the LDV/SOF±RBV 24 week arms. RBV does not substantially impact overall SVR12 or relapse rates. As discussed in Section 7, no safety concern is currently identified precluding extending LDV/SOF duration up to 24 weeks; however, concomitant RBV use is associated with greater treatment-emergent AEs compared with LDV/SOF regimens without RBV. These factors led the review team to frame LDV/SOF treatment regimen considerations in the following HCV GT 1 populations, categorized by HCV treatment history and cirrhosis status. Labeling discussions are ongoing and no definite agreements have been reached at the time of this review.

HCV GT 1 Treatment-Naïve, Non-Cirrhotic Population

In ION-3, high SVR12 rates ranging 93-96% are observed across treatment arms. RBV does not significantly impact SVR12 rates between the LDV/SOF±RBV 8 week arms,

and no statistically significant difference in SVR12 rates is observed between the LDV/SOF 8 and 12 week durations.

Relapse rate was a pre-specified secondary endpoint, and higher relapse rates occur with the LDV/SOF±RBV 8 week duration (4.2-5.1%) compared with the LDV/SOF 12 week duration (1.4%), with similar relapse rates occurring between the LDV/SOF+RBV and LDV/SOF 8 week arms.

- Post hoc pooled LDV/SOF±RBV 8 week and LDV/SOF 12 week analyses of relapse rates in ION-3 demonstrate a 3.3% proportion difference (95% CI 0.2%, 6.0%) between the two groups, favoring the 12 week duration.
- Exploratory analyses of baseline predictors of relapse identify that high baseline viral load appears to account for most of the relapse rate differences between the 8 and 12 week durations, and the baseline viral load HCV RNA 6 million IU/mL cutoff value has the largest proportion difference between the 8 and 12 week durations in subjects with low and high baseline viral load.
  - Baseline HCV RNA ≥6 million IU/mL is associated with a relapse rate of 8.9% (15/169 subjects) in the pooled LDV/SOF±RBV 8 week group versus 1.2% (1/85 subjects) and in the LDV/SOF 12 week group [proportion difference 7.7%, 95% CI (1.9%, 13.3%)].
  - Baseline HCV RNA <6 million IU/mL is associated with a relapse rate of 1.9% (5/260 subjects) in the pooled LDV/SOF±RBV 8 week group versus 1.5% (2/131 subjects) in the LDV/SOF 12 week group, [proportion difference 0.4% (-3.7%, 3.2%)].

These efficacy data are used in support of a LDV/SOF 12 week treatment duration in the HCV GT 1 treatment-naïve, non-cirrhotic population. Optimizing treatment success with the first LDV/SOF regimen and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options are factors contributing to this treatment recommendation, in addition to the acceptable LDV/SOF safety profile. A LDV/SOF 8 week duration in patients with viral load below a cutoff value (e.g., baseline HCV RNA < 6 million IU/mL) is a consideration due to similar relapse rates between the pooled 8-week and 12-week durations.

HCV GT 1 Treatment-Naïve, Cirrhotic Population

In ION-1, high SVR12 rates ranging 94-100% are achieved among subjects with cirrhosis treated with LDV/SOF±RBV for 12 weeks. A single subject with multiple negative baseline predictive factors relapsed in the LDV/SOF 12 week group (2.9%, 1/34 subjects with baseline cirrhosis). There is a possible concern that wider use of a LDV/SOF 12 week duration in the HCV GT 1 treatment-naïve population with cirrhosis and other baseline factors traditionally associated with a lower response to HCV treatment may result in lower response rates than observed in the phase 3 trials, and that a longer duration and/or addition of RBV may optimize response rates by decreasing relapse. However, the ION-1 data clearly demonstrate high SVR12 rates

and low relapse rates in this cirrhotic subgroup, supporting a recommendation for LDV/SOF 12 week treatment duration in this population.

HCV GT 1 Treatment-Experienced, Non-Cirrhotic Population

In the ION-2 non-cirrhotic subgroup, SVR12 rates of 95-100% and 99% are observed in the LDV/SOF±RBV 12 week and LDV/SOF±RBV 24 week groups, respectively. Relapse occurs only in the LDV/SOF 12 week arm (4.7%, 4/86 subjects). All subjects experiencing relapse have baseline NS5A resistance associated polymorphisms, resulting in a relapse rate of 21.1% (4/19 subjects) among those with baseline NS5A resistance associated polymorphisms. Age ≥50 years and IL28B non-C/C genotype are additional baseline factors present in all subjects with relapse, though the IL28B non-C/C genotype is present in the majority (86.9%, 304/350 subjects) of the ION-2 non-cirrhotic subgroup. These efficacy data are used in support of LDV/SOF 12 week treatment duration in the HCV GT 1 treatment-experienced, non-cirrhotic population, with consideration for 24 week duration in patients with baseline factors associated with a lower response to HCV treatment. Optimizing treatment success with the LDV/SOF regimen, especially for patients with previous PI-failure and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options are factors contributing to this treatment recommendation. As discussed in Section 7.4, no safety concerns are identified in the treatment-experienced, non-cirrhotic population precluding use of the LDV/SOF 24 week duration.

HCV GT 1 Treatment-Experienced, Cirrhotic Population

In the ION-2 cirrhotic subgroup, SVR12 rates of 82-86% and 100% are observed in the LDV/SOF±RBV 12 week and LDV/SOF±RBV 24 week groups, respectively. Relapse accounts for all treatment failure in the 12 week group, with relapse rates of 13.6-18.2%. Pooled LDV/SOF±RBV 12 week and LDV/SOF±RBV 24 week analysis demonstrate that compared with the 12 week duration, the 24 week treatment duration reduces the relapse rate by approximately 16% (95% CI 6.5%, 29.8%). These efficacy data are used to support a LDV/SOF 24 week duration for treatment of HCV GT 1 treatment-experienced, cirrhotic patients to minimize relapse rates. The consequences of HCV treatment failure in patients with cirrhosis include risk of progressing to hepatic decompensation and development of hepatocellular carcinoma; therefore, optimizing treatment success with the LDV/SOF regimen, especially for patients with previous PI-failure, and minimizing development of NS5A and/or NS5B substitutions, which may negatively impact future retreatment options, are of particular importance. As discussed in Section 7.4, no safety concerns are identified in the compensated cirrhotic population precluding use of the LDV/SOF 24 week duration.

In summary, high SVR12 rates following LDV/SOF treatment are observed in the HCV GT 1 TN and TE populations, including subjects with cirrhosis and with prior PI-failure. RBV is not identified as necessary to achieve these high response rates, and is

associated with greater safety events compared with LDV/SOF alone regimens. LDV/SOF regimens provide an effective, all oral, once daily, interferon-free and RBV-free regimen option for HCV GT 1 treatment, an advantage in convenience and in an improved safety profile compared with PEG/RBV-containing regimens. In addition, LDV/SOF regimens provide a treatment option for patients with chronic HCV GT 1 infection who cannot take interferon and/or RBV and for patients who have failed a prior PI-containing regimen, addressing an unmet need in these populations.

6.1 Indication

The Applicant's proposed indication is the following:

- [TRADENAME] is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.

6.1.1 Methods

The efficacy data from the three pivotal phase 3 trials (ION-1, ION-2, ION-3) are reviewed in support of the proposed indication.

The following definitions were used to define the treatment experience of chronic hepatitis C subjects in the pivotal trials, based upon previous responses to a PEG/RBV-containing treatment regimen.

Treatment Naïve: no prior exposure to any IFN, RBV, or other approved or experimental HCV-specific DAA agent

Treatment Experienced: failed prior therapy with PEG/RBV-containing treatment with any one of the following treatment responses:

- Nonresponse: did not achieve undetectable HCV RNA levels (HCV RNA ≥LLOQ) while on treatment. For PEG/RBV nonresponders, subjects were further defined as null or partial responders as follows:
  - Null Responder: <2 $\log_{10}$ reduction in HCV RNA during the first 12 weeks of treatment
  - Partial Responder: ≥2 $\log_{10}$ reduction in HCV RNA during the first 12 weeks of treatment
- Relapse/Breakthrough: HCV RNA undetectable (<LLOQ) during treatment or within 4 weeks of the end of treatment, but did not achieve an SVR

Statistical Methods

This section describes the statistical methods used by the Applicant and FDA for the pivotal trials efficacy analyses. Statistical approaches and definitions used by the Applicant include:

Imputation for missing values of HCV RNA data
For analyses of categorical HCV RNA data, if a data point was missing and was preceded and followed in time by values that were "<LLOQ TND", then the missing data point was set to "<LLOQ TND". If a data point was missing and preceded and followed by values that were "<LLOQ detected", or preceded by "<LLOQ detected" and followed by "<LLOQ TND", or preceded by "<LLOQ TND" and followed by "<LLOQ detected", then the missing value was set to "<LLOQ detected"; otherwise the data point was termed a failure (i.e., ≥ LLOQ detected).

Nomenclature used for virologic failures
On-treatment virologic failure (breakthrough, rebound and nonresponse) and relapse were defined as follows:

- On-treatment virologic failure:
  - Breakthrough: HCV RNA ≥LLOQ after having previously had HCV RNA <LLOQ while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be post-treatment), or last available on-treatment measurement with no subsequent follow up values
  - Rebound: >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment, confirmed with 2 consecutive values (note, second confirmation value can be post-treatment), or last available measurement with no subsequent follow up value
  - Non-response: HCV RNA persistently ≥LLOQ through 8 weeks of treatment
- Relapse:
  - HCV RNA ≥LLOQ during the post-treatment period having achieved HCV RNA <LLOQ at the last observed on-treatment HCV RNA measurement, confirmed with consecutive values or last available post-treatment measurement

GS-US-337-0102 (ION-1)

The primary efficacy hypothesis was that the SVR12 rate in each treatment arm was superior to the historical control rate of 60%. The Division agreed with a 60% historical control SVR rate although the Applicant and the Division approached the calculations differently. Please refer to the Statistical Review for further details. The two-sided one-sample binomial test was used to evaluate whether the SVR12 rate was superior to the 60% historical SVR rate in each treatment group. The CI for the SVR12 rate was constructed for each treatment arm using the Clopper-Pearson method. Type I error was controlled using Bonferroni correction method. The Bonferroni correction method ensured control of family-wise type I error rate at the 0.05 level, and ensured controls of

individual type I error rate at the 0.0125 level for comparison of the SVR12 rate in each treatment group against the historical rate of 60%.

GS-US-337-0108 (ION-3)

The primary efficacy hypothesis was the same as for ION-1: the SVR12 rate in each treatment arm was superior to the historical control SVR rate of 60%, selected using the same rationale as used for ION-1. The two-sided one-sample binomial test was used to evaluate whether the SVR12 rate was superior to the 60% historical SVR rate in each treatment group. The CI for the SVR12 rate was constructed for each treatment arm using the Clopper-Pearson method. The SVR12 rates in the three groups were tested following a sequential testing procedure. If the SVR12 rate for the 12-week LDV/SOF was statistically significant compared to the 60% historical SVR rate at the 0.05 significance level, the SVR12 rates for the two 8-week groups were compared to the null rate of 60%, respectively, each at the 0.025 significance level.

GS-US-337-0109 (ION-2)

The primary efficacy hypothesis was that the SVR12 rate in each treatment group was superior to the historical SVR rate of 25%. The Division agreed with a 25% historical control SVR rate although the Applicant and the Division approached the calculations differently. Please refer to the Statistical Review for further details. The one-sample binomial test was performed to evaluate whether the SVR12 rate in each treatment group was superior to the 25% historical SVR rate. A Hochberg procedure was applied to control the family-wise type I error rate.

The two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors) was carried out to evaluate the difference in SVR12 rate between the treatment groups.

Please refer to Statistical Review by Dr. Karen Qi for detailed assessment of Statistical Methods used by FDA for analyses.

6.1.2 Demographics

GS-US-337-0102 (ION-1)

The demographics and baseline characteristics for subjects in ION-1 are shown in Table 17, including the LDV/SOF±RBV 24 week durations. Overall, the demographics and baseline characteristics, such as age, sex, race and BMI, are comparable between the treatment groups and no major differences are noted. Approximately 40% European subjects enrolled into ION-1. Compared with Europe subjects, US subjects had more HCV GT1a infection (73% US vs 59% Europe), men (64% US vs 52% Europe), were

black or African-American race (20% US vs 2% Europe), and had a BMI ≥ 30 kg/m^2 (27% US vs 9% Europe).

Table 17 Demographics and Baseline Characteristics, ION-1 (GS-US-337-0102: Safety Analysis Set)

Characteristics	LDV/SOF 12 Week (N=214)	LDV/SOF+RBV 12 Week (N=217)	LDV/SOF 24 Week (N=217)	LDV/SOF+RBV 24 Week (N=217)
Age at Baseline (Years)				
Median	54	54	55	54
Min, Max	18, 75	18, 78	22, 80	24, 77
Sex				
Male	127 (59.3%)	128 (59.0%)	139 (64.1%)	119 (54.8%)
Female	87 (40.7%)	89 (41.0%)	78 (35.9%)	98 (45.2%)
Race				
Black or African American	24 (11.2%)	26 (12.0%)	32 (14.7%)	26 (12.0%)
White	187 (87.4%)	188 (86.6%)	177 (81.6%)	183 (84.3%)
Asian	1 (0.5%)	0	5 (2.3%)	5 (2.3%)
American Indian/ Alaska Native	0	1 (0.5%)	0	1 (0.5%)
Hawaiian or Pacific Islander	0	0	1 (0.5%)	0
Other	2 (0.9%)	1 (0.5%)	2 (0.9%)	1 (0.5%)
Not Disclosed	0	1 (0.5%)	0	1 (0.5%)
Ethnicity				
Hispanic or Latino	26 (12.1%)	20 (9.2%)	29 (13.4%)	26 (12.0%)
Not Hispanic or Latino	187 (87.4%)	197 (90.8%)	188 (86.6%)	190 (87.6%)
Not Disclosed	1 (0.5%)	0	0	1 (0.5%)
Region				
US	125 (58.4%)	118 (54.4%)	132 (60.8%)	137 (63.1%)
Europe	89 (41.6%)	99 (45.6%)	85 (39.2%)	80 (36.9%)
Baseline Body Mass Index (kg/m^2)				
Median	26.1	25.9	26.0	25.5
Min, Max	18.0, 41.3	18.1, 42.0	18.1, 47.6	18.0, 47.5
Baseline Body Mass Index Category				
≥30 kg/m^2	38 (17.8%)	46 (21.2%)	49 (22.6%)	40 (18.4%)

Source: Integrated Datasets, ADSL (ION-1)

The median age is 54 years, with an overall age range of 18 to 80 years. The majority of subjects are white (85%), males (59%) and enrolled from United States region (59%).

Table 18 shows ION-1 baseline disease characteristics. The majority of subjects (67%) are HCV GT1a and IL28B non-C/C (70%). Approximately 16% of subjects had cirrhosis. The methods of cirrhosis determination were liver biopsy (53%, 462 subjects),

Fibroscan (33%, 284 subjects), and FibroTest and APRI (13%, 116 subjects). Subjects with cirrhosis had a lower median baseline platelet count compared with subjects without cirrhosis (134 vs 234 x 10^3/μL, respectively).

Table 18 Selected Baseline Disease Characteristics, ION-1 (GS-US-337-0102: Safety Analysis Set)

Disease Characteristics	LDV/SOF 12 Weeks (N=214)	LDV/SOF+RBV 12 Weeks (N=217)	LDV/SOF 24 Weeks (N=217)	LDV/SOF+RBV 24 Weeks (N=217)
HCV Genotype				
Genotype 1a	144 (67.3%)	148 (68.2%)	146 (67.3%)	143 (65.9%)
Genotype 1b	66 (30.8%)	68 (31.3%)	68 (31.3%)	71 (32.7%)
Genotype 1 (no confirmed subtype)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Genotype 4	1 (0.5%)	0	0	1 (0.5%)
Missing	2 (0.9%)	0	2 (0.9%)	1 (0.5%)
Cirrhosis				
No	178 (83.2%)	183 (84.3%)	184 (84.8%)	181 (83.4%)
Yes	34 (15.9%)	33 (15.2%)	33 (15.2%)	36 (16.6%)
Missing	2 (0.9%)	1 (0.5%)	0	0
IL28B				
CC	55 (25.7%)	76 (35.0%)	52 (24.0%)	73 (33.6%)
Non-CC	159 (74.3%)	141 (65.0%)	165 (76.0%)	144 (66.4%)
CT	113 (52.8%)	107 (49.3%)	119 (54.8%)	112 (51.6%)
TT	46 (21.5%)	34 (15.7%)	46 (21.2%)	32 (14.7%)
Baseline HCV RNA (log_{10} IU/mL)				
Median	6.5	6.5	6.4	6.4
Min, Max	1.6, 7.5	4.4, 7.6	3.7, 7.4	3.2, 7.5
Baseline HCV RNA Category				
< 800,000 IU/mL	45 (21.0%)	44 (20.3%)	49 (22.6%)	44 (20.3%)
>= 800,000 IU/mL	169 (79.0%)	173 (79.7%)	168 (77.4%)	173 (79.7%)
Baseline ALT (U/L)				
Median	63	62	59	62
Min, Max	16, 557	16, 485	17, 360	7, 321
Baseline ALT Category				
> 1.5 x ULN	120 (56.1%)	119 (54.8%)	109 (50.2%)	112 (51.6%)

Source: Adapted from NDA 205834 ION-1 Clinical Study Report, Table 8-5

GS-US-337-0108 (ION-3)

The demographics and baseline characteristics for subjects in ION-3 are shown in Table 19. Overall, the demographics and baseline characteristics, such as age, sex, race and BMI, are comparable between the treatment groups and no major differences are noted. The median age is 55 years, with an overall age range of 20 to 75 years. The majority of subjects are white (78%) and male (58%).

Table 19 Demographics and Baseline Characteristics, ION-3 (GS-US-337-0108: Safety Analysis Set)

Subject Disposition	LDV/SOF 8 Weeks (N = 215)	LDV/SOF+RBV 8 Weeks (N = 216)	LDV/SOF 12 Weeks (N = 216)
	n (%)	n (%)	n (%)
Age at Baseline (Years)			
Median	55	54	55
Min, Max	22, 75	21, 71	20, 71
Sex			
Male	130 (60.5%)	117 (54.2%)	128 (59.3%)
Female	85 (39.5%)	99 (45.8%)	88 (40.7%)
Race			
Black or African American	45 (20.9%)	36 (16.7%)	42 (19.4%)
White	164 (76.3%)	176 (81.5%)	167 (77.3%)
Asian	5 (2.3%)	2 (0.9%)	3 (1.4%)
American Indian/ Alaska Native	0	1 (0.5%)	0
Hawaiian or Pacific Islander	0	1 (0.5%)	0
Other	1 (0.5%)	0	3 (1.4%)
Not Disclosed	0	0	1 (0.5%)
Ethnicity			
Hispanic or Latino	13 (6.0%)	12 (5.6%)	14 (6.5%)
Not Hispanic or Latino	200 (93.0%)	204 (94.4%)	202 (93.5%)
Not Disclosed	2 (0.9%)	0	0
Baseline Body Mass Index (kg/m2)			
Median	27.1	27.4	27.1
Min, Max	18.1, 42.7	18.4, 56.2	19.1, 44.8
Baseline Body Mass Index Category			
>= 30 kg/m^2	64 (29.8%)	64 (29.6%)	57 (26.4%)

Source: Adapted from NDA 205834 ION-3 Clinical Study Report, Table 8-4

Table 20 shows ION-3 baseline disease characteristics. The majority of subjects (80%) are HCV GT1a and are IL28B non-C/C (73%). No subjects had cirrhosis as per the trial design. The methods of cirrhosis determination were liver biopsy (69%, 448 subjects), FibroTest and APRI (30%, 197 subjects) and Fibroscan (0.3%, 2 subjects).

Table 20 Selected Baseline Disease Characteristics, ION-3 (GS-US-337-0108: Safety Analysis Set)

Subject Disposition	LDV/SOF 8 Weeks (N = 215)	LDV/SOF+RBV 8 Weeks (N = 216)	LDV/SOF 12 Weeks (N = 216)
	n (%)	n (%)	n (%)
HCV Genotype			
Genotype 1 (no confirmed subtype)	1 (0.5%)	0	0
Genotype 1a	171 (79.5%)	172 (79.6%)	172 (79.6%)
Genotype 1b	43 (20.0%)	44 (20.4%)	44 (20.4%)
IL28B			
CC	56 (26.0%)	60 (27.8%)	56 (25.9%)
Non-CC	159 (74.0%)	156 (72.2%)	160 (74.1%)
CT	120 (55.8%)	128 (59.3%)	124 (57.4%)
TT	39 (18.1%)	28 (13.0%)	36 (16.7%)
Baseline HCV RNA (log10 IU/mL)			
Median	6.6	6.6	6.6
Min, Max	1.4, 7.8	3.9, 7.7	2.3, 7.8
Baseline HCV RNA Category			
< 800,000 IU/mL	34 (15.8%)	45 (20.8%)	44 (20.4%)
>= 800,000 IU/mL	181 (84.2%)	171 (79.2%)	172 (79.6%)
Baseline ALT (U/L)			
Median	49	58	56
Min, Max	11, 281	15, 362	9, 384
Baseline ALT Category			
> 1.5 x ULN	87 (40.5%)	95 (44.0%)	99 (45.8%)

Source: Adapted from NDA 205834 ION-3 Clinical Study Report, Table 8-5

GS-US-337-0109 (ION-2)

The demographics and baseline characteristics for subjects in ION-2 are shown in Table 21. Overall, the demographics and baseline characteristics, such as age, sex, race and BMI, are comparable between the treatment groups and no major differences are noted. The median age is 57 years, with an overall age range of 24 to 75 years. The majority of subjects were white (81%) and male (65%).

Table 21 Demographics and Baseline Characteristics, ION-2 (GS-US-337-0109: Safety Analysis Set)

Characteristics	LDV/SOF 12 Weeks (N=109)	LDV/SOF+RBV 12 Weeks (N=111)	LDV/SOF 24 Weeks (N=109)	LDV/SOF+RBV 24 Weeks (N=111)
Age at Baseline (Years)				
Median	57	59	58	56
Min, Max	24, 67	27, 75	25, 68	28, 70
Sex				
Male	74 (67.9%)	71 (64.0%)	74 (67.9%)	68 (61.3%)
Female	35 (32.1%)	40 (36.0%)	35 (32.1%)	43 (38.7%)
Race				
Black or African American	24 (22.0%)	16 (14.4%)	17 (15.6%)	20 (18.0%)
White	84 (77.1%)	94 (84.7%)	91 (83.5%)	89 (80.2%)
Asian	1 (0.9%)	0	0	0
Hawaiian or Pacific Islander	0	1 (0.9%)	0	1 (0.9%)
Other	0	0	1 (0.9%)	1 (0.9%)
Ethnicity				
Hispanic or Latino	7 (6.4%)	12 (10.8%)	11 (10.1%)	11 (9.9%)
Not Hispanic or Latino	100 (91.7%)	99 (89.2%)	98 (89.9%)	99 (89.2%)
Not Disclosed	2 (1.8%)	0	0	1 (0.9%)
Baseline Body Mass Index (kg/m^2)				
Median	28.5	27.1	27.4	27.5
Min, Max	19.0, 46.8	18.9, 44.6	18.6, 41.3	18.6, 49.9
Baseline Body Mass Index Category				
≥ 30 kg/m^2	43 (39.4%)	37 (33.3%)	34 (31.2%)	29 (26.1%)

Source: Adapted from NDA 205834 ION-2 Clinical Study Report, Table 8-4

Table 22 shows ION-2 baseline disease characteristics. The majority of subjects (79%) are HCV GT1a and are IL28B non-C/C (87.5%), a higher percentage than enrolled in the ION-1 and ION-3 HCV GT 1 TN trials. Overall 20% of subjects had cirrhosis. The methods of cirrhosis determination were liver biopsy (78%, 342 subjects) and FibroTest and APRI (22%, 96 subjects). Consistent with advanced liver disease, subjects with cirrhosis had a lower median baseline platelet count than subjects without cirrhosis (144 vs 233 x 10^3/µL, respectively).

Approximately 56% subjects had prior relapse/breakthrough and 44% had prior nonresponse to PEG/RBV-containing treatment. Over half (53%) of subjects failed prior PI+PEG/RBV therapy. Of the 231 subjects who failed prior PI+PEG/RBV therapy (58% failed telaprevir; 29% failed boceprevir; and 12% failed investigational PIs), 62% of subjects had relapse/breakthrough and 38% of subjects had nonresponse. Of the 207 subjects who failed prior PEG/RBV therapy, 49% of subjects had relapse/breakthrough and 51% of subjects had nonresponse. The majority of prior PEG/RBV nonresponders (60%, 64 subjects) were null responders.

Table 22 Selected Baseline Disease Characteristics, ION-2 (GS-US-337-0109: Safety Analysis Set)

Disease Characteristics	LDV/SOF 12 Weeks (N=109)	LDV/SOF+RBV 12 Weeks (N=111)	LDV/SOF 24 Weeks (N=109)	LDV/SOF+RBV 24 Weeks (N=111)
HCV Genotype				
Genotype 1a	86 (78.9%)	88 (79.3%)	85 (78.0%)	88 (79.3%)
Genotype 1b	23 (21.1%)	23 (20.7%)	24 (22.0%)	23 (20.7%)
Cirrhosis				
No	87 (79.8%)	88 (79.3%)	86 (78.9%)	89 (80.2%)
Yes	22 (20.2%)	22 (19.8%)	22 (20.2%)	22 (19.8%)
Missing	0	1 (0.9%)	1 (0.9%)	0
IL28B				
CC	10 (9.2%)	11 (9.9%)	16 (14.7%)	18 (16.2%)
Non-CC	99 (90.8%)	100 (90.1%)	93 (85.3%)	93 (83.8%)
CT	70 (64.2%)	77 (69.4%)	68 (62.4%)	68 (61.3%)
TT	29 (26.6%)	23 (20.7%)	25 (22.9%)	25 (22.5%)
Baseline HCV RNA (log_{10} IU/mL)				
Median	6.6	6.5	6.5	6.6
Min, Max	5.0, 7.5	4.6, 7.3	4.7, 7.4	3.1, 7.4
Baseline HCV RNA Category				
< 800,000 IU/mL	6 (5.5%)	13 (11.7%)	16 (14.7%)	15 (13.5%)
≥ 800,000 IU/mL	103 (94.5%)	98 (88.3%)	93 (85.3%)	96 (86.5%)
Baseline ALT (U/L)				
Median	58	55	59	51
Min, Max	20, 186	20, 245	23, 422	19, 386
Baseline ALT Category				
> 1.5 x ULN	53 (48.6%)	51 (45.9%)	60 (55.0%)	49 (44.1%)
Response to Prior HCV Treatment				
Relapse/Breakthrough	60 (55.0%)	65 (58.6%)	60 (55.0%)	60 (54.1%)
Non-Responder	49 (45.0%)	46 (41.4%)	49 (45.0%)	51 (45.9%)
Prior HCV Treatment Category and Response to Prior HCV Treatment				
PEG/RBV	43 (39.4%)	47 (42.3%)	58 (53.2%)	59 (53.2%)
Relapse/Breakthrough	21 (48.8%)	23 (48.9%)	25 (43.1%)	32 (54.2%)
Non-Responder	22 (51.2%)	24 (51.1%)	33 (56.9%)	27 (45.8%)
Null	17 (77.3%)	12 (50.0%)	19 (57.6%)	16 (59.3%)
Partial	5 (22.7%)	12 (50.0%)	14 (42.4%)	11 (40.7%)
PI+PEG/RBV	66 (60.6%)	64 (57.7%)	50 (45.9%)	51 (45.9%)
Relapse/Breakthrough	39 (59.1%)	42 (65.6%)	35 (70.0%)	28 (54.9%)
Non-Responder	27 (40.9%)	22 (34.4%)	15 (30.0%)	23 (45.1%)
Other	0	0	1 (0.9%)	1 (0.9%)
Relapse/Breakthrough	0	0	0	0
Non-Responder	0	0	1 (100.0%)	1 (100.0%)

Source: Adapted from NDA 205834 ION-2 Clinical Study Report, Table 8-5

6.1.3 Subject Disposition

GS-US-337-0102 (ION-1)

Subject disposition is shown in Table 23. A total of 865 subjects were randomized and treated. Five subjects (0.6%) were randomized but not treated either due to

investigator's discretion or withdrawal of consent. One subject (Subject #5663-71589, LDV/SOF 24 Week) had lack of efficacy due to non-adherence, supported by PK data.

A total of 97% (838/865) subjects completed study treatment. More subjects discontinued study treatment in the 24 week arms, with the main reason being discontinuations due to AEs (2% LDV/SOF 24 Week; 3% LDV/SOF+RBV 24 Week).

Table 23 Subject Disposition in ION-1 (GS-US-337-0102)

Subject Disposition	LDV/SOF 12 Week	LDV/SOF+RBV 12 Week	LDV/SOF 24 Week	LDV/SOF+RBV 24 Week
Subjects Randomized	217	218	217	218
Randomized but Never Treated	3	1	0	1
Subjects Randomized and Treated (Safety Analysis Set)	214	217	217	217
Study Treatment Status				
Completed Study Treatment	212 (99%)	213 (98%)	208 (96%)	205 (94%)
Discontinued Study Treatment	2 (1%)	4 (2%)	9 (4%)	12 (6%)
Reason for Premature Discontinuation of Study Treatment				
Adverse Event	0	0	4 (2%)	6 (3%)
Withdrew Consent	0	1 (<1%)	3 (1%)	3 (1%)
Lost to Follow-Up	1 (<1%)	2 (1%)	0	1 (<1%)
Protocol Violation	1 (<1%)	1 (<1%)	0	2 (1%)
Lack Of Efficacy	0	0	1 (<1%)	0
Non-Compliance with Study Drug	0	0	0	0
Pregnancy	0	0	1 (<1%)	0

Source: ION-1 DS and DM datasets

GS-US-337-0108 (ION-3)

A total of 647 subjects were randomized and treated. Subject disposition is shown in Table 24.

A total of 99% (639/647) subjects completed study treatment. Eight subjects discontinued: no subjects in the LDV/SOF 8 week group, three subjects in the LDV/SOF+RBV 8 week group (two lost to follow up and one AE) and five subjects in the LDV/SOF 12 week group (two lost to follow up, two AEs, one non-compliance).

Table 24 Subject Disposition in ION-3 (GS-US-337-0108)

Subject Disposition	LDV/SOF 8 Week	LDV/SOF+ RBV 8 Week	LDV/SOF 12 Week
Subjects Randomized	215	216	216
Randomized but Never Treated	0	0	0
Subjects Randomized and Treated (Safety Analysis Set)	215	216	216
Study Treatment Status			
Completed Study Treatment	215 (100%)	213 (99%)	211 (98%)
Discontinued Study Treatment	0	3 (1%)	5 (2%)
Reason for Premature Discontinuation of Study Treatment			
Adverse Event	0	1 (<1%)	2 (1%)
Withdrew Consent	0	0	0
Lost to Follow-Up	0	2 (1%)	2 (1%)
Protocol Violation	0	0	0
Lack Of Efficacy	0	0	0
Non-Compliance with Study Drug	0	0	1 (<1%)
Pregnancy	0	0	0

Source: ION-3 DS and DM datasets

GS-US-337-0109 (ION-2)

Subject disposition is shown in Table 25. A total of 440 subjects were randomized and treated. One subject (0.2%) was randomized but not treated due to withdrawal of consent.

A total of 99% (437/440) subjects completed study treatment. Three subjects discontinued: no subjects in the LDV/SOF or LDV/SOF+RBV 12 week groups, two subjects in the LDV/SOF 24 week group (two protocol violations – each subject received 12 weeks of treatment) and one subject in the LDV/SOF+RBV 24 week group (lack of efficacy). Subject #7864-79383 discontinued study treatment Day 46 due to lack of efficacy associated with study drug non-adherence, supported by PK data.

Table 25 Subject Disposition in ION-2 (GS-US-337-0109)

Subject Disposition	LDV/SOF 12 Week	LDV/SOF+ RBV 12 Week	LDV/SOF 24 Week	LDV/SOF+ RBV 24 Week
Subjects Randomized	109	111	110	111
Randomized but Never Treated	0	0	1	0
Subjects Randomized and Treated	109	111	109	111
Study Treatment Status				
Completed Study Treatment	109 (100%)	111 (100%)	107 (98%)	110 (99%)
Discontinued Study Treatment	0	0	2 (2%)	1 (1%)
Reason for Premature Discontinuation of Study Treatment				
Adverse Event	0	0	0	0
Withdrew Consent	0	0	0	0
Lost to Follow-Up	0	0	0	0
Protocol Violation	0	0	2 (2%)	0
Lack Of Efficacy	0	0	0	1 (1%)
Non-Compliance with Study Drug	0	0	0	0
Pregnancy	0	0	0	0

Source: ION-2 DS and DM datasets

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint used in the LDV/SOF pivotal phase 3 trials is SVR12 (SVR at 12 weeks after completion of a scheduled course of therapy), as recommended in the October 2013 *Draft Guidance for Industry, Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment*. Observational data support the use of SVR as a validated surrogate of HCV disease progression and, therefore, use of SVR is the recommended primary efficacy endpoint for traditional approval in trials evaluating CHC treatments. The FDA examined the correlation between SVR12 and SVR24 in more than 13,000 subjects pooled from multiple clinical trials of PEG-based regimens (Chen, Florian, et al. 2013) and found a high rate of concordance between SVR12 and SVR24. Sensitivity and specificity for SVR12 was 99% and 98%, respectively; therefore, SVR12 is considered a suitable primary endpoint for registrational trials. For the LDV/SOF phase 3 trials, SVR12 is defined as HCV RNA <LLOQ 12 weeks after the last dose of study drug.

Primary Efficacy Results in GS-US-337-0102 (ION-1)

The primary efficacy endpoint is the proportion of subjects achieving SVR12. The primary efficacy endpoint analysis in ION-1 was conducted when all subjects in the LDV/SOF±RBV 12 week groups completed the post-treatment Week 12 visits or

prematurely discontinued from the trial, as previously agreed upon with the Division. The SVR12 rate in the LDV/SOF 12 Week treatment group is 99%, similar to the SVR12 rate in the LDV/SOF+RBV 12 Week treatment group of 97% (Table 26). The primary trial endpoint of superiority to the historical control SVR rate of 60% (p<0.001 based on one-sample binomial test) is met for both 12 week groups. The difference in SVR12 rates between the two arms is not statistically significant.

One subject was found to have HCV GT 4 HCV infection and is excluded from the primary analysis. Three additional subjects did not have SVR12 data included in the original NDA submission. During the review cycle, the Applicant provided the updated SVR12 data for these subjects, and these data are incorporated into Table 26's result. Failure to achieve SVR12 is mainly due to 'other' reasons (e.g., lost to follow up).

Table 26 Primary Efficacy Results and Relapse Rates in ION-1 (All Treated)

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

Overall relapse rate at post-treatment Week 12 is <1% (one subject) in the LDV/SOF 12 week arm, and 0% in the LDV/SOF+RBV 12 week arm.

Primary Efficacy Results in GS-US-337-0108 (ION-3)

The SVR12 rate across the three arms ranges 93-96% (Table 27). In the LDV/SOF 8 Week treatment group SVR12 is 93%, in the LDV/SOF+RBV 8 Week group SVR12 is 94% and in the LDV/SOF 12 Week group SVR12 is 96%. The primary trial endpoint of superiority to the historical control SVR rate of 60% (p<0.001 based on one-sample binomial test) is met for all groups. Two subjects did not have SVR12 data included in the original NDA submission. During the review cycle, the Applicant provided the updated SVR12 for these subjects and is reflected in Table 27. In the 8 week arms

relapse is the main reason for not achieving SVR12, while in the 12 week arm 'other' reasons (e.g., lost to follow up) account for more failure to achieve SVR12 than relapse.

Table 27 Primary Efficacy Results and Relapse Rates in ION-3 (All Treated)

	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

The strata-adjusted differences (95% CI) in the proportions between the LDV/SOF ± RBV 8 week groups, between the LDV/SOF 8 and 12 week groups and between the LDV/SOF+RBV 8 week and LDV/SOF 12 week groups are not statistically significant (Table 28).

Table 28 Inter Group Comparison of SVR12 Rates in ION-3 (All Treated)

	Proportion Difference (97.5% CI)[1]
8-Week LDV/SOF vs. 8-Week LDV/SOF+RBV	0.9% (-3.9%, 5.7%)
8-Week LDV/SOF vs. 12-Week LDV/SOF	-2.3% (-7.2%, 2.5%)
8-Week LDV/SOF+RBV vs. 12-Week LDV/SOF	-3.2% (-8.2%, 1.8%)

[1]Differences in proportions between treatment groups and associated 97.5% CI were calculated based on stratum-adjusted Mantel-Haenszel proportions.
Source: Dr. Karen Qi, Statistical Reviewer

Overall relapse rate at post-treatment Week 12 is 5.1% in the LDV/SOF 8 week arm, 4.2% in the LDV/SOF+RBV 8 week arm and 1.4% in the LDV/SOF 12 week arm.

Primary Efficacy Results in GS-US-337-0109 (ION-2)

The SVR12 rate across the four arms ranges 94-99% (Table 29). In the LDV/SOF 12 Week group SVR12 is 94%, in the LDV/SOF+RBV 12 Week group SVR12 is 96% and in the LDV/SOF ± RBV 24 Week groups SVR12 is 99%. The primary trial endpoint of superiority to the historical control SVR rate of 25% ($p<0.001$ based on one-sample

binomial test) is met for all groups. Relapse accounts for all failure to achieve SVR12 in the LDV/SOF±RBV 12 week arms.

Table 29 Primary Efficacy Results and Relapse Rates in ION-2 (All Treated)

	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, Statistical Reviewer

Overall relapse rate at post-treatment Week 12 is 6.5% in the LDV/SOF 12 week arm and 3.6% in the LDV/SOF+RBV 12 week arm. No relapse occurred in the LDV/SOF±RBV 24 week arms.

6.1.5 Analysis of Secondary Endpoints(s)

Other secondary efficacy endpoints analyzed are:

- Relapse
- Proportion of subjects with HCV RNA <LLOQ by study visit
- Proportion of subjects achieving SVR4, SVR24
- HCV RNA (log_{10} IU/mL) and HCV RNA change from baseline through Week 8
- On-treatment virologic failure
- Characterization of HCV drug resistance substitutions at baseline, during, and after therapy with LDV/SOF

Please refer to FDA Statistical and Clinical Microbiology Reviews for complete details of analyses performed. Summary information pertaining to relapse and proportion of subjects with HCV RNA <LLOQ by study visit is presented in this section.

Relapse in ION-1 and ION-3

ION-1 and ION-3 relapse rates by post-treatment Week 4 and Week 12 are shown in Table 30.

Table 30 Relapse Rates in ION-1 and ION-3 (All Treated)

	ION-1		ION-3		
	LDV/SOF 12 Weeks (N=214)	LDV/SOF +RBV 12 Weeks (N=217)	LDV/SOF 8 Weeks (N=215)	LDV/SOF +RBV 8 Weeks (N=216)	LDV/SOF 12 Weeks (N=216)
Number of virologic responders at end of treatment	213	217	215	214	216
Relapse					
By 4 weeks post-treatment	0.5% (1/213)	0% (0/217)	3.7% (8/215)	2.8% (6/214)	1.4% (3/216)
By 12 weeks post-treatment	0.5% (1/213)	0% (0/217)	5.1% (11/215)	4.2% (9/214)	1.4% (3/216)

Source: Dr. Karen Qi, Statistical Reviewer

ION-1

A single relapse occurred in ION-1, in the LDV/SOF 12 week group. This subject had cirrhosis along with presence of a baseline NS5A resistance associated polymorphism, non-IL28B C/C genotype and baseline viral load >6 million IU/mL.

ION-3

In ION-3, the LDV/SOF 12 week group has a lower relapse rate (1.4%) compared with the 8 week duration groups (4.2-5.1%). All relapse occurs by post-treatment Week 4 in the LDV/SOF 12 week group, while in the LDV/SOF±8 week groups 30% relapse occurs between post-treatment Week 4-12.

Although SVR12 rates are high and range 93-96% across ION-3 treatment groups, the observed differences in relapse rates between the 8 and 12 week durations led to post hoc exploratory analyses to further characterize these differences. Statistical analyses determine RBV does not affect relapse rates between the LDV/SOF and LDV/SOF+RBV 8 week arms. Therefore, for subsequent relapse rate analyses, the ION-3 8 week arms are pooled. Both the unpooled LDV/SOF 8 versus 12 week and pooled LDV/SOF±RBV 8 week versus LDV/SOF 12 week analyses demonstrate a statistically significant lower relapse rate in the 12 week group as shown in Table 31. The difference in the relapse rates between the combined LDV/SOF 8 week arms and the LDV/SOF 12 week arm is 3.3% (95% CI 0.2%, 6.0%).

Table 31 Comparison of Relapse Rates Between Different Treatment Durations in ION-3 (All Treated)

	Proportion Difference in Relapse Rate	95% Exact CI[1]
8-Week LDV/SOF vs. 12-Week LDV/SOF	3.7%	(0.4%, 7.7%)
Combination of 8-Week LDV/SOF and 8-Week LDV/SOF+RBV vs. 12- Week LDV/SOF	3.3%	(0.2%, 6.0%)

[1]based on inverting a two-sided test
Source: Dr. Karen Qi, Statistical Reviewer

Additional subgroup analyses for relapse were performed in ION-3 to identify any HCV GT 1 non-cirrhotic subset that may benefit from a longer treatment duration (i.e., 12 weeks), or conversely receive LDV/SOF 8 week treatment duration while minimizing the consequence of relapse. Subject demographic and baseline HCV disease characteristic subgroups include age, body weight, gender, race, BMI, HCV GT 1 subtype, IL28B genotype and baseline HCV viral load.

Exploratory analyses of baseline predictors of relapse identify baseline viral load as an important predictor, with an HCV RNA 6 million IU/mL cutoff value having the largest proportion difference between the 8 and 12 week durations in subjects with low and high baseline viral load (Table 32). Baseline HCV RNA ≥6 million IU/mL is associated with a relapse rate of 8.9% (15/169 subjects) in the pooled LDV/SOF±RBV 8 week group versus 1.2% (1/85 subjects) and in the LDV/SOF 12 week group [proportion difference 7.7%, 95% CI (1.9%, 13.3%)]. Baseline HCV RNA <6 million IU/mL is associated with a relapse rate of 1.9% (5/260 subjects) in the pooled LDV/SOF±RBV 8 week group versus 1.5% (2/131 subjects) in the LDV/SOF 12 week group, [proportion difference 0.4% (-3.7%, 3.2%)].

Table 32 Relapse Rates by Baseline Viral Load for 8-Week and 12-Week Regimens in ION-3 (All Treated)

	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
Baseline viral load (IU/mL) < 1 million > 1 million	0% (0/99) 5.9% (20/339)	0% (0/51) 1.8% (3/165)	0% (-7.8%, 3.8%) 4.1% (0.2%, 7.5%)	not significant
< 1.5 million ≥ 1.5 million	0% (0/114) 6.4% (20/315)	0% (0/60) 1.9% (3/156)	0% (-3.3%, 6.7%) 4.4% (0.3%, 8.1%)	not significant
< 2 million ≥ 2 million	1.4% (2/146) 6.4% (18/283)	1.4% (1/72) 1.4% (2/144)	0% (-6.6%, 3.7%) 5.0% (0.9%, 8.8%)	0.34
< 2.5 million ≥ 2.5 million	1.9% (3/160) 6.3% (17/269)	1.2% (1/83) 1.5% (2/133)	0.7% (-4.9%, 4.4%) 4.8% (0.5%, 8.8%)	0.46
< 3 million ≥ 3 million	1.7% (3/179) 6.8% (17/250)	1.1% (1/94) 1.6% (2/122)	0.6% (-4.3%, 4.0%) 5.2% (0.6%, 9.4%)	0.46
< 3.5 million ≥ 3.5 million	1.5% (3/195) 7.3% (17/234)	1.0% (1/98) 1.7% (2/118)	0.5% (-4.2%, 3.6%) 5.6% (0.7%, 10.1%)	0.44
< 4 million ≥ 4 million	1.9% (4/213) 7.4% (16/216)	0.9% (1/107) 1.8% (2/109)	0.9% (-3.6%, 4.2%) 5.6% (0.4%, 10.3%)	0.53
< 5 million ≥ 5 million	2.1% (5/243) 8.1% (15/186)	0.8% (1/123) 2.2% (2/93)	1.2% (-2.7%, 4.1%) 5.9% (-0.1%, 11.4%)	1.0
< 6 million ≥ 6 million	1.9% (5/260) 8.9% (15/169)	1.5% (2/131) 1.2% (1/85)	0.4% (-3.7%, 3.2%) 7.7% (1.9%, 13.3%)	0.20
< 7 million ≥ 7 million	2.8% (8/286) 8.4% (12/143)	1.4% (2/145) 1.4% (1/71)	1.4% (-2.3%, 4.3%) 7.0% (0.2%, 13.2%)	0.55
< 8 million ≥ 8 million	3.6% (11/306) 7.3% (9/123)	1.3% (2/151) 1.5% (1/65)	2.3% (-1.4%, 5.4%) 5.8% (-2.3%, 12.4%)	1.0
< 9 million ≥ 9 million	3.8% (12/318) 7.2% (8/111)	1.3% (2/158) 1.7% (1/58)	2.5% (-1.3%, 5.6%) 5.5% (-2.9%, 12.4%)	1.0
< 10 million ≥ 10 million	3.6% (12/332) 8.3% (8/97)	1.2% (2/166) 2.0% (1/50)	2.4% (-1.2%, 5.3%) 6.2% (-3.1%, 13.9%)	1.0

[1]based on inverting a two-sided test
Source: Dr. Karen Qi, Statistical Reviewer

Additionally, differences in the relapse rate between the two treatment durations were more apparent in male subjects, subjects with HCV GT1a subtype and subjects with age ≥50 years, although the LDV/SOF 12 week duration has numerically lower relapse rates in almost all subgroups and there are no statistically significant interactions between treatment duration and subgroups (Table 33).

Table 33 Selected Subgroup Relapse Rates for LDV/SOF 8 Week and 12 Week Regimens in ION-3 (All Treated)

	8-Week LDV/SOF & 8-Week LDV/SOF+ RBV (N=431)	12-Week LDV/SOF (N=216)	Proportion Difference (Exact 95% CI[1])	P-value for interaction based on Zelen's test
# of responders at end of treatment	429	216		
Age				0.34
< 50 years	1.6% (2/129)	1.6% (1/63)	-0.04% (-7.5%, 4.2%)	
⩾ 50 years	6.0% (18/300)	1.3% (2/153)	4.7% (0.9%, 8.3%)	
Weight				1.0
< 82 kg	3.6% (8/222)	0.9% (1/112)	2.7% (-1.8%, 6.3%)	
⩾ 82 kg	5.8% (12/207)	1.9% (2/104)	3.9% (-1.9%, 8.5%)	
Sex				1.0
Female	1.1% (2/183)	0% (0/88)	1.1% (-3.2%, 4.0%)	
Male	7.3% (18/246)	2.3% (3/128)	5.0% (0.04%, 9.4%)	
Race				1.0
Black	8.6% (7/81)	2.4% (1/42)	6.3% (-5.0%, 15.0%)	
Other	3.7% (13/348)	1.2% (2/174)	2.6% (-0.9%, 5.5%)	
BMI				1.0
< 30 kg/m^2	5.0% (15/301)	1.9% (3/159)	3.1% (-1.0%, 6.6%)	
⩾ 30 kg/m^2	3.9% (5/128)	0% (0/57)	3.9% (-2.7%, 8.9%)	
Genotype				0.45
GT 1a	4.9% (17/341)	1.2% (2/172)	3.8% (0.5%, 6.9%)	
GT 1b	3.4% (3/88)	2.3% (1/44)	1.1% (-9.3%, 7.8%)	
IL28B				1.0
CC	1.7% (2/115)	0% (0/56)	1.7% (-4.9%, 6.2%)	
Non-CC	5.7% (18/314)	1.9% (3/160)	3.9% (-0.5%, 7.5%)	

[1]based on inverting a two-sided test
Source: Dr. Karen Qi, Statistical Reviewer

Reviewer Comment: These exploratory relapse rate analyses are supportive of a LDV/SOF 12 week duration for treatment of HCV GT 1 treatment-naïve, non-cirrhotic patients to minimize relapse rates. Optimizing treatment success with the first LDV/SOF regimen and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options are factors contributing to this treatment recommendation, in additional to the acceptable LDV/SOF safety profile as discussed in Section 7. A LDV/SOF 8 week duration in patients with viral load below a cutoff value (e.g., baseline HCV RNA < 6 million IU/mL) is a consideration based on the above analyses. (b) (4) *LDV/SOF 8 week versus 12 week comparison is displayed. The relapse rate in subjects with baseline HCV RNA < 6 million IU/mL is 2% for both the LDV/SOF 8 and 12 week arms; whereas the relapse rate in subjects with HCV RNA ≥ 6 million IU/mL is 10% for the 8 week arm and 1% for the 12 week arm.*

Relapse rates for subjects with baseline NS5A resistance polymorphisms are higher in the 8 week arms, 6.3% (3/48 subjects) for the LDV/SOF 8 week arm and 8.2% (4/49 subjects) for the LDV/SOF+RBV 8 week arm, compared with 0% (0/56 subjects) for the LDV/SOF 12 week arm. Additional analyses performed by Dr. Karen Qi did not identify significant interactions between LDV/SOF treatment duration, early viral response and relapse.

ION-2

ION-2 relapse rates by post-treatment Week 4 and Week 12 are shown in Table 34. No relapse occurs in the LDV/SOF±RBV 24 week groups compared with 6.5% and 3.6% in the LDV/SOF 12 week and LDV/SOF+RBV 12 week groups, respectively. All but one relapse occurs by post-treatment Week 4.

Table 34 Relapse Rates in ION-2 (All Treated)

	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)**
Number of virologic responders at end of treatment	108	111	109	110
Relapse				
By 4 weeks post-treatment	5.6% (6/108)	3.6% (4/111)	0% (0/109)	0% (0/110)
By 12 weeks post-treatment	6.5% (7/108)	3.6% (4/111)	0% (0/109)	0% (0/110)

Source: Dr. Karen Qi, Statistical Reviewer

Additional analyses were performed to characterize the observed differences in relapse rates between the 12 and 24 week durations. The LDV/SOF±RBV 24 week duration significantly reduces overall relapse rates compared with the LDV/SOF±RBV 12 week duration. The proportion difference in relapse rates between the LDV/SOF 12 and 24 week durations is 6.5% (95% CI 2.7%, 13.0%) and between the LDV/SOF+RBV 12 and 24 week durations is 3.6% (95% CI 0.1%, 9.0%).

Overall, relapse rates are numerically lower in the LDV/SOF+RBV 12 week arm compared to the LDV/SOF 12 week arm; however, no relapse occurs in the 24 week groups, regardless of RBV use. Table 35 presents SVR12 and relapse rates based upon cirrhosis status. In non-cirrhotic subjects relapse in the LDV/SOF 12 week arm is 4.7% (4/86 subjects) versus 0% in the LDV/SOF+RBV 12 week arm. In cirrhotic subjects, RBV does not appear to decrease relapse rates as the relapse rate is lower in the LDV/SOF 12 week arm (13.6%, 3/22 subjects) versus the LDV/SOF+RBV 12 arm (18.2%, 18/22 subjects). Thus, RBV appears to have a minimal impact on overall relapse rates which is not statistically significant.

Table 35 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

Treatment-Experienced, Cirrhotic Population

In cirrhotic subjects, as noted above, relapse rates range 13.6-18.2% in the LDV/SOF±RBV 12 week arms, with no relapse occurring in the LDV/SOF±RBV 24 week arms. Further analyses pooled the LDV/SOF±RBV 12 week and LDV/SOF±RBV 24 week arms based upon similar relapse patterns in the two 12-week and two 24-week treatment arms and to provide larger sample sizes for subgroup analyses (Table 36). Presence of cirrhosis is identified as an important baseline factor predictive of treatment response. 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: the two 95% confidence intervals do not overlap. No apparent interaction between treatment duration and any additional subgroup is identified, including age, sex, race, HCV GT subtype, IL28B genotype, prior HCV therapy and prior response to HCV therapy.

Table 36 Results for Selected Subgroup Relapse Rates for 12-Week and 24-Week Regimens in ION-2 (All Treated)

	12-Week LDV/SOF & LDV/SOF+RBV (N=220)	24-Week LDV/SOF & LDV/SOF+RBV (N=220)	Proportion Difference (Exact 95% CI[1])
# of responders at end of treatment	219	219	
Age			
< 50 years	0% (0/31)	0% (0/41)	0% (-8.9%, 13.0%)
≥ 50 years	5.9% (11/188)	0% (0/178)	5.9% (3.2%, 10.4%)
Sex			
Female	2.7% (2/74)	0% (0/78)	2.7% (-2.1%, 10.2%)
Male	6.2 (9/145)	0% (0/141)	6.2% (3.1%, 11.7%)
Race			
Black	2.6% (1/39)	0% (0/37)	2.6% (-7.3%, 14.1%)
Other	5.6% (10/180)	0% (0/182)	5.6% (2.9%, 10.0%)
Sub-genotype			
GT1a	4.6% (8/173)	0% (0/172)	4.6% (2.2%, 9.0%)
GT1b	6.5% (3/46)	0% (0/47)	6.5% (-1.5%, 18.6%)
Cirrhosis			
No	2.3% (4/174)	0% (0/174)	2.3% (0.1%, 6.0%)
Yes	15.9% (7/44)	0% (0/44)	15.9% (6.5%, 29.8%)
IL28B			
CC	0% (0/21)	0% (0/33)	0% (-10.4%, 16.7%)
Non-CC	5.6% (11/198)	0% (0/186)	5.6% (3.0%, 9.9%)
Baseline HCV viral load			
< 800K copies/mL	5.3% (1/19)	0% (0/31)	0% (-6.1%, 26.4%)
≥ 800K copies/mL	5.0% (10/200)	0% (0/188)	5.0% (2..6%, 9.0%)
Previous HCV trt history			
PEG/RBV	5.6% (5/90)	0% (0/116)	5.6% (1.9%, 12.8%)
PI + PEG/RBV	4.7% (6/129)	0% (0/101)	4.7% (0.8%, 10.1%)
Response to Prior HCV trt			
Relapse/breakthrough	4.0% (5/124)	0% (0/119)	4.0% (0.8%, 9.3%)
Non-responder	6.3% (6/95)	0% (0/98)	6.3% ((2.2%, 13.7%)

Source: Dr. Karen Qi, Statistical Reviewer

Please refer to Dr. Karen Qi's review for additional details, including assessment of treatment duration, early viral response and relapse which is also influenced by cirrhosis status. In addition, please refer to Dr. Lisa Naeger's review for details regarding NS5A substitutions.

Reviewer Comment: These exploratory relapse rate analyses support a LDV/SOF 24 week duration for treatment of HCV GT 1 treatment-experienced, cirrhotic patients to minimize relapse rates. The consequences of HCV treatment failure in patients with cirrhosis include risk of progressing to hepatic decompensation and development of hepatocellular carcinoma; therefore, optimizing treatment success with the LDV/SOF regimen and minimizing development of NS5A and/or NS5B substitutions, especially for patients with previous PI-failure, are of particular importance. As discussed in Section

7.4, no safety concerns are identified precluding use of the LDV/SOF 24 week duration in the cirrhotic population.

Treatment-Experienced, Non-Cirrhotic Population

In non-cirrhotic subjects, relapse occurs only in the LDV/SOF 12 week arm (4.7%, 4/86 subjects). These four subjects experiencing relapse all have baseline NS5A resistance associated polymorphisms, resulting in a relapse rate of 21.1% (4/19) among those with baseline NS5A resistance associated polymorphisms (Table 37).

Age ≥50 years and IL28B non-C/C genotype are additional baseline factors present in all subjects with relapse; however, the IL28B non-C/C genotype is present in the majority (86.9%, 304/350 subjects) of this ION-2 treatment-experienced, non-cirrhotic population, reflecting prior treatment failure with an interferon-based regimen.

Table 37 Relapse by Baseline NS5A Resistance Associated Polymorphisms, IL28B, Age, Non-Cirrhotic Population, ION-2 (Limited to LDV/SOF±RBV 12 Week and LDV/SOF 24 Week arms)

	LDV/SOF 12 week	LDV/SOF+RBV 12 week	LDV/SOF 24 week
Number of responders at end of treatment	86	88	86
Relapse Rate By			
(+)BL NS5A Resistance Associated Polymorphisms	21.1% (4/19)	0% (0/18)	0% (0/16)
(-)BL NS5A Resistance Associated Polymorphisms	0% (0/68)	0% (0/70)	0% (0/70)
IL28B			
C/C	0% (0/9)	0% (0/8)	0% (0/13)
Non C/C	5.2% (4/77)	0% (0/80)	0% (0/73)
Age			
<50	0% (0/13)	0% (0/12)	0% (0/14)
≥50	5.5% (4/73)	0% (0/76)	0% (0/72)

NS5A Resistance Associated Polymorphisms include any change at NS5A positions 24, 28, 30, 31, 58, 92 or 93
Source: ION-1, ION-2, ION-3 ADEFFOUT datasets; Dr. Karen Qi, Statistical Reviewer; Dr. Lisa Naeger, Virology Reviewer

Early viral response analyses do not predict relapse in the non-cirrhotic ION-2 population. Please refer to Dr. Karen Qi's review for details.

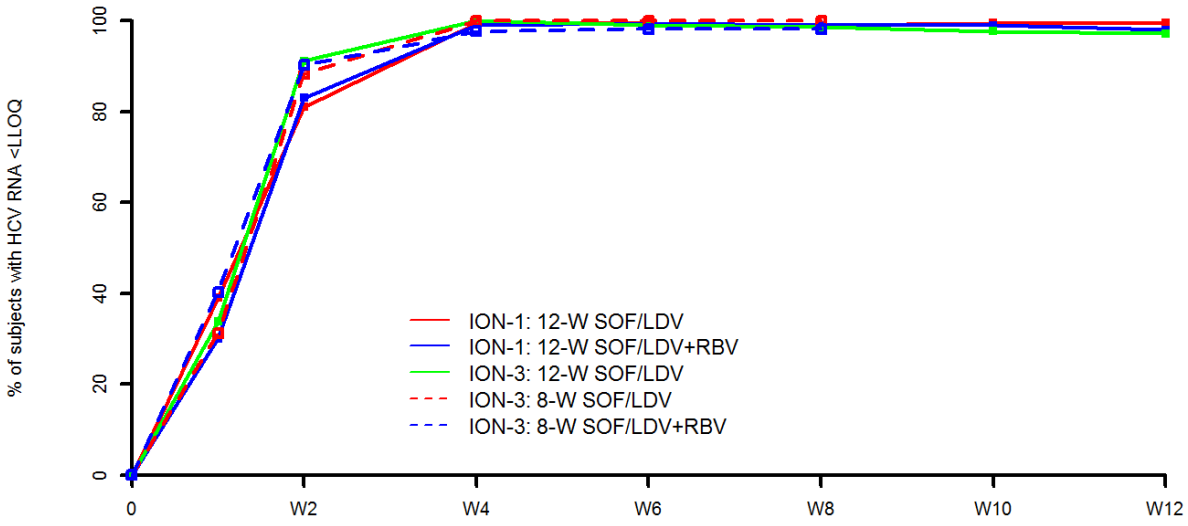
Reviewer Comment: In the HCV GT 1 treatment-experienced, non-cirrhotic subject subset with baseline NS5A resistance associated polymorphisms, no relapse occurs in the LDV/SOF 24 week and LDV/SOF+RBV 12 week arms compared with 21% relapse rate in the LDV/SOF 12 week arm, suggesting that extending treatment duration or

adding RBV may optimize response rates in this subset. Age ≥50 years and IL28B non-C/C genotype are additional baseline factors present in all non-cirrhotic subjects with relapse, though not statistically significant. These efficacy data are used in support of LDV/SOF 12 week treatment duration in the HCV GT 1 treatment-experienced, non-cirrhotic population, with consideration for 24 week duration in patients with baseline factors associated with a lower response to HCV treatment. Optimizing treatment success with the LDV/SOF regimen, especially for patients with previous PI-failure and minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options, are factors contributing to this treatment recommendation. As discussed in Section 7.4, no safety concerns are identified precluding use of the LDV/SOF 24 week duration in the non-cirrhotic population.

On-Treatment Viral Response

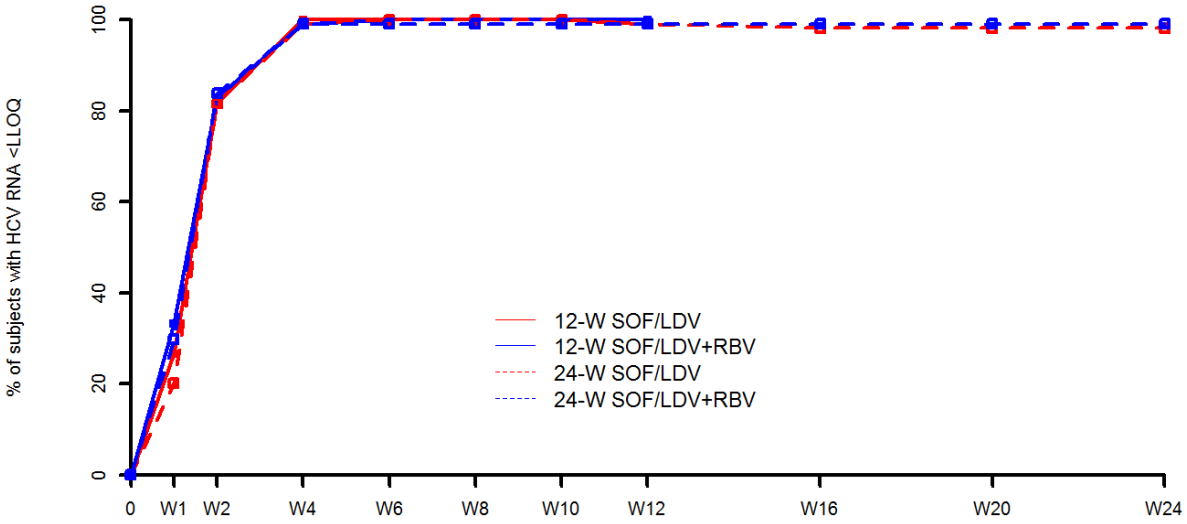
Figures 2 and 3 display on-treatment virologic response in the pivotal phase 3 trials. Most subjects achieve HCV RNA <LLOQ within four weeks and maintain virologic suppression while on-treatment, regardless of treatment duration.

Figure 2 On-Treatment Virologic Response by Treatment Groups in ION-1 and ION-3 (All Treated, NC=F)



Source: Dr. Karen Qi, Statistical Reviewer

Figure 3 On-Treatment Virologic Response by Treatment Groups in ION-2 (All Treated, NC=F)



Source: Dr. Karen Qi, Statistical Reviewer

6.1.6 Other Endpoints

Several other statistical analyses were done by the FDA Reviewers. Please refer to FDA Clinical Pharmacology, Clinical Microbiology and Statistical Reviews for additional details.

6.1.7 Subpopulations

Response and Relapse Rates in Subjects with Cirrhosis

The ION-1 and ION-2 trials both enrolled a proportion of subjects with baseline cirrhosis, 16% and 20%, respectively. Only the ION-1 cirrhotic subpopulation is discussed in this section. Please see Section 6.1.5 for discussion of the ION-2 cirrhotic subpopulation.

ION-1 SVR12 and relapse rates in the cirrhotic subpopulation are shown in Table 38.

Table 38 Response and Relapse Rates in Subjects with Cirrhosis, ION-1

	LDV/SOF 12 Week	LDV/SOF+RBV 12 Week
Total Subjects with Cirrhosis	34	33
Cirrhosis - Yes		
SVR12	94% (32/34)	100% (33/33)
Relapse	2.9% (1/34)	0% (0/33)

Source: ION-1 ADEFFOUT datasets

ION-1

In ION-1 among treatment-naïve subjects with cirrhosis, SVR12 is 94% (32/34 subjects) in LDV/SOF 12 week group and 100% (33/33 subjects) in the LDV/SOF+RBV 12 week group. Relapse occurs in a single subject in the LDV/SOF 12 week group (2.9%, 1/34 subjects) as described in Section 6.1.5.

Reviewer Comment: In ION-1, high SVR12 rates ranging 94-100% are achieved among subjects with cirrhosis treated with LDV/SOF±RBV for 12 weeks. A single subject with multiple negative baseline predictive factors relapsed in the LDV/SOF 12 week group (2.9%, 1/34 subjects). In the ION-1 LDV/SOF±RBV 12 week arms, approximately 3% (14/431 subjects) of enrolled subjects have baseline cirrhosis, IL28B non-C/C genotype and HCV RNA ≥6 million IU/mL. Although the Division has not received ION-1 LDV/SOF±RBV 24 week data for review, the Applicant notes in a response received June 19, 2014 that a single subject receiving LDV/SOF 24 weeks also relapsed, and this subject had cirrhosis, IL28B T/T genotype, a baseline NS5A resistance associated polymorphism and baseline HCV RNA 3.6 million IU/mL. There is a possible concern that wider use of LDV/SOF for 12 weeks in the HCV GT 1 treatment-naïve population with cirrhosis and other baseline factors traditionally associated with a lower response to HCV treatment may result in lower response rates than observed in the phase 3 trials, and that a longer duration and/or the addition of RBV may optimize response rates by decreasing relapse. The consequences of HCV treatment failure in patients with cirrhosis include risk of progression to decompensation and hepatocellular carcinoma. However, the ION-1 data clearly demonstrate high SVR12 rates and low relapse rates in this cirrhotic subgroup, supporting a recommendation for LDV/SOF 12 week treatment duration in this population.

ION-2

In ION-2 among treatment-experienced subjects with cirrhosis, SVR12 is 82-86% in the LDV/SOF±RBV 12 week groups and 100% in the LDV/SOF±RBV 24 week groups. Relapse rates are the reason for all treatment-failure in the cirrhotic population.

Response Rates based on HCV GT1a versus GT1b

Table 39 shows SVR12 rates in the LDV/SOF phase 3 HCV GT1a and GT1b subpopulations. In ION-1 within each treatment group, SVR12 is similar between subjects with HCV GT1a (97%) versus HCV GT1b (99-100%).

In ION-3 within each treatment group, SVR12 is numerically higher in subjects with HCV GT1b versus HCV GT1a.

In ION-2, SVR12 is numerically lower in the HCV GT1b subjects (87%) in the LDV/SOF 12 week group versus HCV GT1a subjects (95%), a difference not observed in the other ION-2 treatment groups.

Table 39 SVR12 Based on HCV Genotype 1 Subtype (ION-1, ION-2, ION-3)

	LDV/SOF 8 Week	LDV/SOF +RBV 8 Week	LDV/SOF 12 Week	LDV/SOF +RBV 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 24 Week
ION-1, N	-	-	214	217	-	-
HCV GT1a	-	-	98% (142/145)	97% (143/148)	-	-
HCV GT1b	-	-	100% (67/67)	99% (67/68)	-	-
ION-3, N	215	216	216			
HCV GT1a	93% (159/171)	92% (159/172)	96% (165/172)	-	-	-
HCV GT1b	98% (42/43)	95% (42/44)	98% (43/44)	-	-	-
ION-2, N			109	111	109	111
HCV GT1a	-	-	95% (82/86)	95% (84/88)	99% (84/85)	99% (87/88)
HCV GT1b	-	-	87% (20/23)	100% (23/23)	100% (24/24)	100% (23/23)

Source: ION-1, ION-2, ION-3 ADEFFOUT datasets

Reviewer Comment: The HCV GT1b population was observed to have lower responses rates compared to the HCV GT1a population in the NEUTRINO and PHOTON-1 trials supporting the SOF approval, as described in the SOF NDA 204671 reviews and reflected in the currently approved SOF label. A similar observation is not observed in the collective LDV/SOF pivotal phase 3 SVR12 data. The only treatment group with lower SVR12 rates in HCV GT1b subjects compared with HCV GT1a subjects is the ION-2 LDV/SOF 12 week group. It should also be noted that two of the three HCV GT1b subjects who relapsed within this group also had cirrhosis, all had baseline HCV RNA >4 million IU/mL and all had IL28B non-C/C genotype.

Response Rates Based on Prior HCV Treatment

ION-2 enrolled subjects who failed prior PEG/RBV-based treatment, including 53% who failed prior PI+PEG/RBV treatment. Similar SVR12 rates are observed within each treatment arm, regardless of prior HCV treatment history as displayed in Table 40.

Table 40 Response Rates in Subjects Based on Prior HCV Treatment History (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
Prior HCV Treatment History*				
PI+PEG/RBV	94% (62/66)	97% (62/64)	98% (49/50)	100% (51/51)
PEG/RBV	93% (40/43)	96% (45/47)	100% (58/58)	98% (58/59)

*Two subjects categorized as "other" and not included in the denominators. Neither subject relapsed.
Source: ION-2 ADEFFOUT dataset

Reviewer Comment: LDV/SOF provides an HCV treatment option achieving high SVR12 rates for patients who have failed a prior PI-containing regimen, a population currently in need of effective therapy.

Additional subgroup analyses evaluating response rates based upon age, gender, race, geographic region, BMI, baseline ALT, IL28B genotype, response to prior HCV treatment and presence of baseline NS5A resistance associated polymorphisms were evaluated by the Statistical and Virology reviewers. Please refer to the Statistical and Clinical Microbiology Reviews for detailed assessment of subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Collaborative statistical, virology and clinical analyses performed to support LDV/SOF dosing recommendations for the various HCV GT 1 patient populations are integrated into Section 6.1.5. This decision is made to allow comprehensive analyses relevant to dosing recommendations to be presented in a more uniform manner in Section 6.1.5.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

SVR12 and SVR24 Concordance

Evaluation of SVR at 24 weeks (SVR24) post-treatment cessation has been the historically accepted time point to assess virologic response. As discussed in Section 6.1.4, FDA analysis of over 13,000 subjects pooled from multiple clinical trials of PEG-based regimens found a high rate of concordance between SVR12 and SVR24.

In the LDV/SOF pivotal phase 3 trials, SVR24 is a secondary endpoint to further evaluate the persistence of treatment effects and concordance between SVR12 and SVR24 in non-IFN based regimens. Available data from ION-1 (Part A) and ION-2 were evaluated by Dr. Qi. SVR24 data was unavailable from ION-3, so no concordance assessments could be performed for that trial. Overall, there is 100% concordance between SVR12 and SVR24 based on the available data. These data further support the use of SVR12 as the primary endpoint in interferon-free trials.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

The observed safety profile of LDV/SOF-containing treatment is favorable. No safety event warrants Warnings and Precautions labeling consideration at this time. No on-treatment deaths occur in the phase 3 program. The overall percentage of SAEs (2.6%) and discontinuations due to AEs (0.7%) is low. A LDV/SOF regimen has an improved safety profile compared with a LDV/SOF+RBV regimen with a lower incidence of treatment-emergent AEs, Grade 3 or higher AEs, and AEs leading to dose modification or interruption. No safety signal is identified precluding administration of LDV/SOF treatment duration up to 24 weeks. LDV/SOF treatment durations of 8 and 12 weeks have similar safety profiles in treatment-naïve, non-cirrhotic subjects. LDV/SOF treatment durations of 12 and 24 weeks have similar safety profiles overall and in cirrhotic subjects.

The safety review includes detailed safety information of particular events based upon preclinical signals, labeled SOF events, potentially related SAEs or apparent clustering of events.

Due to a potential class effect related to an investigational agent halted for cardiac toxicity, a detailed safety evaluation focusing on cardiac disorders was conducted. No potential safety concerns are identified in regards to cardiac toxicity associated with LDV/SOF use based on review of available clinical data at this time.

The SOF label contains safety information pertaining to creatine kinase elevations, lipase elevations and depression and suicidal events. No safety concern of rhabdomyolysis or myopathy is identified associated with LDV/SOF use based on available safety data: creatine kinase laboratory data was not routinely collected in the phase 3 trials. Treatment-emergent lipase elevations in the phase 3 LDV/SOF trials are observed with similar incidence to lipase elevations reported in the current SOF label; however, no obvious association with clinical signs or symptoms of pancreatitis is identified. Overall depression and suicidal events are low, generally occurring in subjects with an associated psychiatric history.

Due to a potential LDV preclinical signal for ocular toxicity, a review of ocular events was performed. No safety concern of clinical ocular toxicity associated with LDV/SOF use is identified.

SOF has a preclinical signal for gastrointestinal toxicity. No obvious safety concern of serious gastrointestinal toxicity associated with LDV/SOF use is identified. Nausea and diarrhea are recommended labeled events.

Because LDV/SOF use occurs in a population with underlying liver disease, a detailed hepatic review was performed. No obvious safety concern of hepatotoxicity is identified. Bilirubin laboratory elevations occur 4-7% across the LDV/SOF alone treatment arms, primarily ≤Grade 2. LDV is primarily eliminated by biliary excretion and therefore a potential causal relationship exists with bilirubin elevations supporting a recommendation to include bilirubin information in the product label. A separate analysis of gallbladder events does not identify an obvious causal association between LDV/SOF use and cholelithiasis and/or cholecystitis.

Focused analyses of the development of Factor VIII inhibition, myocardial ischemia, chest pain, rash events, hypersensitivity, anaphylaxis, angioedema, fall and fracture events, palpitations, renal events were performed based on potentially related SAEs or clustering of events. From these analyses, no safety concerns associated with LDV/SOF are identified at this time.

Overall ≥Grade 2 thrombocytopenia occurs in 2.3% of subjects in the phase 3 trials, predominantly in subjects with cirrhosis and did not lead to study treatment discontinuation. The majority of subjects with ≥Grade 2 thrombocytopenia have abnormal baseline values experiencing a single grade increase on treatment. Most subjects experienced either an isolated decrease or fluctuations within a generally stable on-treatment platelet range.

No unique safety concerns are identified based on analyses of sex, race and age. Asthenia is reported more frequently in European subjects compared with US subjects based on safety analyses of region.

In summary, LDV/SOF provides an all-oral treatment option for patients with chronic HCV GT 1 infection. A LDV/SOF regimen offers an improved safety profile compared to known toxicities associated with both interferon-based and RBV-based regimens, and provides a therapeutic option for patients who cannot take interferon and/or RBV, addressing an unmet need in this population.

Based on the review of the submitted data, no major safety issues associated with LDV/SOF use have been identified to date. The noted safety profile of LDV/SOF is acceptable.

7.1 Methods

Safety data for this NDA are submitted by the Applicant as clinical overview, summary of clinical safety, final clinical study reports, and electronic datasets. The Integrated Summary of Safety (ISS) includes information on deaths, SAEs, discontinuations due to AEs and other significant AEs (e.g., liver-related events). Narratives and Case Report Forms (CRFs) are provided for all subjects who died, developed an SAE, became pregnant, or discontinued from the trial because of an AE. Narratives for subjects with evidence of on-treatment liver injury in completed Gilead-sponsored phase 2 and 3 trials where subjects were treated with both SOF and LDV or LDV/SOF are also provided.

Summary results of integrated pivotal phase 3 safety analyses are presented, with pertinent phase 2 and Safety Update Report (SUR) data included where deemed appropriate. The SUR submitted May 5, 2014, includes safety data from 10 ongoing LDV/SOF-containing trials or trial arms that were not included with the original NDA. Please refer to Section 7.7 for additional details.

Minor differences between the Applicant's results and FDA's results can be attributed to differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms are used in the analyses of AE tables in this review.

A subject may report more than one AE; therefore, the total number of AEs reported may be greater than the number of subjects in the trial. Each AE is listed only once in summary tables, regardless of the number of times it occurred for each subject. An exception to this approach occurs for duration analyses where each AE is listed once per each week window (e.g., ≤Week 8 versus >Week 8 window). Based upon protocol defined study visit windows, Week 8 study window extends to Day 63 and Week 12 study window extends to Day 98.

For cirrhosis subgroup analyses, subjects with missing cirrhosis categorization data are excluded.

7.1.1 Clinical Trials Used to Evaluate Safety

The LDV/SOF safety data derived from the three pivotal phase 3 trials (ION-1, ION-2, ION-3) constitute the main safety population used in FDA analyses of key safety signals using these integrated datasets. Data from phase 1 trials, phase 2 trials and other ongoing trials constitute supporting safety data with pertinent aspects discussed in relevant sections of this review.

Entry criteria for the pivotal phase 3 trials include:

- Screening ECG without clinically significant abnormalities
- Subjects must have the following laboratory parameters at screening:

  - ALT and AST ≤ 10 × the upper limit of normal (ULN)
  - Direct bilirubin ≤ 1.5 × ULN (Note: ≤ ULN in ION-3)
  - Platelets ≥ 50,000/mm^3 (Note: >90,000/mm^3 in ION-3)
  - HbA1c ≤ 8.5%
  - Creatinine clearance (CLcr) ≥ 60 mL /min
  - Hemoglobin ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects.
  - Albumin ≥ 3g/dL
  - INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.
- Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator.
- Subjects are not to be enrolled if:
  - Current or prior history of any of the following:
    - Clinically-significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol
    - Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug
    - Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal hemorrhage)
    - Solid organ transplantation
    - Significant pulmonary disease, significant cardiac disease or porphyria
    - Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Subjects with psychiatric illness that is well-controlled on a stable treatment regimen for at least 12 months prior to randomization or has not required medication in the last 12 months may be included
    - Malignancy diagnosed or treated within 5 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to screening); subjects under evaluation for malignancy are not eligible.
  - Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis).
  - Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).
  - Clinically-relevant drug abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator.
  - Alcohol misuse as defined by a Alcohol Use Disorders Identification Test (AUDIT) score ≥ 8

- Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day).

Reviewer Comment: The safety analyses and conclusions in this review are primarily based upon the enrolled pivotal phase 3 trial population. The trial entry criteria may mitigate potential safety concerns that may be observed with wider LDV/SOF usage in the HCV GT 1 population.

7.1.2 Categorization of Adverse Events

AEs are coded by Medical Dictionary for Regulatory Activities (MedDRA) 16.0. The NDA includes the AE dictionary files that consist of all investigator verbatim and the preferred/dictionary-derived terms to which they were mapped as SAS transport files for the three pivotal phase 3 trials and phase 2 trials LONESTAR and ELECTRON (parts 4-6). In addition, information describing the current AE coding process at Gilead is included in this application. The Applicant's categorization of closely related events and coding of AE verbatim terms to preferred terms is considered appropriate.

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. A treatment-emergent AE met one of the following criteria: (1) AEs with onset dates on or after the start of treatment and up to 30 days after the discontinuation of all the study drugs, (2) continuing AEs diagnosed prior to the start of treatment and worsening in severity grade, nonserious AEs at baseline which became serious, or AEs resulting in treatment discontinuation after the start of treatment. All AEs discussed throughout this review are treatment-emergent unless indicated otherwise and are referred to as AEs for the purposes of this review. AEs related to study drug are defined using clinical judgment and considerations of: (1) a temporal relationship between the AE onset and administration of investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies, (2) the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational medicinal product, (3) in case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge. It should be noted that the pivotal trials were open-label and therefore subject to bias. Events for which the investigator did not record relationship to study drug are considered related to study drug by the Applicant for summary purposes.

A serious adverse event (SAE) is any adverse drug experience that results in any one of the following outcomes: death, life-threatening situation, in-patient hospitalization or prolonged existing hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect in the offspring of a subject who received study drug, other important medically significant events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the above outcomes.

The severity of grading of AEs and laboratory abnormalities is assigned by the investigator and is assessed as Grade 1, 2, 3 or 4 using the Gilead Sciences, Inc. (GSI) Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. Grade 1, 2, 3, and 4 AEs are considered mild, moderate, severe, and life-threatening, respectively.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from the LDV/SOF-containing treatment groups are pooled across trials ION-1, ION-2 and ION-3, where applicable, due to similar treatment regimens and durations. In general, the main inclusion and exclusion criteria across these trials were similar. It is noted that differences exist in prior HCV treatment (ION-1 and ION-3 are treatment-naïve trials, ION-2 is a prior HCV treatment-experienced trial), cirrhosis status (ION-1 and ION-2 allowed subjects with compensated cirrhosis to enroll, ION-3 was conducted in non-cirrhotic subjects with entry criteria of higher platelet count and lower direct bilirubin compared with the two other trials), and region (ION-2 and ION-3 were conducted in the United States, ION-1 was multinational).

The safety evaluation in this review compares the following treatment groups for the integrated safety population:

LDV/SOF x 8 weeks: subjects receiving LDV/SOF for 8 weeks in ION-3.
LDV/SOF x 12 weeks: subjects receiving LDV/SOF for 12 weeks in ION-1, ION-2 and ION-3.
LDV/SOF x 24 weeks: subjects receiving LDV/SOF for 24 weeks in ION-1, ION-2.
LDV/SOF+RBV x 8 weeks: subjects receiving LDV/SOF+RBV for 8 weeks in ION-3.
LDV/SOF+RBV x 12 weeks: subjects receiving LDV/SOF+RBV for 12 weeks in ION-1, ION-2.
LDV/SOF+RBV x 24 weeks: subjects receiving LDV/SOF for 24 weeks in ION-1, ION-2.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant presents LDV/SOF safety data from a total of 11 clinical trials consisting of three pivotal phase 3 trials, three phase 2 trials and five phase 1 trials. Supportive data for the individual LDV and SOF components are also provided.

A total of 2462 subjects received at least LDV/SOF or LDV 90 mg+SOF 400 mg dose in the LDV/SOF clinical program, including 1952 subjects in the pivotal phase 3 trials, 253 subjects in the phase 2 trials LONESTAR, ELECTRON (parts 4 and 6), and

ELECTRON-2 (Cohort 2, Groups 3 and 4), and 257 subjects in the phase 1 trials. The number of subjects enrolled into phase 2 or 3 LDV+SOF or LDV/SOF±RBV trial arms by duration include approximately: 2180 subjects LDV/SOF±RBV x ≥ 8 week; 1708 subjects LDV/SOF±RBV x ≥ 12 week; 654 subjects LDV/SOF±RBV x 24 week, of whom 630 completed study treatment.

In the three pivotal phase 3 trials 1958 subjects were randomized and 1952 received at least one LDV/SOF dose, comprising the integrated primary safety population. Table 41 presents the subject disposition of the integrated LDV/SOF phase 3 safety population. Please refer to Section 6.1.2 for trial participant demographic and baseline characteristic information.

LDV/SOF Groups, Phase 3 Trials

A total of 215 subjects received LDV/SOF treatment for 8 weeks (ION-3), with a mean (standard deviation [SD]) duration of exposure of 8.1 (0.15) weeks. All subjects completed LDV/SOF 8 week treatment.

A total of 539 subjects received LDV/SOF treatment for 12 weeks (ION-1, ION-2, ION-3), with a mean (SD) duration of exposure of 12.1 (0.79) weeks. Most subjects (99%, 532 subjects) completed LDV/SOF 12 week treatment. Seven subjects (1.3%) discontinued treatment: three were lost to follow-up, two discontinued due to AE, one was non-compliant with study drug, and one had a protocol violation.

A total of 326 subjects received LDV/SOF treatment for 24 weeks (ION-1, ION-2), with a mean (SD) duration of exposure of 23.7 (2.31) weeks. Most subjects (97%, 315 subjects) completed LDV/SOF 24 week treatment. Eleven subjects (3.4%) discontinued treatment: four subjects discontinued due to AE, three withdrew consent, two had a protocol violation, one had lack of efficacy and one became pregnant.

LDV/SOF+RBV Groups, Phase 3 Trials

A total of 216 subjects received LDV/SOF+RBV treatment for 8 weeks (ION-3), with a mean (SD) duration of exposure of 8.0 (0.88) weeks. Most subjects (99%, 213 subjects) completed LDV/SOF+RBV 8 week treatment. Three subjects (1.4%) discontinued treatment: two subjects were lost to follow-up, one discontinued due to AE.

A total of 328 subjects received LDV/SOF+RBV treatment for 12 weeks (ION-1, ION-2), with a mean (SD) duration of exposure of 12.1 (0.57) weeks. Most subjects (99%, 324 subjects) completed LDV/SOF+RBV 12 week treatment. Four subjects discontinued treatment: two subjects were lost to follow-up, one withdrew consent, one had a protocol violation.

A total of 328 subjects received LDV/SOF+RBV treatment for 24 weeks (ION-1, ION-2), with a mean (SD) duration of exposure of 23.8 (1.83) weeks. Most subjects (96%, 315 subjects) completed LDV/SOF+RBV 24 week treatment. Thirteen subjects discontinued treatment: six subjects discontinued due to AE, three withdrew consent, two had a protocol violation, one was lost to follow-up, one had lack of efficacy.

Overall, across all phase 3 LDV/SOF-containing groups, the majority of subjects completed their assigned treatment with a low discontinuation rate (1.9%, 38 subjects). Numerically there is a higher discontinuation rate (3.7%) in the LDV/SOF± RBV 24 week arms compared with the shorter duration arms (1.1%). The difference in overall discontinuation rates between RBV-free and RBV-containing arms is <1%. Overall, the most common reason for discontinuation is due to AE (0.7%, 13 subjects), followed by lost to follow-up (0.4%, 8 subjects) and withdrawal of consent (0.4%, 7 subjects).

Table 41 ION-1, ION-2, ION-3: Subject Disposition for LDV/SOF Phase 3 Integrated Safety Population

Reason Study Drug Not Completed	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Number of Subjects	215 n (%)	539 n (%)	326 n (%)	216 n (%)	328 n (%)	328 n (%)
Study Treatment Discontinuation						
	0	7 (1.3%)	11 (3.4%)	3 (1.4%)	4 (1.2%)	13 (4.0%)
Reason for Study Treatment Discontinuation						
Adverse Event	0	2 (0.4%)	4 (1.2%)	1 (0.5%)	0	6 (1.8%)
Lack of Efficacy	0	0	1 (0.3%)	0	0	1 (0.3%)
Lost to Follow-Up	0	3 (0.6%)	0	2 (0.9%)	2 (0.6%)	1 (0.3%)
Non-Compliance with Study Drug	0	1 (0.2%)	0	0	0	0
Pregnancy	0	0	1 (0.3%)	0	0	0
Protocol Violation	0	1 (0.2%)	2 (0.6%)	0	1 (0.3%)	2 (0.6%)
Withdrew Consent	0	0	3 (0.9%)	0	1 (0.3%)	3 (0.9%)

Source: Integrated Datasets, ADSL (ION-1, ION-2, ION-3)

Reviewer Comment: Overall an adequate safety database of exists for the proposed LDV/SOF dose and duration. In addition, approximately 630 subjects have received LDV/SOF±RBV for 24 weeks.

7.2.2 Explorations for Dose Response

Data from dose-ranging and phase 2 dose-finding safety and efficacy trials, P7977-0221 and P7977-0422, within the SOF single-agent development program supported selection of the currently approved SOF 400 mg dose for the treatment of chronic HCV

infection in combination with RBV or PEG/RBV. Please refer to the SOF NDA 204671 for additional details.

The phase 3 LDV dose of 90 mg once daily (QD) was selected for coformulation with SOF 400 mg based on the results from the proof-of-concept phase 1b trial (GS-US-256-0102) and the data from the phase 2 trial in HCV GT 1 subjects (GS-US-248-0120).

GS-US-256-0102 evaluated LDV doses of 1, 3, 10, 30, and 90 mg QD administered as monotherapy for 3 days to HCV-infected subjects with GT1a or 1b infection. Except at the 1 mg dose, LDV plasma concentrations at the end of the dosing interval exceeded the protein-adjusted mean EC_{90} for GT 1. LDV PK was similar between subjects with HCV GT1a and 1b at the evaluated 10 mg dose. The Emax modeling indicated exposures achieved following administration of LDV ≥ 30 mg provide >95% of maximal antiviral response in HCV GT1a subjects, and doses >90 mg are unlikely to cause further meaningful reductions in HCV RNA. Based on the safety, antiviral activity, and PK of LDV, which supported QD administration, LDV doses of 30 and 90 mg were selected for evaluation in a phase 2 dose-finding trial (GS-US-248-0120).

GS-US-248-0120 studied LDV 30 mg or 90 mg once QD, administered in combination with vedroprevir (VDV, an investigational PI) plus tegobuvir (TGV, an investigational non-nucleoside NS5B inhibitor) plus RBV, in treatment-naïve subjects with chronic HCV GT1a or 1b infection. Treatment with LDV 90 mg plus other DAAs for 12 or 24 weeks resulted in higher SVR24 rates compared to LDV 30 mg plus DAAs (59% vs 48%). Furthermore, the incidence of virologic breakthrough was approximately half in the LDV 90 mg-containing arm (11%) compared to the LDV 30 mg-containing arm (20%), supportive of the LDV 90 mg dose for LDV/SOF clinical development. AEs occurring in ≥10% were similar between the LDV 30 and 90 mg arms as described in Section 5.3.

Please refer to the Clinical Pharmacology Review for complete details.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate nonclinical testing was performed. Please refer to Section 4.3 and Dr. Christopher Ellis' review for details.

7.2.4 Routine Clinical Testing

The routine clinical testing was performed at pre-specified regular intervals during the trial and is considered adequate. In ION-1 and ION-2, study visits were scheduled for Screening, Baseline/Day 1, Weeks 1, 2, 4, 6, 8, 10, 12 for all groups, and additional Weeks 16, 20, 24 for the LDV/SOF±RBV 24 week groups. In ION-3, study visits were scheduled for Screening, Baseline/Day 1, Weeks 1, 2, 4, 6, 8 for all groups, and additional Weeks 10, 12 for the LDV/SOF 12 week group. Post-treatment visits were scheduled at Weeks 4, 12 and 24. Safety assessments included, but were not limited to,

the following: physical examinations, measurement of vital signs, clinical laboratory tests. Additional testing was performed as indicated during the trials.

Reviewer Comment: *The pivotal trial phase 3 safety monitoring visits occurred every two weeks Week 2 through Week 12 (as applicable in ION-3), and every four weeks thereafter in the 24 week duration arms. This robust safety monitoring within the clinical trial setting may mitigate safety concerns that may be observed with wider usage.*

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction workup was adequate. Please refer to Section 4.4 and to the Clinical Pharmacology Review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

SOF is the only approved NS5B nucleotide polymerase inhibitor. There are currently no approved NS5A inhibitors.

(b) (4)

Although sofosbuvir is structurally different (SOF is a 2'-F, 2'-Me uridine monophosphate analogue prodrug (b) (4) at the time of the original SOF NDA review, a detailed safety evaluation focused on cardiac disorders was done to identify any potential safety signal due to class effect.

As included in the current Sovaldi label Section 13.2, preclinical findings of heart degeneration and inflammation were observed in rats following GS-9851 (a stereoisomeric mixture containing approximately 50% sofosbuvir) doses of 2000 mg/kg/day for up to 5 days. At this dose, AUC exposure to the predominant metabolite GS-331007 is approximately 29-fold higher than human exposure at the recommended clinical dose. No heart degeneration or inflammation was observed in rats following sofosbuvir doses of up to 500 mg/kg/day for 6 months at a GS-331007 AUC exposure approximately 9-fold higher than human exposure at the recommended clinical dose. In dogs and mice, heart degeneration and inflammation were not observed following sofosbuvir doses of up to 500 and 1000 mg/kg/day for 9 and 3 months, respectively, the highest doses tested. At these doses, GS-331007 AUC exposures are approximately 27- and 41-fold higher, respectively, than human exposure at the recommended clinical dose.

Based on the review of the submitted NDA 204671 data, no obvious safety issue related to cardiac toxicity was identified at that time. Please refer to the NDA 204671 Clinical

Review for complete details of the analyses. 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 exposures approximately 9-fold the exposure in humans at the recommended clinical dose.

Cardiac Disorder System Organ Class Adverse Events

A detailed safety evaluation of cardiac disorders was again conducted with this LDV/SOF NDA review. Table 42 displays all phase 3 MedDRA preferred term treatment-emergent AEs occurring within the Cardiac Disorder System Organ Class. Approximately 1% (28 subjects) of all enrolled subjects experienced a Cardiac Disorder treatment-emergent AE. A single SAE of Grade 4 unstable angina was reported in the LDV/SOF 24 week group (ION-1), considered not related to study drug by the investigator. Most subjects experienced Grade 1 events (79%, 22/28 subjects), with Grade 2 events occurring in five subjects (bradycardia (2), angina, palpitations (2)) and a single reported Grade 4 event (angina). Section 7.3.5, Myocardial Ischemia contains additional details regarding the angina event.

Palpitations are the most common treatment-emergent AE occurring within this SOC, occurring more in RBV-containing arms (1.5%, 13 subjects) compared with non-RBV-containing arms (0.5%, 5 subjects). Two subjects in ION-1 discontinued due to palpitations:

- Subject #2493-71034 (LDV/SOF+RBV 24 week, ION-1)
  56 year old Caucasian woman experienced Grade 1 palpitations Day 63 and dyspnea Day 69. Events suspected associated with coffee intake or anxiety related. Work up including ECG, echocardiography, Holter monitoring was unremarkable. Consultations with neurology, cardiology, psychiatry, obstetrics and ENT were unrevealing. Study medications stopped Day 92 and events resolved the same day. The events were considered not related to study drugs by the investigator.
- Subject #0446-71357 (LDV/SOF 24, ION-1)
  54 year old Caucasian woman with history of hypertension, tobacco use experienced Grade 2 palpitations Day 95. Work up including ECG, echocardiography, Holter monitoring and stress test was unremarkable. Metoprolol was started for hypertension. Day 112 experienced another episode of palpitations and the following day stopped study medication. The event resolved 23 days after discontinuing treatment and was considered related to study drug by the investigator.

Table 42 Cardiac Disorder System Organ Class Treatment-Emergent Adverse Events, All Cause, All Grade, LDV/SOF Phase 3 Integrated Safety Population

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
#Subjects with AE (%) within Cardiac Disorder SOC	1 (<1%)	2 (<1%)	9 (3%)	4 (2%)	9 (3%)	3 (1%)
Sinus Bradycardia	0	1 (<1%)	0	0	0	0
Angina Pectoris	0	1 (<1%)	0	0	0	0
Angina Unstable	0	0	1 (<1%)	0	0	0
Cardiac Flutter	0	0	1 (<1%)	0	0	0
Heart Valve Incompetence	0	0	1 (<1%)	0	0	0
Palpitations	0	0	5 (2%)	2 (1%)	8 (2%)	3 (1%)
Ventricular Extrasystoles	0	0	1 (<1%)	0	0	0
Bradycardia	1 (<1%)	0	0	0	0	0
Sinus Tachycardia	0	0	0	0	1 (<1%)	0
Tachycardia	0	0	0	1 (<1%)	1 (<1%)	0
Atrial Tachycardia	0	0	0	1 (<1%)	0	0

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

Reviewer Comment: No safety concern is identified based upon review of phase 3 LDV/SOF Cardiac Disorder SOC treatment-emergent AEs. Palpitation events in the RBV-containing arms may be confounded by concomitant RBV administration, which is known to cause hemolytic anemia. Some of the symptoms of anemia are fatigue, dyspnea and tachycardia. The Applicant was queried for their assessment of palpitation and arrhythmia events. The response received May 21, 2014 contains their assessment that "Phase 2 and Phase 3 data analysis suggests LDV/SOF is unlikely to be a causal factor in AEs of palpitations or arrhythmia". Based on the currently available data, I agree with the Applicant's assessment.

Cardiac Failure, Cardiomyopathy Events

No treatment-emergent events of cardiac failure or cardiomyopathy occur in the pivotal phase 3 LDV/SOF trials. The Applicant was queried for all cases of cardiac failure and/or cardiomyopathy occurring in the SOF and LDV/SOF development programs. Their response received May 20, 2014 is summarized in this section.

Sofosbuvir Clinical Development Program
More than 4000 subjects have received SOF treatment in the SOF clinical development program, including 470 subjects receiving SOF as part of the compassionate use program. Three subjects have experienced treatment-emergent cardiomyopathy and one subject experienced treatment-emergent congestive heart failure. All cases occur within the compassionate use program, in patients with advanced liver disease who are

post-liver transplantation (Table 43). Additional narrative information for these subjects follows.

Table 43 Events of Cardiomyopathy or Cardiac Failure in the Sofosbuvir Clinical Development Program

Case #	Trial/ Treatment	Cardiac Event	Investigator Causality Assessment	Action Taken	Additional Information
2013-0071663	IN-334-0141/ SOF+RBV	Congestive Heart Failure	Not related	None	Transient episode 2º volume overload, anemia; resolved with ongoing SOF+RBV therapy
55 year old man with history including hepatocellular carcinoma (HCC) resulting in liver transplant (b) (6). Due to clinical deterioration including decompensated cirrhosis with refractory ascites, started SOF+RBV 04 February 2013. In (b) (6), the subject was noted to have congestive heart failure in the setting of volume overload and anemia. Medical management directed at diuresis and correcting anemia, including decreasing RBV, led to symptom resolution. Continued SOF+RBV until received a second liver transplant (b) (6). The transient episode of congestive heart failure was assessed as unrelated to SOF by the investigator and due to volume overload.					
2013-0074548	IN-334-0141/ SOF+RBV	Cardiomyopathy	Not related	None	Multi-organ failure in the setting of progressive end stage liver disease; subject died after second liver transplant
46 year old man with history including chronic HBV, HCV requiring liver transplant (b) (6), complicated by severe fibrosing cholestatic hepatitis, hepatic decompensation. Started SOF+RBV through compassionate use program 20 November 2012. Despite virologic suppression, was hospitalized (b) (6) due to worsening hepatic and renal function. Diagnosed with cirrhotic cardiomyopathy and underwent liver retransplantation (b) (6), complicated by portal vein thrombosis and severe hypotension. Post-transplantation developed atrioventricular block requiring a pacemaker. Echocardiogram revealed moderately dilated left and right ventricles, severe atrial dilatation and mitral and tricuspid insufficiency with ejection fraction (EF) 30%. Cardiac function deterioration believed related to severe strain of the intraoperative and postoperative complications in the setting of cirrhotic cardiomyopathy. The subject's condition continued to decline with multi-organ failure and died (b) (6). Autopsy results revealed dilated cardiomyopathy without coronary artery disease. The investigator, in consultation with his local cardiologist, assessed cardiomyopathy as unrelated to SOF and due to worsening underlying liver disease and progressive multi-organ failure.					
2013-0088657	IN-334-0141/ SOF+RBV +DCV	Cardiomyopathy, Cardiac Failure	Related	None	Multi-organ failure in the setting of progressive end

					stage liver disease and sepsis; subject died
50 year old man with HCV/HIV-1 co-infection, liver transplant (b) (6) enrolled in compassionate use program based on rapidly progressing cholestatic hepatitis with decompensated liver disease. Started SOF+RBV 16 September 2013 with plans for liver retransplantation. Due to refractory anemia, RBV discontinued and daclatasvir (DCV) initiated (b) (6). Despite virologic suppression, MELD scores increased from 14 at the time of SOF+RBV initiation to 26. Hospitalized (b) (6) with septic shock and worsened encephalopathy requiring intubation and pressor support. Echocardiogram with EF 30-40% and severe pulmonary hypertension (pulmonary arterial pressure 60 mmHg), worsened from echocardiogram (b) (6) (b) (6) (EF 62% with pulmonary arterial pressure 30 mmHg). Developed Staphylococcal bacteremia, and his clinical condition continued to deteriorate. Day (b) (6), echocardiogram with global hypokinesis, dilatation of the right ventricle, and cardiac MRI with left-sided EF 13%, right-sided EF 9%. Renal failure ensued, and the subject died (b) (6). The Applicant concludes this clinical picture is consistent with cirrhotic cardiomyopathy unmasked by the hemodynamic stress of septic shock. Pre-existing evidence of elevated pulmonary arterial pressure suggest early right-sided heart disease, and in the setting of severe sepsis, the subject developed cardiomyopathy with comparatively worsened right-sided function.					
2014-0094359	IN-334-0141/ SOF+RBV	Cardiomyopathy	Not related	Study drug discontinued	Newly diagnosed hypothyroidism coincident with cardiomyopathy which resolved with thyroid replacement
51 year old woman underwent liver transplant due to chronic HCV and hepatopulmonary syndrome. One month post-transplant, started SOF+RBV through the compassionate use program due to rapidly progressive early HCV recurrence. Achieved virologic suppression and clinically improved on treatment. Approximately 4 months after starting treatment (b) (6) presented with new onset dilated cardiomyopathy. She was found to have profound hypothyroidism (TSH 40.3 IU/mL), believed to be the most likely etiology of cardiac dysfunction. All non-essential medications discontinued, including SOF+RBV and the subject began thyroid replacement therapy. Subsequently she had TSH normalization, resolution of clinical symptoms and return of cardiac function to baseline: echocardiogram performed (b) (6) with EF 64%.					

Ledipasvir/Sofosbuvir Clinical Development Program

More than 3000 subjects have been treated in the LDV/SOF development program to date. Six subjects have experienced treatment-emergent cardiac failure and/or cardiomyopathy (Table 44). In five cases, subjects had significant underlying heart disease. In the sixth case, the subject was a liver transplant recipient and developed cardiac failure in the setting of decompensated cirrhosis, hepatopulmonary syndrome, and Clostridium perfringens bacteremia.

Table 44 Events of Cardiomyopathy or Cardiac Failure in the LDV/SOF Clinical Development Program

Case #	Trial/ Treatment	Cardiac Event	Investigator Causality Assessment	Action Taken	Additional Information
2014-0091125 (#2760-84468)	GS-337-0133/ LDV/SOF +GS-9669*	Cardiomyopathy	Not related	Study drug discontinued	Subject with pre-existing heart failure, as evidence by abnormal BNP at baseline and abnormal ECG (LBBB)
59 year old man with history including hypertension, smoking and prior chest pain/ECG indicative of left ventricular hypertrophy 2011. Screening ECG with new left bundle branch block (LBBB). Started LDV/SOF+GS-9669 (250 mg QD). Day 7 and Day 14 visits missed due to work issues. Day 18 experienced progressive exertional dyspnea and subsequently seen by a cardiologist Day 22. Echocardiogram with EF 20-24%, severe impairment of left ventricular function with global hypokinesis, regional wall motion abnormalities consistent with coronary artery disease. Further cardiac evaluation included cardiac catheterization demonstrating a right dominant coronary artery system, 100% occlusion of right coronary artery, minimal left coronary artery disease (no intervention performed); elevated BNP 839 pg/mL (ref range 0-100) with noted elevated baseline BNP 387 pg/mL from stored sample (same laboratory used). Study drugs discontinued Day 29. On Day 34 received a pacemaker and implantable cardioverter defibrillator. On Day 39 the subject was feeling significantly improved with plans to return to work. The Applicant discussed this case with a consulting cardiologist who noted that the subject's right coronary artery disease was anatomically inconsistent with a LBBB, suggestive of a pre-existing cardiomyopathy. The elevated baseline BNP prior to study drug initiation is supportive of this assessment.					
2014-0092896 (#2130-71707)	GS-337-0102/ LDV/SOF +RBV	Ischemic Cardiomyopathy	Not related	N/A; completed treatment	Subject with severe 2-vessel CAD
64 year old Hispanic man completed 24 weeks LDV/SOF+RBV. Post-treatment Day 92 experienced chest pain after swimming and suffered cardiac arrest, myocardial infarction. Cardiac catheterization showed severe two vessel coronary artery disease of left anterior descending artery and right coronary artery. There was severely elevated left sided filling pressures, no atrial stenosis, no mitral regurgitation and moderately reduced left ventricular systolic function leading to diagnosis of ischemic cardiomyopathy (Post-treatment Day 93). Underwent successful suction thrombectomy, percutaneous coronary angioplasty, and stenting of proximal LAD in addition to medical management. Discharged post-treatment Day 97.					
2014-0097660 2014-0099487	GS-337-0123/ LDV/SOF +RBV	Congestive Heart Failure	Not related	None	Subject with peri-operative NSTEMI during prior liver transplantation
66 year old man with history including HCC s/p liver transplant (b) (6) with peri-operative non-ST elevation myocardial infarction (NSTEMI), hypertension, diabetes mellitus started LDV/SOF+RBV 26 February 2014. On (b) (6), experienced shortness of breath and					

was hospitalized. Echocardiogram with EF 40-45% and regional wall motion abnormalities. A cardiology consult determined the subject to have congestive heart failure secondary to his previous peri-operative NSTEMI. On (b) (6), the subject was discharged from the hospital. On (b) (6), readmitted for congestive heart failure exacerbation thought to be secondary to poor diet, inadequate diuresis, and poorly controlled blood pressure. No new signs of ischemia were noted; troponin levels were reported as unremarkable. The subject was subsequently discharged on (b) (6).					
2014-0099083	CO-337-0117/ LDV/SOF	Congestive Heart Failure	Not related	N/A; completed treatment	Subject with pre-existing CHF (EF 47%)
65 year old man with history including coronary artery disease, myocardial infarction 2008 with angioplasty and stent, hypertension, congestive heart failure since 2009 (EF 47%) was enrolled in NIAID CO-US-337-0117 (SYNERGY) and completed 12 weeks of LDV/SOF. Approximately three months off study drug, hospitalized due to a congestive heart failure exacerbation. Cardiac perfusion (stress testing) revealed a new fixed-perfusion defect in the mid-apical anterior wall. EF 41%. Medical management was instituted and the subject was discharged home two days following initial hospitalization.					
2014-0100151	GS-337-0113/ LDV/SOF +RBV	Congestive Heart Failure	Related	N/A; completed treatment	Subject with abnormal ECG at screening, including atrial fibrillation, marked ST depressions, and PVCs, suggestive of pre-existing disease. Lack of rate control in may have been contributory
77 year old Japanese woman started LDV/SOF+RBV 29 November 2013. Screening ECG notable for atrial fibrillation. Study therapy completed 20 February 2014. Two days later, ECG showed atrial fibrillation with rapid ventricular rate (125 bpm). On (b) (6), hospitalized in atrial fibrillation with a rapid ventricular rate (120-140 bpm), and in congestive heart failure. On admission, BNP 604.4 pg/mL, and EF 45%. Medical management was instituted, including bisoprolol and furosemide, with symptom resolution. (b) (6) EF 59%.					
2014-0101472	GS-337-0123/ LDV/SOF +RBV	Cardiomyopathy	Not related	Study drug discontinued	s/p liver transplant, EF 20% in setting of decompensated cirrhosis, hepato-pulmonary syndrome, and C. perfringens bacteremia; after medical management, EF 65%.
63 year old Caucasian woman with history including decompensated cirrhosis (CPT B), HCC s/p liver transplant 2007, hepatic encephalopathy, bacterial peritonitis, diabetes started LDV/SOF+RBV. Day 11 ECG showed new atrial fibrillation with rapid ventricular response (140 beats per minute). Echocardiogram with EF 65%. Day 29 ECG again revealed atrial fibrillation with rapid ventricular response. Day 63 experienced shortness of breath and mental status changes with hypoxia. Admitted for hepatic encephalopathy with concern for possible					

hepatopulmonary syndrome. Blood cultures positive for Clostridium perfringens, and abdominal CT demonstrated possible colitis thought to be a potential bacteremia source. Day 68 echocardiogram with EF 20%, moderately dilated left atrium, normal sized left ventricle, severe global hypokinesis to akinesis, mild concentric LV hypertrophy, evidence of pulmonary arteriovenous malformations. LDV/SOF discontinued Day 70 (RBV stopped on Day 61 due to nausea). Based on the clinical findings and input from subspecialty consultations, the investigator considered the new onset cardiomyopathy differential diagnosis to include uncontrolled, prolonged tachycardia, high output cardiac failure secondary to bacteremia (in the setting of AV shunting/ hepatopulmonary syndrome), or study drug related. Clinical status improved with Day 77 echocardiogram estimated EF 55-65%.

*GS-9669 is an investigational non-nucleoside NS5B inhibitor

Summary

More than 7000 subjects have received SOF or LDV/SOF in the clinical development program, including 470 subjects receiving SOF through compassionate use. The reviewed cases of cardiac failure and/or cardiomyopathy have confounding factors such as underlying coronary artery disease, baseline LBBB, atrial fibrillation, intercurrent illness (e.g., hypothyroidism, bacteremia) and/or decompensated cirrhosis. All cases in the SOF clinical development program occur in subjects receiving treatment through compassionate use. The Applicant concludes:

> "This updated analysis of cardiac SAEs in ongoing Phase 2 and Phase 3 SOF studies and compassionate use programs does not raise concern for any study drug-related cardiac dysfunction.
>
> All cases of cardiomyopathy and/or congestive heart failure in the SOF program occurred in patients in the compassionate use program in patients who had advanced liver disease and substantial comorbidities offering alternate etiologies for the cardiac events. Specifically with respect to the only new case of cardiomyopathy in the SOF program, the development of dilated cardiomyopathy in a subject with significant hypothyroidism and its prompt resolution upon treatment of the underlying endocrine disorder suggests SOF did not contribute to this event.
>
> All cases of cardiomyopathy and/or congestive heart failure in the LDV/SOF program occurred in subjects who had pre-existing heart disease as an alternative explanation for their cardiac events.
>
> Based on the totality of preclinical and clinical data to date, Gilead has not found evidence for SOF-related cardiotoxicity, and the review presented here supports the safety of SOF and LDV/SOF."

Reviewer Comment: Based on the currently available information, an obvious causal association between SOF and/or LDV/SOF use and development of cardiac failure and/or cardiomyopathy is not identified. Any potential signals will continue to be monitored in the postmarketing setting.

7.3 Major Safety Results

7.3.1 Deaths

No on-treatment deaths occurred in the submitted LDV/SOF phase 2 or phase 3 trials. One death occurred in the post-treatment period in ION-1 which was not considered related to study treatment by the investigator.

Subject #5871-71038 Hepatic Failure

> 63 year old Hispanic man with a history of alcoholism, alcoholic cirrhosis, chronic low back pain, arthritis, pedal edema and ascites received LDV/SOF for 12 weeks and achieved SVR12. The only reported on-treatment AE was Grade 1 influenza-like illness Days 13-28. On-treatment laboratories were ≤Grade 1 with the exception of a single Grade 2 non-fasting elevated glucose level. On post-treatment Day 38, he experienced an SAE of hepatic failure secondary to HCV infection and alcohol use. Over the following months his clinical status worsened including events of spontaneous bacterial peritonitis, hepatorenal syndrome, pulmonary embolism, and he was reported to die of hepatic failure on post-treatment Day 121. This event was considered not related to study drug by the investigator and to be related to the underlying disease and pre-existing condition.

Reviewer Comment: This single death occurring in the post-treatment period does not raise a safety concern. Based upon the reported information, I agree with the investigator's assessment of the events that were considered to be unlikely related to study drugs.

The SUR reports nine additional deaths in LDV/SOF+RBV-treated subjects enrolled in ongoing trials:

- One subject died of a cardiac arrest in the Japanese trial GS-US-337-0113 and is further discussed in Section 7.3.5 Myocardial Ischemia Events.
- Eight subjects died in the ongoing SOLAR-1 trial evaluating LDV/SOF+RBV in subjects with advanced liver disease or who are post-liver transplantation, including those with decompensated cirrhosis. Overall there is no clustering of events. Please see Section 7.4.5 Special Safety Studies/Clinical Trials for discussion of these cases.

Two deaths occurred from phase 2 trials with LDV in combination with other investigational DAAs±RBV±PEG/RBV. Subject #1264-1034 (GS-US-248-0121, LDV/VDV+PEG/RBV) died 138 days after completed study treatment. The cause of death was not reported as the subject was found in a hotel room. Subject #5743-8336 (GS-US-256-0148 LDV/VDV+PEG/RBV) 59 year old man with a history of hypertension died of respiratory failure Day 32 following a hemorrhagic stroke associated with elevated blood pressure.

Reviewer Comment: Based upon the reported information, these additional cases from the SUR and from phase 2 trials with LDV in combination with other investigational DAAs (e.g., VDV) and PEG/RBV do not raise an obvious safety concern. The decompensated liver disease/post-transplant population has known associated comorbidities and is overall a sicker population compared with the population enrolled in the phase 3 trials. The cases in the LDV-containing trials are unlikely related to LDV use. One case death is more than four months after last study drug dose, and the other case occurs in the setting of VDV (investigational PI) and PEG/RBV use. The pegylated interferon product label includes warnings and precautions regarding cerebrovascular disorders: Ischemic and hemorrhagic cerebrovascular events have been observed in patients treated with interferon alfa-based therapies, including PEGASYS. Events occurred in patients with few or no reported risk factors for stroke, including patients less than 45 years of age.

7.3.2 Nonfatal Serious Adverse Events

An SAE was defined in the phase 3 trials as any adverse drug experience occurring at any dose that resulted in any of the following outcomes:

- Death
- Life-threatening situation (subject was at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other medically significant events that were not immediately life-threatening or resulted in death or hospitalization, but based upon appropriate medical and scientific judgment, may have jeopardized the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above

In the pooled phase 3 safety population, ≤3% of subjects overall experienced an SAE (2.6%, 51 of 1952 subjects). The treatment-emergent SAEs reported in the pivotal phase 3 trials are summarized by System Organ Class and MedDRA preferred terms in Table 45.

Table 45 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, LDV/SOF Phase 3 Integrated Safety Population

Body System or Organ Class Dictionary-Derived Term	LDV/SOF 8 Weeks	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks	LDV/SOF +RBV 8 Weeks	LDV/SOF +RBV 12 Weeks	LDV/SOF +RBV 24 Weeks
	215	539	326	216	328	328
Number of Subjects with	4 (2%)	6 (1%)	24 (7%)	1 (<1%)	7 (2%)	9 (3%)

SAE (%)						
Blood And Lymphatic System Disorders						
Anemia	0	0	0	0	1 (<1%)	0
Factor VIII Inhibition*	0	0	1 (<1%)	0	0	0
Cardiac Disorders						
Angina Unstable*	0	0	1 (<1%)	0	0	0
Gastrointestinal Disorders						
Abdominal Discomfort*	0	0	1 (<1%)	0	0	0
Abdominal Pain*	0	1 (<1%)	0	0	0	0
Colitis*	1 (<1%)	0	1 (<1%)	0	0	0
Intestinal Perforation*	0	1 (<1%)	0	0	0	0
Lower Gastrointestinal Hemorrhage*	1 (<1%)	0	0	0	0	0
Mesenteric Vein Thrombosis*	0	0	1 (<1%)	0	0	0
Upper Gastrointestinal Hemorrhage*	0	0	1 (<1%)	0	0	0
General Disorders And Administration Site Conditions						
Chest Pain*	0	1 (<1%)	1 (<1%)	0	0	0
Non-Cardiac Chest Pain*	0	0	2 (1%)	0	1 (<1%)	0
Hepatobiliary Disorders						
Bile Duct Stone*	0	1 (<1%)	0	0	0	0
Cholecystitis Acute*	0	0	0	0	0	1 (<1%)
Jaundice*	0	1 (<1%)	0	0	0	0
Immune System Disorders						
Anaphylactic Reaction*	1 (<1%)	0	0	0	0	0
Infections And Infestations						
Cellulitis	0	0	1 (<1%)	0	0	0
Gastroenteritis	0	0	2 (1%)	0	0	0
Pneumonia	0	0	0	0	1 (<1%)	1 (<1%)
Progressive Multifocal Leukoencephalopathy-Restaging	0	0	1 (<1%)	0	0	0
Salpingitis*	0	0	1 (<1%)	0	0	0
Urinary Tract Infection	0	0	1 (<1%)	0	0	0
Wound Infection	0	0	0	0	0	1 (<1%)
Injury, Poisoning And Procedural Complications						
Alcohol Poisoning	0	0	0	0	0	1 (<1%)
Concussion	0	0	0	0	0	1 (<1%)
Fall*	0	0	1 (<1%)	0	0	0
Foot Fracture*	0	0	1 (<1%)	0	0	0
Hand Fracture*	0	0	2 (1%)	0	0	0
Lower Limb Fracture*	0	0	1 (<1%)	0	0	0
Rib Fracture*	0	0	0	0	0	1 (<1%)
Road Traffic Accident*	0	1 (<1%)	0	0	0	0
Skeletal Injury*	0	1 (<1%)	0	0	0	0

Tibia Fracture*	0	0	0	0	1 (<1%)	0
Metabolism And Nutrition Disorders						
Diabetes Mellitus Inadequate Control	1 (<1%)	0	0	0	0	0
Hypoglycemia	0	1 (<1%)	0	0	0	0
Musculoskeletal And Connective Tissue Disorders						
Intervertebral Disc Protrusion	0	0	1 (<1%)	0	1 (<1%)	0
Lumbar Spinal Stenosis	0	0	1 (<1%)	0	0	0
Rhabdomyolysis*	0	1 (<1%)	0	0	0	0
Spondylolisthesis	0	0	1 (<1%)	0	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)						
Pituitary Tumor*	0	0	0	1 (<1%)	0	0
Squamous Cell Carcinoma*	0	0	0	0	0	1 (<1%)
Squamous Cell Carcinoma Of Lung*	0	1 (<1%)	0	0	0	0
Nervous System Disorders						
Carotid Artery Stenosis	0	0	0	0	0	1 (<1%)
Convulsion*	0	0	1 (<1%)	0	0	0
Headache*	0	0	1 (<1%)	0	0	0
Hepatic Encephalopathy	0	0	1 (<1%)	0	0	0
Migraine	0	0	0	0	1 (<1%)	0
Psychiatric Disorders						
Alcohol Withdrawal Syndrome	0	0	0	0	0	1 (<1%)
Depression*	0	0	0	0	0	1 (<1%)
Mental Status Changes	0	1 (<1%)	0	0	0	0
Substance Abuse	0	0	0	0	0	1 (<1%)
Renal And Urinary Disorders						
Calculus Ureteric	0	0	0	0	0	1 (<1%)
Reproductive System And Breast Disorders						
Breast Mass	0	0	1 (<1%)	0	0	0
Vaginal Prolapse	0	0	0	0	0	1 (<1%)
Respiratory, Thoracic And Mediastinal Disorders						
Hemothorax*	0	1 (<1%)	0	0	0	0
Respiratory Failure*	0	1 (<1%)	0	0	0	0
Vascular Disorders						
Hypertension*	1 (<1%)	0	0	0	1 (<1%)	0

*Case narratives described within the NDA 205834 clinical review
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

The incidence of SAEs is low and generally comparable across treatment groups. The LDV/SOF 24 week group has a higher rate (7%) compared with the other groups (<1% to 3%); however, many SAEs occur during the first 12 weeks of treatment. The incidence of SAEs considered related to study drug by the investigator is <1% (5 subjects). These SAEs are: headache, salpingitis, mesenteric vein thrombosis and

Factor VIII inhibition in the LDV/SOF 24 week arm, and anemia in the LDV/SOF+RBV 12 week arm.

SAEs occurring in >1 subject are non-cardiac chest pain, chest pain, colitis, gastroenteritis, hand fracture, hypertension, intervertebral disc protrusion, and pneumonia, with no event occurring in more than 3 subjects. There is no apparent clustering of SAEs observed within the SOCs.

Selected case narratives of SAEs are summarized below due to the investigator's causality assessment and/or due to their clinical significance. The case of anemia occurs in a RBV-treated subject and thus is not discussed below as anemia is known to occur with RBV treatment. The case of Factor VIII inhibition is described in Section 7.3.5.

- Subject #2024-71789 (LDV/SOF 24 Weeks, ION-1) Headache
  48 year old Caucasian woman experienced mild headache while on study treatment. Twenty days following study completion, had increased intensity headache leading to hospitalization. Imaging and cerebrospinal fluid analyses unrevealing. Headache resolved and discharged two days later.

Reviewer Comment: Headache is reported with LDV/SOF use and is recommended to be a labeled event. The increased intensity headache approximately 3 weeks off LDV/SOF may suggest an alternative etiology, although a causal relationship to study drug cannot be excluded.

- Subject #2012-71373 (LDV/SOF 24 Weeks, ION-1) Salpingitis
  34 year old woman with intrauterine device (IUD) experienced vaginal mycosis while on treatment and Day 4 diagnosed with salpingitis, treated with antibiotics and IUD removal. Subsequently the subject became pregnant as discussed in Section 7.6.2.

Reviewer Comment: Based on no other cases reported in the phase 3 LDV/SOF program and confounding of IUD, I believe a causal association between LDV/SOF use and salpingitis is low and does not warrant labeling at this time.

- Subject #5667-71227 (LDV/SOF 24 weeks, ION-1) Mesenteric Vein Thrombosis
  52 year old Caucasian man with cirrhosis, portal hypertension, splenomegaly was diagnosed with mesenteric vein thrombosis Day 49 after sudden onset nausea and vomiting with CT confirming the diagnosis. Received medical management including anticoagulation and was discharged two days later. Follow up CT scans showed improvement in superior mesenteric vein (SMV) thrombosis, and the event was considered resolved Day 160 when CT indicated questionable residual tiny non-occlusive SMV thrombus. That same day, the subject was hospitalized with abdominal discomfort associated with nausea, vomiting, diarrhea and elevated ALT (133 U/L), AST (161 U/L). LDV/SOF was interrupted for two days. Work up negative

for infectious etiology, although an intercurrent illness was suspected. The subject was discharged the following day after events resolved. LDV/SOF continued and Day 171 had normal ALT (34 U/L), AST (30 U/L).

Reviewer Comment: This subject has cirrhosis and portal hypertension which are risk factors for venous thrombotic events. Based on the available information that the events nausea, vomiting, diarrhea associated with transient elevation of ALT, AST followed by resolution while on LDV/SOF suggest an intercurrent infectious etiology.

- Subject #2111-79260 (LDV/SOF 24 Week, ION-2) Convulsion

41 year old Caucasian woman with history of bipolar disorder, alcohol dependence, alcohol withdrawal symptoms (including delirium tremens) on concomitant Lamictal and Seroquel, experienced seizure Day 47. Reports suggest the subject had recently been trying to decrease alcohol consumption, and it was suspected this event represented an alcohol withdrawal seizure. The subject recovered after receiving medical management including Ativan taper and banana bag, and was discharged two days later. The investigator assessed the event as not related to study drug.

Reviewer Comment: I agree with the investigator's assessment.

7.3.3 Dropouts and/or Discontinuations

Subjects with virologic failure while receiving study drug were discontinued from study treatment. In addition, subjects meeting any of the following criteria were required to stop all study drug(s):

- Confirmed elevation of ALT or AST >5 x Day 1 (baseline) value or nadir
- Confirmed elevation of ALT >3 x Day 1 (baseline) value and total bilirubin >2 x ULN
- Confirmed elevation of ALT >15 x ULN
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 AE or laboratory abnormality assessed as related to LDV/SOF

As displayed in Table 46 overall <1% of subjects receiving LDV/SOF with or without RBV (0.7%, 13 of 1952 subjects) has an AE leading to discontinuation of study treatment. The only AEs leading to discontinuation of LDV/SOF in more than one subject are palpitations and anxiety (2 subjects each, ≤Grade 2).

Table 46 Adverse Events Leading to Discontinuation from Study Drug, LDV/SOF Phase 3 Integrated Safety Population

Dictionary-Derived Term	LDV/SOF 8 Weeks	LDV/SOF 12 Weeks	LDV/SOF 24 Weeks	LDV/SOF +RBV 8 Weeks	LDV/SOF +RBV 12 Weeks	LDV/SOF +RBV 24 Weeks
Total Number of Subjects	215	539	326	216	328	328
Subjects who Discontinued Study Treatment Due to Adverse Event						
	0	2 (0.4%)	4 (1.2%)	1 (0.5%)	0	6 (1.8%)
Number of Subjects (%)						
Anxiety	0	0	0	0	0	2 (0.6%)
Arthralgia	0	1 (0.2%)	0	0	0	0
Chest Pain*	0	0	1 (0.3%)	0	0	0
Dizziness*	0	0	1 (0.3%)	0	0	0
Dyspnea*	0	0	0	0	0	1 (0.3%)
Ear Pain	0	0	0	0	0	1 (0.3%)
Eyelid Edema*	0	0	0	0	0	1 (0.3%)
Factor VIII Inhibition*	0	0	1 (0.3%)	0	0	0
Fatigue	0	0	0	0	0	1 (0.3%)
Gastrointestinal Viral Infection	0	0	0	0	0	1 (0.3%)
Hemorrhage*	0	0	1 (0.3%)	0	0	0
Headache*	0	0	0	0	0	1 (0.3%)
Palpitations*	0	0	1 (0.3%)	0	0	1 (0.3%)
Road Traffic Accident*	0	0	0	1 (0.5%)	0	0
Sensory Disturbance	0	0	0	0	0	1 (0.3%)
Squamous Cell Carcinoma Of Lung*	0	1 (0.2%)	0	0	0	0
Throat Tightness*	0	0	1 (0.3%)	0	0	0
Vertigo	0	0	0	0	0	1 (0.3%)

*Case narratives described within the NDA 205834 clinical review
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

7.3.4 Significant Adverse Events

The majority of subjects receiving LDV/SOF experienced at least one AE. The overall incidence of SAEs (2.6%) and discontinuations due to AE (0.7%) is low. With longer duration of treatment, there is an observed increase in total treatment-emergent AEs, treatment-related AEs, SAEs (in general), Grade 3/4 AEs and AEs leading to permanent

discontinuation. The following Table 47 provides an overall summary of AEs in the integrated data from the pivotal phase 3 trials.

Table 47 Overall Summary of Adverse Events in the Phase 3 LDV/SOF Trials (Integrated Safety Population)

	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
	215	539	326	216	328	328
Number (%) of Subjects Experiencing Any:						
Any AE	145 (67%)	390 (72%)	265 (81%)	165 (76%)	280 (85%)	300 (91%)
Treatment-related AE	82 (38%)	237 (44%)	165 (51%)	133 (62%)	229 (70%)	255 (78%)
Serious AE	4 (2%)	6 (1%)	24 (7%)	1 (<1%)	7 (2%)	9 (3%)
Treatment-related SAE	0	0	4 (1%)	0	1 (<1%)	0
Grade 3 or 4 AE	2 (1%)	13 (2%)	31 (10%)	8 (4%)	17 (5%)	20 (6%)
Treatment-related Grade 3 or 4 AE	0	2 (<1%)	9 (3%)	6 (3%)	10 (3%)	11 (3%)
AE Leading to Permanent LDV/SOF Discontinuation	0	2 (<1%)	4 (1%)	1 (<1%)	0	6 (2%)
AE Leading to Permanent Discontinuation from Any of Study Drugs	0	2 (<1%)	4 (1%)	2 (1%)	1 (<1%)	8 (2%)
AE Leading to LDV/SOF Interruption	0	2 (<1%)	4 (1%)	1 (<1%)	1 (<1%)	5 (2%)
AE Leading to Modification or Interruption of Any Study Drug	0	2 (<1%)	4 (1%)	17 (8%)	46 (14%)	55 (17%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

The addition of RBV to LDV/SOF is associated with an increase in the total incidence of AEs, treatment-related AEs and AEs leading to study drug modification or interruption, for all treatment durations. The most common reason for dose modification or interruption is anemia.

Overall the incidence of SAEs is low in the phase 3 population, with <8% SAEs occurring in any LDV/SOF-containing group. Table 48 displays ≥Grade 3 Clinical AEs from the phase 3 trials. Grade 4 AEs are reported in four subjects, all considered unrelated to study treatment by the investigator. One subject had six Grade 4 AEs occurring post-treatment Day 4: road traffic accident with resultant rhabdomyolysis, skeletal injury, mental status changes, hemothorax, and respiratory failure. All events

except for skeletal injury resolved. Three other subjects experienced Grade 4 AEs: unstable angina (subject with a history of heart disease), anaphylactic reaction (to lidocaine, triamcinolone), and hypoglycemia (subject with a history of diabetes receiving insulin). The events of unstable angina and hypoglycemia did not result in any changes to study drug dose and the event of anaphylactic reaction occurred on post-treatment Day 9. The investigator's assessments seem reasonable. Please see Section 7.3.5 for additional details regarding the cases of anaphylaxis and unstable angina.

Overall, the most frequently reported Grade 3 AEs are fatigue (0.7%), headache (0.6%), and anemia (0.3%). All Grade 3 AEs of anemia occur in subjects receiving LDV/SOF+RBV.

Table 48 Overall Summary of ≥Grade 3 Clinical AEs in the Phase 3 LDV/SOF Trials, Reported in Two or More Subjects (Integrated Data)

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Number of Subjects	215	539	326	216	328	328
Number of Subjects (%)	2 (1%)	13 (2%)	31 (10%)	8 (4%)	17 (5%)	20 (6%)
Fatigue	0	0	3 (1%)	2 (1%)	4 (1%)	5 (2%)
Headache	0	2 (<1%)	4 (1%)	2 (1%)	0	3 (1%)
Anemia	0	0	0	2 (1%)	2 (1%)	1 (<1%)
Migraine	0	1 (<1%)	2 (1%)	0	0	1 (<1%)
Hypertension	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0
Abdominal Pain	0	3 (1%)	0	0	0	0
Neck Pain	0	0	2 (1%)	0	0	0
Chest Pain	0	1 (<1%)	1 (<1%)	0	0	0
Back Pain	0	0	1 (<1%)	1 (<1%)	0	0
Cellulitis	0	0	1 (<1%)	0	0	1 (<1%)
Non-Cardiac Chest Pain	0	0	1 (<1%)	0	1 (<1%)	0
Jaundice	0	1 (<1%)	0	0	1 (<1%)	0
Mental Status Changes	0	1 (<1%)	0	0	1 (<1%)	0
Nausea	0	0	0	0	1 (<1%)	1 (<1%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

Adverse Events of Interest Based Upon SOF Labeling

Rhabdomyolysis/Myopathy Events

The SOF label contains information regarding creatine kinase elevations:

Creatine kinase was assessed in the FISSION and NEUTRINO trials. Isolated, asymptomatic creatine kinase elevation of greater than or equal to 10xULN was observed in <1%, 1% and 2% of subjects in the peginterferon alfa + ribavirin 24 weeks, SOVALDI + peginterferon alfa + ribavirin 12 weeks and SOVALDI + ribavirin 12 weeks groups, respectively.

Creatine kinase was not routinely collected in the phase 3 pivotal trials. One subject in the LDV/SOF 12 week group experienced rhabdomyolysis on post-treatment Day 12 following a motor vehicle accident. This event was not considered related to study drug. No other events of rhabdomyolysis or myopathy occurred in the phase 1, 2 or 3 LDV/SOF trials.

Reviewer Comment: Although creatine kinase was not routinely collected in the LDV/SOF phase 3 trials, no potential related cases of rhabdomyolysis or myopathy are reported. Ongoing trials do include creatine kinase monitoring, and events of rhabdomyolysis/myopathy will be monitored postmarketing.

Lipase Elevations/Pancreatitis Events

The SOF label contains information regarding lipase elevations:

Isolated, asymptomatic lipase elevation of greater than 3xULN was observed in <1%, 2%, 2%, and 2% of subjects in the SOVALDI + peginterferon alfa + ribavirin 12 weeks, SOVALDI + ribavirin 12 weeks, SOVALDI + ribavirin 24 weeks and peginterferon alfa + ribavirin 24 weeks groups, respectively.

No cases of pancreatitis were reported in the SOF registrational trials for NDA 204671 in subjects receiving SOF-containing treatment.

The Applicant proposes similar labeling for the LDV/SOF label:

Transient, asymptomatic lipase elevations of greater than 3xULN were observed in ≤1%, 2% and 3% of subjects treated with [TRADENAME] for 8, 12 and 24 weeks, respectively.

In the LDV/SOF phase 3 trials a numerical trend of increased incidence of treatment-emergent lipase elevations occur with longer duration ranging 9-17%; however the differences across the 8 to 24 week durations are <5% within any grade. Few subjects experience ≥Grade 3 lipase elevations (<2%, 33 subjects) across treatment arms (Table 49). Numerically more lipase elevations occurred in the LDV/SOF arms without RBV. None of these generally sporadic elevations are associated with clinical signs or symptoms of pancreatitis, no elevations led to study drug discontinuation and no on-treatment pancreatitis cases occur. There is no consistent temporal pattern to the timing of onset of lipase elevations, and most values improved or normalized while remaining on study treatment.

Table 49 Lipase Elevations in the LDV/SOF Phase 3 Integrated Safety Population

Lipase Maximum Toxicity Grade	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Number of Subjects in Analysis	215	538	325	214	328	328
Total Subjects with ≥Grade 1 Elevations	20 (9%)	53 (10%)	56 (17%)	16 (7%)	32 (10%)	36 (11%)
Grade 1 (>1 to 1.5x ULN)	12 (6%)	19 (4%)	28 (9%)	10 (5%)	20 (6%)	23 (7%)
Grade 2 (>1.5 to 3x ULN)	6 (3%)	23 (4%)	18 (6%)	5 (2%)	8 (2%)	8 (2%)
Grade 3 (>3 to 5x ULN)	2 (1%)	7 (1%)	6 (2%)	1 (<1%)	1 (<1%)	5 (2%)
Grade 4 (>5x ULN)	0	4 (1%)	4 (1%)	0	3 (1%)	0

Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

Non-Treatment Emergent Lipase Elevation/Pancreatitis Events

One subject (#2760-79085, ION-2, LDV/SOF 24 weeks) experienced acute on chronic pancreatitis on post-treatment Day 65. This 50 year old man with HCV GT1a infection, cirrhosis, esophageal varices, prior upper gastrointestinal bleed, chronic pancreatitis, stable non-enhancing pancreatic lesions, pancreatic insufficiency on pancreatin completed 24 weeks LDV/SOF. Baseline lipase was Grade 1, and on-treatment experienced transient Grade 2 lipase Week 16 and Grade 1 lipase Week 24. On post-treatment Day 65 he was hospitalized with epigastric pain, lipase Grade 1 and diagnosed with acute on chronic pancreatitis. Treatment included intravenous fluids, pain management and pantoprazole. CT of abdomen and pelvis showed 1.5 cm pancreatic head hypodensity which may represent a sidebranch intraductal papillary mucinous neoplasm. This event was considered not related to study drug by the investigator and resolved on post-treatment Day 67.

Pancreatitis Events in Phase 2 Trials with LDV in Combination with Other Investigational DAAs ± RBV ± PEG/RBV

Two cases of pancreatitis are reported in LDV-containing phase 2 trials.

- Subject #1225-6268 (GS-US-248-0120)
  54 year old woman started treatment with LDV 30 mg+VDV+TGV+RBV. Day 98-101 hospitalized with nausea, vomiting, and diarrhea diagnosed as viral gastroenteritis, review of systems notable for (+)sick contacts. The subject had no history of pancreatitis or gallstones, denied history of alcohol use; however, per the patient screening interview, prior alcohol use was recorded. Day 105 hospitalized with intractable nausea, vomiting and abdominal pain. Abdominal ultrasound showed unremarkable gallbladder, biliary tree, liver and pancreas. Admission laboratory tests showed Grade 3 lipase. Diagnosed with acute pancreatitis and received medical

management including bed rest, nothing by mouth and intravenous hydration. The following day lipase had normalized and she was discharged two days later. Study drugs were continued without interruption and the subject recovered. The investigator assessed the event as related to study drugs.

- Subject #5859-4612 (GS-US-248-0132)

56 year old man started LDV+VDV+RBV on 09 Jan 2012. The subject's medical history was significant for incisional hernia with abdominal pain, status post cholecystectomy. Day 11 experienced an increase in abdominal pain related to the incisional hernia and was admitted to the hospital. The subject's amylase and lipase were found to be elevated and he was diagnosed with acute pancreatitis. The subject recovered and was discharged from the hospital two days later. The investigator assessed the event to be not related to the study medications.

Reviewer Comment: Treatment-emergent lipase elevations in the LDV/SOF phase 3 trials are observed with similar incidence to lipase elevations reported in the current SOF label. None of these generally sporadic elevations was associated with clinical signs or symptoms of pancreatitis, no elevations led to study drug discontinuation and no on-treatment pancreatitis cases occurred. The mechanism of these lipase elevations remains unclear. The non-treatment emergent and phase 2 cases are confounded by underlying comorbidities and/or concomitant medication use. I agree with the Applicant's proposed labeling to convey this laboratory information to health care providers. Events of pancreatitis will be monitored in the postmarketing setting.

Depression and Suicidal Events

The SOF label includes language in the *Less Common Adverse Reactions Reported in Clinical Trials* section:

Psychiatric Disorders: severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

An analysis of depression and suicidal events in LDV/SOF phase 3 trials pooled terms from the MedDRA High Level Group Terms "Depressed Mood Disorders and Disturbances" and "Suicidal and Self-Injurious Behaviours NEC". As shown in Table 50, the overall incidence of depression and suicidal events is 3.9% (76/1952 subjects), with lower percentage occurring in the LDV/SOF pooled arms than in the RBV-containing pooled arms (2.7% versus 5.4%, respectively). The majority of subjects (60%) have a reported psychiatric disorder history. All events are ≤Grade 2 and no subject discontinued LDV/SOF due to an event. A single SAE of depression occurring in the LDV/SOF+RBV 24 week group is considered not related to study drug by the investigator. This 50 year old man (Subject #1081-71416) with a history including ongoing depression experienced alcohol intoxication/poisoning, rib fracture and concussion due to a motorcycle accident and worsened depression on Day 72.

Following hospitalization and psychiatric evaluation and management, the subject recovered.

Approximately two-thirds of pooled depression and suicidal ideation events have onset within the first 8 weeks (67%, defined as onset ≤Study Day 63), and 86% have onset within the first 12 weeks (defined as onset ≤Study Day 98).

Table 50 Depression and Suicidal Events, Treatment-Emergent, LDV/SOF Phase 3 Integrated Safety Population

	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
All Grades, n (%)	7 (3%)	10 (2%)	12 (4%)	8 (4%)	14 (4%)	25 (8%)
Anhedonia	0	0	0	0	0	1 (<1%)
Depression	4 (2%)	9 (2%)	8 (2%)	7 (3%)	10 (3%)	14 (4%)
Depressed Mood	1 (<1%)	1 (<1%)	2 (1%)	0	3 (1%)	7 (2%)
Major Depression	0	0	1 (<1%)	0	1(<1%)	1(<1%)
Suicidal Ideation	1 (<1%)	0	0	1(<1%)	0	1(<1%)
Tearfulness	1 (<1%)	0	1 (<1%)	0	0	1(<1%)
Maximum Grade						
Grade 1, n (%)	4 (2%)	7 (1%)	6 (2%)	5 (2%)	9 (3%)	21 (6%)
Grade 2, n (%)	3 (1%)	3 (1%)	6 (2%)	3 (1%)	5 (2%)	4 (1%)
Related events, n (%)	4 (2%)	6 (1%)	4 (1%)	6 (3%)	7 (2%)	13 (4%)
Time to onset of first event, days – median (range)	29 (2-74)	20 (8-65)	78 (1-183)	49 (16-86)	30.5 (4-108)	55 (1-155)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

Three events of suicidal ideation occur in the phase 3 trials, none are SAEs and all subjects continued study medication.

- Subject #0532-71351: 55 year old woman in LDV/SOF + RBV x 24 week arm. Medical history includes ongoing depression on escitalopram. Experienced Grade 1 suicidal ideation Day 106-130 treated with stopping escitalopram and starting duloxetine. The event is considered not related to study drug by the investigator.
- Subject #0334-73185: 51 year old man in LDV/SOF + RBV x 8 week arm. Medical history includes ongoing anxiety on alprazolam. Experienced Grade 2 suicidal ideation Day 50-60. The event is considered related to study drug by the investigator.
- Subject #3054-73119: 55 year old woman in LDV/SOF x 8 week arm. Medical history includes bipolar disorder on fluoxetine, anxiety on diazepam, panic attack, insomnia, prior substance use, prior suicide attempt (2003). Experienced Grade

2 suicidal ideation Day 46 lasting one day. The event is considered not related to study drug by the investigator.

Suicidal Events in Phase 2 LDV/SOF Trials and Phase 2 Trials with LDV in Combination with Other Investigational DAAs ± RBV ± PEG/RBV

In the phase 2 trials enrolling >1300 subjects, six events of suicidal ideation/suicide attempt are identified associated with SAEs or study treatment discontinuation. These events occur in subjects receiving RBV in all cases, and receiving PEG in two cases. Five of the six subjects have a history of psychiatric disorder. The case of suicidal ideation in a LDV/SOF-treated subject and the case of suicide attempt are described in more detail:

- Subject #2760-2704 (LDV/SOF+RBV in GS-US-337-0118)
67 year old Hispanic woman with a history including depression and anxiety began study treatment 21 December 2012. Concomitant medications included paroxetine and hydroxyzine. On 14 March 2013, study treatment completed (b) (6) (b) (6) the subject was admitted for suicidal ideation and severe anemia. On (b) (6) (b) (6), the subject was discharged from the hospital and the event of suicidal ideation was considered resolved. The investigator assessed the events as not related to LDV/SOF.
- Subject #2075-4654 (LDV/VDV/TGV/RBV in GS-US-248-0132)
47 year old Caucasian woman with history including anxiety (15-20 year history), depression, insomnia, history of drug abuse and a drinking problem began study treatment 07 Feb 2012. Concomitant medications included quetiapine, alprazolam, rabeprazole, escitalopram, oxycodone. On 23 Apr 2012, the subject discontinued study medications. On (b) (6), the subject was found unconscious and admitted to the hospital with attempted suicide by overdose on quetiapine and alprazolam. She was intubated and urine toxicology test was positive for opiate and benzodiazepine. On (b) (6), the subject was extubated; she stated she had a fight with her partner and that caused her to take the pills. The event of suicide attempt resolved and the subject was discharged. On (b) (6) ((b) (6) follow-up study visit), the subject expressed suicidal ideation. When the subject went to the washroom, she stated she ingested two medications (unspecified). She became unresponsive and admitted for suspected overdose. The subject reported increased anxiety and onset of depressed mood since starting treatment for hepatitis C two to three months ago. The subject tested positive for opioids and benzodiazepines. Hospital notes indicate an overdose of quetiapine, alprazolam, and escitalopram. On (b) (6), the events of suicide ideation and questionable medication overdose resolved and the subject was discharged. The investigator assessed the events as not related to study drug, but related to acute depression.

Reviewer Comment: Based upon the review of data submitted to date, overall depression and suicidal events are low. Within the phase 3 LDV/SOF trials, all subjects experiencing suicidal ideation have an underlying psychiatric history, none of the events

are SAEs or >Grade 2, and no event led to LDV/SOF discontinuation. In the phase 2 trials, one SAE occurs in a LDV/SOF+RBV-treated subject. The phase 2 events are confounded by concomitant RBV ± PEG use with the majority of events occurring in subjects with an underlying psychiatric history. Although a strong causal relationship between LDV/SOF use and depression and suicidal events is not evident based upon the phase 3 data, I believe it is appropriate to include wording in the LDV/SOF label (b) (4) *based upon (1) consistency with the SOF label, (2) the SAE occurring in the -0118 trial, and (3) due to the potential seriousness of these events.*

7.3.5 Submission Specific Primary Safety Concerns

Ocular Events

Preclinical studies demonstrate LDV, which absorbs UV light, accumulates in the uveal tract of the eye in pigmented (but not albino) rats. SOF does not absorb UV light.

An analysis of ocular events was performed due to a concern these preclinical findings represented a potential ocular safety signal, assessing all Eye Disorder SOC treatment-emergent events in the pooled phase 3 trials. Ocular-related events range 3-6% across the LDV/SOF treatment arms, with no trend with increased duration or with RBV use. All events are Grade 1-2, and no SAEs occur. The most common overall events are blurred vision, (1%, 19 events) and dry eye (1%, 15 events).

A single subject (Subject #0330-71316, LDV/SOF 24 Week, ION-1) discontinued LDV/SOF due to eyelid edema Day 86 and subsequently was found to have a sinonasal mass diagnosed as squamous cell carcinoma. The investigator assessed the event of squamous cell carcinoma as not related to study drugs, but due to a pre-existing condition and intercurrent illness of nasal congestion of greater than a year's duration.

Outside of the pivotal phase 3 trials, two notable ocular SAEs occurred (iritis/vitritis, uveal suffusion syndrome,).

- Subject #2012-0052520 Iritis, Vitritis

  67 year old woman was enrolled in GS-US-248-0120 and received LDV/VDV/TGV/RBV starting 18 October 2011. On 20 March 2012, the subject reported awareness of painless "floaters" in right eye, which had begun 12 days prior and was diagnosed with iritis and vitritis. The investigator assessed the events as possibly related to LDV, VDV, TGV and RBV.

- Subject #2013-0079963 Right eye uveal effusion syndrome, Right eye lens subluxation

  40 year old woman was enrolled in GS-US-337-0122 and started LDV/SOF 17 May 2013. On 19 July 2013, she presented with a three day history of blurred vision in the right eye and was diagnosed with right eye uveal effusion syndrome. On (b) (6)

(b) (6) the subject was assaulted, being struck in the face, fist versus right eye, and diagnosed with right eye lens subluxation. On (b) (6) she underwent right vitrectomy, lensectomy, laser and air-gas exchange. The investigator assessed the events to be not related to LDV/SOF.

Division of Transplant and Ophthalmology Products Consultation

A consultation was placed to the Division of Transplant and Ophthalmology Products (DTOP) for their assessment of this potential preclinical ocular signal and assessment of ocular-related events occurring in the LDV/SOF development program. They conclude neither of the above SAE narrative events appears to represent a treatment-related event; specifically, neither appears to represent a phototoxicity-related event. Their consultative summary comments are presented below:

DTOP Reviewer's Summary Comments and Recommendations:

1. We agree that LDV has low potential for ocular toxicities based on the information provided.
2. Human adverse event reporting has identified no clinically significant ocular adverse events.
3. No additional clinical monitoring, other than continued ocular adverse event collection, is recommended at this time.
4. We have no suggested revisions to the product labeling.

Reviewer Comment: No clinically significant ocular AE signal is identified based upon the available data submitted to the NDA. On June 29, 2014, the Applicant submitted an in vivo study in pigmented rats to assess potential ocular phototoxicity risk. This study was negative at up to the highest dose level tested, resulting in LDV AUC exposure ~8-fold higher than that in humans at the recommended LDV dose. Therefore, no clear signal between LDV use and ocular toxicity is identified. Please refer to the Pharmacology/Toxicology Review for further details.

Factor VIII Inhibition

HCV-infected patients with hemophilia are a population who may benefit from interferon-free therapies. Due to two cases of Factor VIII inhibition occurring in hepatitis C subjects with hemophilia, one in the LDV/SOF development program and one in the SOF development program, a further review was performed to assess for a potential causal associated with LDV/SOF or SOF. The cases are summarized below:

- Subject #5295-71745 (LDV/SOF, ION-1)

45 year old Caucasian man with history including mild hemophilia, treated with Factor VIII since (b) (6) began LDV/SOF. Day (b) (6) Factor VIII inhibitor level negative. Approximately 5 months on treatment, experienced spontaneous bleeding and found to have developed an inhibitor (Day (b) (6) Factor VIII inhibitor level 5

Bethesda unit (BU)) after failing to respond to recombinant Factor VIII infusion. LDV/SOF was discontinued Day (b) (6). On post-treatment Day (b) (6) experienced spontaneous bleed into the pelvic area. Post-treatment Day (b) (6) hematology results included PT 11.0 sec, INR 1.0, APTT 86.2 sec, APTT ratio 2.9, Factor VIII:c 2.5 IU/dL, and Factor VIII inhibitor level 2 BU. The subject was being followed up by a hematologist. Post-treatment Day (b) (6) hematology results included PT 10.2 sec, INR 0.9, APTT 60.6 sec, APTT ratio 2.0, and Factor VIII:c 1 IU/dL. The subject was still positive in Factor VIII inhibitor but the level had dropped to 1 BU. The investigator assessed the event of development of Factor VIII inhibitor in hemophilia patient to be related to LDV/SOF. In addition, the investigator noted the causality for the event of development of Factor VIII inhibitor in hemophilia patient was unclear: the event onset coincided with the study medication, but the event followed the use of Factor VIII (b) (6) The patient's pre-existing condition was provided as an alternative causality.

- Subject #3976-1675 (SOF+RBV, GS-US-334-0124, PHOTON-1)

47 year old Caucasian man with history including hemophilia A, HIV on darunavir/ritonavir/emtricitabine/tenofovir. Previous treatment with a Factor VIII preparation, Advate (octocog alfa) prophylactically before planned physical activity (approximately once a week). Began SOF+RBV and completed 24 weeks SOF+RBV treatment. Post-treatment Day 47, underwent surgery for a tibia/fibular fracture and received daily high-dose Factor VIII replacement (Advate 36,000 IU). He developed intractable hemarthrosis in his elbows on post-treatment Day 74, received courses of Advate (2000U BID) and was diagnosed with an inhibitor on Day 120, high titer BU. The development of a Factor VIII inhibitor occurred after approximately 4 weeks of high-dose Factor VIII replacement and more than 10 weeks after completing SOF+RBV therapy. The investigator assessed the event as related to SOF. Follow up information notes the subject's cousin with a similar mild phenotype and gene, has also developed a similar titer inhibitor in recent months, for no apparent reason other than for his infrequent Factor VIII therapy.

Based upon FDA request, additional information regarding subjects with hemophilia enrolled in the SOF and LDV/SOF clinical trials was provided on April 25, 2014. A comprehensive review of the SOF (n=2936) and LDV/SOF (including LDV and SOF co-administered as single agent tablets; n=3220) clinical development programs identified 42 subjects with hemophilia A (i.e., those with Factor VIII deficiency) or for whom the type of hemophilia was unknown, including 32 subjects with sufficient medical history data. Overall, 5/32 subjects were found to have had a diagnosis of a Factor VIII inhibitor. Three of the 5 subjects with a Factor VIII inhibitor were diagnosed >12 months prior to the start of study drugs; two of these were taking Factor VIII replacement therapy during the study and did not require a change in the dose of Factor VIII replacement therapy, and it is unknown if the third subject who had developed a Factor VIII inhibitor >12 month prior to starting the study was taking Factor VIII replacement therapy. The remaining 2 subjects are the initial cases described above.

Of the remaining 27 of 32 subjects, in 23 cases the investigator responded that the subject had no history of Factor VIII inhibitor development, and in 4 cases the investigator responded that this information was not known. There were 13 subjects taking Factor VIII supplementation who did not develop a Factor VIII inhibitor.

Division of Hematology Products Consultation

Based upon the two identified cases of Factor VIII inhibition, a consultation was placed to the Division of Hematology Products (DHP). Please refer to their consult for complete details. They conclude the development of Factor VIII inhibitors is unlikely to be related to the drug SOF or the combination of LDV/SOF. The two reported cases encountered thus far in the trials are heavily confounded, and a preliminary look by the Sponsor does not indicate other cases. The cases most likely are coincidental and related to Factor VIII product infusion or variable natural history of hemophilia. Factor VIII Inhibitors may appear in up to 25% of hemophilia A patients, especially those with more severe deficiency, and perhaps 5% of patients with milder hemophilia. Thus, the appearance of an inhibitor among hemophilia patients can be expected with some frequency by chance in the sofosbuvir trials. The evidence to date of the two cases in the trial data does not support a causality inference and no change in labeling is indicated based on these data. No postmarketing commitments or requirements are recommended to address this issue; however, the Applicant should monitor for this event in current trials.

Reviewer Comment: At this time, currently available data do not support a causal relationship between SOF and/or LDV/SOF use and development of Factor VIII inhibition in patients with hemophilia and no labeling is indicated. The ongoing trial, GS-US-334-1274, is assessing the safety and efficacy of LDV/SOF and SOF+RBV in GT 1-4 HCV-infected subjects with inherited bleeding disorders. This trial will capture relevant medical history regarding Factor VIII inhibitor history and Factor VIII replacement therapy as well as assess Factor VIII levels at baseline, during treatment, and in the post-treatment follow-up period. The data from that trial will be reviewed upon FDA submission. In addition, reports of Factor VIII inhibition will be monitored postmarketing.

Gastrointestinal Events

Due to observed findings of gastrointestinal (GI) hemorrhage, and increased frequency and incidence of emesis and diarrhea in male dogs administered SOF, a focused safety evaluation for gastrointestinal AEs was performed. No preclinical GI toxicity signal is identified for LDV.

Sofosbuvir NDA 204671 Clinical Review

As reported in the SOF NDA clinical review, three GI-related SAEs occurred: two cases of abdominal pain, one in setting of hepatocellular carcinoma, and one case of

pancreatitis. In Phase 2 program, one case of ischemic colitis occurred that was attributed to atherosclerosis in a subject receiving SOF+PEG/RBV.

Nausea, Vomiting, Diarrhea Events

In the phase 3 trials, treatment-emergent, treatment-related AEs of nausea range 6-9% in LDV/SOF arms and 13-15% in LDV/SOF+RBV arms; vomiting ranges <1-2% in LDV/SOF arms and 2-3% in LDV/SOF+RBV arms; diarrhea ranges 3-7% in LDV/SOF arms and 4-6% in LDV/SOF+RBV arms. No obvious trend in increased events with longer treatment duration is observed.

Abdominal Pain Events

Abdominal pain preferred terms were pooled (abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal rigidity, abdominal tenderness, gastrointestinal pain). In the phase 3 trials, subjects experiencing treatment-emergent, treatment-related abdominal pain events range 1-<5% in the LDV/SOF arms and 4-6% in the LDV/SOF+RBV arms, with most subjects reporting a Grade 1 event [79% (30/38 subjects) pooled LDV/SOF arms, 84% (36/43 subjects) pooled LDV/SOF+RBV arms]. No trend in increased events with longer treatment duration is observed.

Gastrointestinal Treatment Emergent ≥Grade 3 Events and/or SAEs

Table 51 presents treatment-emergent, all cause, ≥Grade 3 and/or SAEs within the Gastrointestinal (GI) SOC occurring in the phase 3 trials. Twelve subjects experienced GI-related events meeting these criteria, including six subjects with SAEs.

Table 51 Treatment-Emergent ≥Grade 3 and/or SAEs within the Gastrointestinal System Organ Class, LDV/SOF Phase 3 Integrated Safety Population

Treatment Arm	Dictionary-Derived Term	AE Start Day	AE End Day	Toxicity Grade	Serious AE	Related
LDV/SOF 8 Weeks						
GS-US-337-0108-2140-73157	Lower Gastrointestinal Hemorrhage, Colitis	34, 35	52, 53	2	Y	No
LDV/SOF+RBV 8 Weeks						
GS-US-337-0108-0522-73007	Abdominal Pain Lower	71	127	3	N	Yes
GS-US-337-0108-2728-73030	Vomiting	7	70	3	N	Yes
LDV/SOF 12 Weeks						
GS-US-337-0102-1193-71757	Abdominal Pain	56	58	3	N	No
GS-US-337-0108-2130-73381	Abdominal Pain	2	8	3	Y	No
GS-US-337-0108-4488-73366	Abdominal Pain, Intestinal Perforation	111, 115	-	3	N, Y	No
LDV/SOF+RBV 12 Weeks						
GS-US-337-0102-0519-71507	Nausea	22	24	3	N	No
LDV/SOF 24 Weeks						
GS-US-337-0102-0773-71425	Colitis	98	101	2	Y	No
GS-US-337-0102-5667-71227	Mesenteric Vein Thrombosis, Abdominal Discomfort	49, 160	160, 161	3	Y	Yes, No
GS-US-337-0109-0451-79126	Diarrhea	36	37	3	N	No
GS-US-337-0109-2760-79085	Upper Gastrointestinal Hemorrhage	55	59	3	Y	No
LDV/SOF+RBV 24 Weeks						
GS-US-337-0102-5847-71234	Nausea	2	-	3	N	Yes

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

In the phase 3 program six subjects experienced gastrointestinal SAEs, none considered related to study drug(s):

- Subject #2140-73157: Colitis with associated lower GI bleed in a subject with a questionable prior history of colitis and lower GI bleed (2-3 prior episodes). Study medication continued. During this presentation, a biopsy demonstrated inflammatory bowel disease consistent with ulcerative colitis.

Reviewer Comment: The investigator assessment the events are not related to LDV/SOF is reasonable due to the subject's prior history of colitis and lower GI bleed may.

- Subject #0773-71425: Colitis associated with bloody diarrhea, suggestive CT findings. Generally unremarkable EGD. LDV/SOF was interrupted for one day. The differential diagnosis included infectious etiology versus food poisoning versus due to study drug. The event resolved on antibiotics.

Reviewer Comment: The investigator assessment the event is not related to LDV/SOF is reasonable due to a potential infectious etiology.

- Subject #5667-71227: Abdominal discomfort associated with nausea, vomiting, diarrhea and transiently elevated AST (161 U/L), ALT (133 U/L). This subject has underlying cirrhosis, portal hypertension, splenomegaly and recently diagnosed with mesenteric vein thrombosis. LDV/SOF was interrupted for two days. Work up negative for infectious etiology, although an intercurrent illness was suspected. The subject was discharged the following day after events resolved. LDV/SOF continued and Day 171 had normal ALT (34 U/L), AST (30 U/L). Please see Section 7.3.2 for additional narrative details.

- Subject #2130-73381: Abdominal pain due to common bile duct stone leading to ERCP and sphincterotomy. Please see Section 7.3.5 Gallbladder Events for additional narrative details.

- Subject #4488-73366: Abdominal pain, intestinal perforation secondary to rectal trauma.

Reviewer Comment: The investigator assessment the events are not related to LDV/SOF is reasonable due to mechanical, suspected self-induced trauma.

- Subject #2760-79085: Upper gastrointestinal bleed in a subject with cirrhosis due to Grade 4 esophageal varices. Please see Section 7.4.2 for additional narrative details.

Six subjects experienced non-SAE, ≥Grade 3 gastrointestinal events. Events of lower abdominal pain associated with nausea, vomiting associated with migraine and nausea associated with headache and GERD are considered related to study drug by the investigator. Nausea is recommended as a labeled event for LDV/SOF. The event of vomiting is confounded by an associated migraine at the time of the event.

Gastrointestinal Events in Phase 2 LDV/SOF trials

In ELECTRON, there was a case of diverticular perforation with colovesicular fistula approximately two months after starting LDV/SOF+RBV treatment occurring in a subject receiving concomitant methadone.

- Subject #1030-5205 Diverticular Perforation (LDV/SOF+RBV)
  51 year old man on methadone maintenance experienced diverticular perforation with colovesicular fistula Day 61. Prior history notable for diarrhea four weeks prior this event, Study medications were stopped. He received antibiotics and underwent surgical intervention. The pathology report showed diverticulitis with perforation and a colovesical fistula. The colorectal surgeon believed that the event was likely spontaneous rupture from prolonged obstipation from methadone. The investigator assessed the event due to progression of concomitant disease constipation from methadone and due to intake of concomitant drug methadone.

Reviewer Comment: The investigator assessment seems reasonable. Opiate use is associated with increased risk of perforated diverticular disease (Humes DJ 2011).

In ELECTRON-2, there was a case of perforated sigmoid diverticulitis approximately one week after starting LDV/SOF treatment.

- Subject #5868-77124 Diverticular Perforation (LDV/SOF)
  39 year old Caucasian man experienced abdominal pain Day 6 and found to have perforated sigmoid diverticulitis for which he underwent surgery. Discharged Day 16, and study drugs were discontinued per report. The event was not considered related to study drug by the investigator but rather related to an intercurrent illness.

Reviewer Comment: The investigator assessment seems reasonable. The incidence of diverticulitis is increasing and, although this case is from New Zealand, a nationwide inpatient study of hospitalizations in the United States showed an increase in admissions for acute diverticulitis by 26% from 1998 to 2005. The largest increase (82%) was in patients aged 18 to 44 years (Etzoni DA 2009).

Two other SAEs of abdominal pain were reported in ELECTRON-2, both appeared to be associated with constipation and occurred between Weeks 3-6. One subject was on codeine and one on methadone. Both events resolved while LDV/SOF continued.

- Subject #5868-77113 Abdominal Pain (Cohort 2, Group 3)
  36 Year old Caucasian woman with history of inflammatory bowel disease, on codeine experienced Day 20 Grade 3 SAE of abdominal pain associated with constipation, which resolved 8 days after onset; study drug treatment was not interrupted.

- Subject #5868-77150 Upper Abdominal Pain (Cohort 2, Group 3)
  39 year old Caucasian woman on methadone experienced Day 49 Grade 3 SAE of upper abdominal pain associated with nausea, vomiting and constipation, which resolved 2 days after onset; study drug treatment was not interrupted.

Reviewer Comment: Both cases resolved while study drug continued, and concomitant opioid use with labeled constipation and abdominal pain effects confounds both cases making a direct causal association with LDV/SOF less likely.

The Applicant was queried regarding their assessment of gastrointestinal ≥Grade 3 and/or SAEs in the LDV/SOF development program. Their response received May 1,

2014 is summarized here. A total of 36 events (1.1%) are identified out of 3186 subjects within ongoing or completed phase 2 and 3 trials in the LDV/SOF program:

- 19 events (6.2%, 19 out of 307 subjects) from SOLAR-1, an ongoing trial of LDV/SOF+RBV in subjects with advanced liver disease (decompensated liver disease and/or those who are post-liver transplant)
    - Two related events (nausea, diarrhea)
- 17 events (0.6%, 17 out of 2879 subjects) from remaining LDV/SOF program
    - Abdominal pain most common (N=4, 0.1%)
    - All other events occurred in ≤2 subjects (<0.1%)

The Applicant also references an ongoing non-IND double-blind, placebo-controlled trial GS-US-337-0121 (SIRIUS, conducted in France). Note, this trial has not been submitted to the Division for independent data review. A total of 155 subjects with chronic HCV infection and cirrhosis receive either 12 weeks of LDV/SOF (77 subjects) or placebo (78 subjects). The Applicant states after 12 weeks of treatment, gastrointestinal events are similar between the LDV/SOF (33.8%; 26/77 subjects) and placebo groups (28.2%; 22/78 subjects). No SAEs, Grade 3 or Grade 4 GI AEs have been reported.

Their assessment is that "given (a) the overall low frequency of serious and/or, grade 3/4 GI events in the LDV/SOF program, (b) the lack of a difference in the frequency of GI events with LDV/SOF compared to placebo, and (c) the lack of a consistent preclinical toxicity profile, the data to date in the LDV/SOF program do not support a causal relationship between LDV/SOF and gastrointestinal Grade 3/4 and/or serious AEs."

Reviewer Comment: There is no obvious safety concern of serious gastrointestinal toxicity associated with LDV/SOF use identified at this time as assessed by (1) gastrointestinal symptoms of nausea, vomiting, diarrhea and abdominal pain and (2) ≥Grade 3 and/or SAEs occurring in the Gastrointestinal System Organ Class. Serious events of abdominal pain, colitis, diverticulitis, intestinal perforation are associated with potential confounders or alternative explanations such as prior colitis history, suspected infectious etiology, bile duct stone, trauma, opioid use. The totality of the available data does not support related labeling for serious gastrointestinal events at this time in my opinion. Reports of serious gastrointestinal AEs will be monitored postmarketing. Nausea and diarrhea are recommended as labeled events for LDV/SOF. Overall treatment-related vomiting is reported <1-2% across the LDV/SOF without RBV arms, and the single Grade 3 event of vomiting may be confounded by concurrent migraine, thus I do not believe labeling for vomiting is supported at this time.

Hepatic Events

An analysis of hepatic events was performed as LDV/SOF is being administered to subjects with underlying liver disease. Based upon review of the available data, I do not

believe a causal relationship between LDV/SOF use and hepatotoxicity is established at this time. This conclusion incorporates the following considerations:

- Within the phase 2 and 3 LDV/SOF development program of 2205 subjects, no on-treatment cases of serious hepatotoxicity occur and no Hy's Law cases are identified.
- No subject in the phase 3 trials met the protocol specified liver-related stopping rules during the on-treatment phase.
- ALT or AST increases >5x ULN are infrequent (<0.5%), and generally transient.
- The case of acute hepatitis occurring four weeks post-treatment in ION-1 has a pattern of liver enzyme elevation followed by resolution->recurrence->resolution in the absence of LDV/SOF rechallenge suggesting an alternative causal etiology.
- Assessment of supportive safety data from phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV identifies 0.8% (9/1097 subjects) meeting the modified Hy's Law definition. All cases are confounded by concomitant VDV use, an investigational NS3 PI known to increase bilirubin due to inhibition of OATP1B1 hepatic transporters and with preclinical findings of increased liver enzymes. In addition, all cases include at least one additional confounding medication: RBV + either TGV (an investigational non-nucleoside NS5B inhibitor) or PEG. Thus, while the contribution of LDV cannot be fully excluded, the presence of these coadministered drugs are significant confounders and appear to be the more likely causal agent(s).

Details supporting this conclusion are presented in this section.

In the SOF NDA 204671 review, no safety signals related to hepatotoxicity were identified in the SOF treated groups. Please refer to the SOF NDA 204671 for further details.

Preclinically, hepatobiliary findings with LDV including slight increased alkaline phosphatase, ALT, increased gallbladder weights without corresponding histopathology findings, and bile duct hyperplasia were detected in mice and rats, at doses ~8-30 times the estimated human LDV exposure and were not considered adverse. No pertinent findings were detected in dogs. LDV is primarily eliminated through biliary excretion.

Hepatic and Hepatobiliary Events

In the phase 3 LDV/SOF clinical trials, overall hepatic events defined by the MedDRA High Level Group Term Hepatic and Hepatobiliary Disorders are low (0.8%, 16/1952 subjects; Table 52). Most cases of jaundice and all cases of hyperbilirubinemia occur in RBV-treated subjects. The case of jaundice (≥Grade 3, SAE) in the LDV/SOF 12 week arm occurred in the setting of a bile duct stone (please see Gallbladder Events for additional details). No other events are SAEs and no events are Grade 4. Additional

Grade 3 events include acute hepatitis in the LDV/SOF 12 week arm and jaundice and hyperbilirubinemia in the LDV/SOF+RBV 12 week arm.

Table 52 Treatment-Emergent Adverse Events within the Hepatic and Hepatobiliary High Level Group Term, All Grade, LDV/SOF Phase 3 Integrated Safety Population

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
#Subjects with AE (%)	0	3 (1%)	0	0	7 (2%)	6 (2%)
Hepatic Cyst	0	0	0	0	0	1 (<1%)
Hepatitis Acute	0	1 (<1%)	0	0	0	0
Hepatomegaly	0	1 (<1%)	0	0	0	1 (<1%)
Hyperbilirubinemia	0	0	0	0	2 (1%)	1 (<1%)
Jaundice	0	1 (<1%)	0	0	5 (2%)	2 (1%)
Perihepatic Discomfort	0	0	0	0	0	1 (<1%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

The case of acute hepatitis, occurring approximately four weeks after LDV/SOF discontinuation, is further discussed.

Subject #0334-71474 (LDV/SOF 12 week, ION-1) Acute hepatitis

58 year old woman with cirrhosis completed 12 weeks LDV/SOF. Baseline ALT and AST were Grade 1 with normal bilirubin. At the end-of-treatment visit, ALT 51 U/L (Grade 1), AST 41 U/L and total bilirubin 0.2 mg/dL. Four weeks after discontinuing LDV/SOF, ALT 2103 U/L (Grade 4), AST 2656 U/L (Grade 4), and total bilirubin 1.3 mg/dL (Grade 1). Repeat ALT 1130 U/L, AST 690 U/L, total bilirubin 0.8 mg/dL, and alkaline phosphatase was 209 U/L. INR reported as “normal”; however, documentation could not be obtained. Upon subsequent questioning, the subject admitted to feeling fatigued, but otherwise had no complaints and specifically no abdominal pain. The subject denied alcohol abuse or new medications including acetaminophen use. ALT and AST decreased rapidly at subsequent visits and resolved after approximately 29 days, by post-treatment Day 53 (ALT 36 U/L, AST 38 U/L).

However, at post-treatment Day 67, liver enzyme increases recurred: ALT 575 U/L (Grade 4) and AST 884 U/L (Grade 4). A liver biopsy was subsequently performed, and also reviewed by a second pathologist, which showed hepatitis (also present on pre-treatment biopsy) and mild microvesicular steatosis. No electron microscopy was performed. The pathologist believes the histologic and clinical findings do not

support the possibility of drug-induced mitochondrial toxicity and that the degree of microvesicular steatosis is within the range of what may be seen in persons without hepatotoxicity. Additional diagnostic workup was negative for etiology based upon: Anti-Nuclear Antibody, Hepatitis B Surface Ag, Hepatitis B Core Antibody, HBV DNA viral load, Hepatitis A immunoglobulin M, cytomegalovirus viral load, ultrasound examination. The post-treatment HCV RNA viral load was unblinded and was found to be <LLOQ. After approximately 60 days, by post-treatment Week 18, this second event of ALT and AST increase had normalized.

The event was considered related to study drug by the investigator. Due to the rapid decline in this subject's ALT, and the largely asymptomatic presentation, this case was not deemed to meet serious criteria by the investigator. The Applicant concludes that the etiology of this subject's ALT elevation 4 weeks after ceasing therapy, as well as its subsequent normalization, and then re-elevation, remains unclear. While a definitive, alternative explanation for this event is not known, biopsy results suggest continued hepatocellular inflammation, while laboratory data suggests continued insults to the liver weeks after the cessation of LDV/SOF therapy, and therefore may be consistent with continuing exposure to an unknown toxin/drug.

Table 53 Summary of Liver Tests for Subject 71474 in ION-1

	Baseline	End of Treatment	Post-treatment Week 4	Retest Post-treatment Week 4 (Local)	Retest Post-treatment Week 4	Post-treatment Week 5	Post-treatment Week 6 (Local)	Post-treatment Week 8	Post-treatment Week 10	Unscheduled Visit	Post-treatment Week 24
Date	4/24/2013	7/18/2013	8/12/2013	8/13/2013	8/16/2013	8/19/2013	8/26/2013	9/9/2013	9/23/2013	11/22/2013	01/03/2014
ALT (U/L	77	51	2103	1130	406	188	40	36	575	26	28
AST (U/L)	60	41	2656	690	84	35	26	38	885	23	28
Alkaline Phosphatase (U/L)	143	128	193	209	175	178	155	158	146	NA	NA
Total Bilirubin (mg/dL)	0.3	0.2	1.3	0.8	0.6	0.5	0.3	0.5	0.3	0.3	0.4

Source: NDA 205834 SDN 13 Applicant Submission, Table 2

Reviewer Comment: The investigator's and Applicant's evaluation of this case is considered thorough. While the contribution of LDV/SOF to this case of acute hepatitis cannot be fully excluded, the onset occurring four weeks after completing therapy, the pattern of resolution->recurrence->resolution in the absence of LDV/SOF rechallenge suggest another causal etiology.

Liver Laboratory Data

Table 54 presents liver laboratory data from the LDV/SOF pivotal phase 3 trials and may be used as a reference throughout this section.

Table 54 Laboratory Data in Phase 3 LDV/SOF Integrated Safety Population, Liver Laboratories

Laboratory Parameter Maximum Toxicity Grade	**LDV/SOF 8 Week**	**LDV/SOF 12 Week**	**LDV/SOF 24 Week**	**LDV/SOF +RBV 8 Week**	**LDV/SOF +RBV 12 Week**	**LDV/SOF +RBV 24 Week**
Total Number of Subjects in Analysis	215 n (%)	539 n (%)	326 n (%)	216 n (%)	328 n (%)	328 n (%)
Alanine Aminotransferase (U/L)						
Grade 1 (1.25 to 2.5 x ULN)	1 (<1%)	1 (<1%)	7 (2%)	2 (1%)	1 (<1%)	5 (2%)
Grade 2 (>2.5 to 5x ULN)	1 (<1%)	1 (<1%)	4 (1%)	0	2 (1%)	0
Grade 3 (>5 to 10x ULN)	0	1 (<1%)	1 (<1%)	0	0	0
Grade 4 (>10 x ULN)	0	1 (<1%)	0	1 (<1%)	0	0
Aspartate Aminotransferase (U/L)						
Grade 1 (1.25 to 2.5 x ULN)	5 (2%)	10 (2%)	7 (2%)	4 (2%)	3 (1%)	2 (1%)
Grade 2 (>2.5 to 5x ULN)	2 (1%)	3 (1%)	4 (1%)	1 (<1%)	3 (1%)	2 (1%)
Grade 3 (>5 to 10x ULN)	0	0	2 (1%)	0	0	0
Grade 4 (>10x ULN)	0	1 (<1%)	0	1 (<1%)	0	0
Alkaline Phosphatase (U/L)						
Grade 1 (1.25 to 2.5 x ULN)	0	6 (1%)	4 (1%)	0	0	3 (1%)
Total Bilirubin (mg/dL)						
Grade 1 (>1 to 1.5x ULN)	8 (4%)	21 (4%)	16 (5%)	43 (20%)	77 (23%)	68 (21%)
Grade 2 (>1.5 to 2.5x ULN)	6 (3%)	1 (<1%)	5 (2%)	13 (6%)	36 (11%)	39 (12%)
Grade 3 (>2.5 to 5x ULN)	0	0	1 (<1%)	3 (1%)	10 (3%)	7 (2%)
Grade 4 (>5x ULN)	0	0	0	0	1 (<1%)	0

Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

The remainder of this liver laboratory section presents data in the following format to provide a comprehensive liver laboratory data assessment within the LDV/SOF development program.

- Assessment of Potential Hy's Law Cases: ALT or AST > 3x ULN and Bilirubin > 2x ULN
- Stopping Rules Utilized within LDV/SOF Phase 3 Trials
- Grade 3/4 Liver Enzyme Elevations within LDV/SOF Phase 3 Trials
- Bilirubin Elevations within LDV/SOF Phase 3 Trials

(1) Assessment of Potential Hy's Law Cases: AST or ALT >3x ULN and Bilirubin >2x ULN

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice has a poor prognosis. The modified Hy's Law definition used by FDA as indicator of clinical concern for drug-induced liver injury includes: ALT or AST >3x ULN, total bilirubin >2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury). Note, the appropriate application and interpretation of use of this definition in HCV clinical trials in subjects with established chronic liver disease due to HCV is unknown.

No cases satisfying Hy's Law are identified within the LDV/SOF phase 2 and 3 development program. A single subject in ION-1 had ALT and AST values that were appropriately decreasing in response to HCV treatment with bilirubin elevations occurring in the setting of RBV coadministration. A LDV/SOF phase 1 case in a healthy volunteer is confounded by ABC/3TC use and subsequent cholecystitis. Nine cases identified in phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV are confounded by VDV use in all cases, an investigational NS3 PI known to increase bilirubin due to inhibition of OATP1B1 hepatic transporters and with preclinical findings of increased liver enzymes. In addition, all cases include at least one additional confounding medication: RBV + either TGV (an investigational non-nucleoside NS5B inhibitor) or PEG.

Additional details of these cases are presented below.

● **Pivotal Phase 3 LDV/SOF Trials**

A single subject in the LDV/SOF+RBV 12 Week group met this laboratory definition.

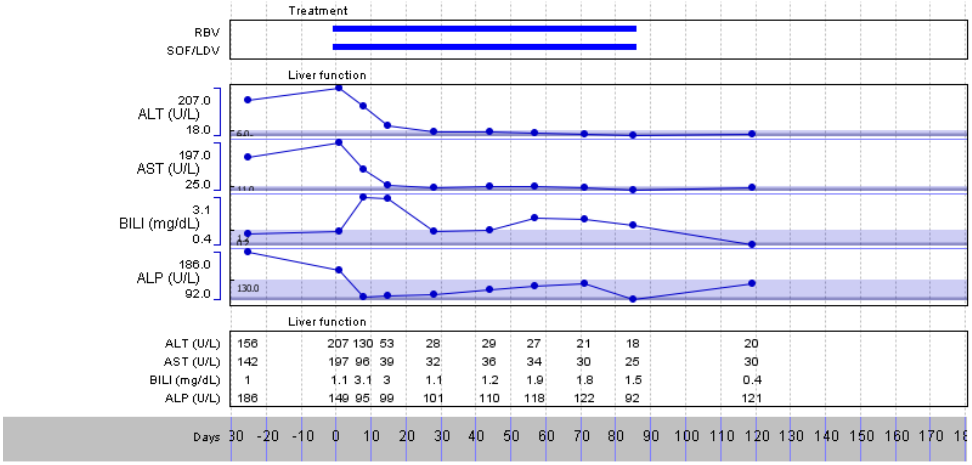
- Subject #4238-71160 (ION-1)

74 year old Caucasian man without cirrhosis experienced total bilirubin >2x ULN on Days 8 and 15 (3.1 mg/dL and 3.0 mg/dL); direct bilirubin 0.8 mg/dL and 0.7 mg/dL. ALT and AST were decreasing from baseline with normalization by Week 4. Alkaline

phosphatase was not elevated. Total bilirubin was within normal range at the Week 4 and 6 visits and then became elevated at Week 8, remaining elevated through the end of treatment to a lesser extent (i.e., <2x ULN). No signs or symptoms of liver disease, including jaundice, were reported. No additional diagnostic testing was performed to evaluate the laboratory abnormality. AEs ongoing at the time of the laboratory abnormalities included Grade 2 musculoskeletal pain, Grade 1 chromaturia, Grade 1-2 fatigue, Grade 2 cough, Grade 3 anemia, and Grade 2 chest pain. The hyperbilirubinemia was considered by the sponsor to be consistent with RBV-associated hemolysis. Total bilirubin returned to within normal range after treatment was discontinued. AST and ALT elevations at the initiation of therapy were considered by the sponsor to be consistent with the subject's pre-existing HCV disease, which normalized on therapy. Study drugs were discontinued Day 85 after completing 12 weeks of treatment per protocol. The final bilirubin value was 0.4 mg/dL at the follow-up Week 4 visit on post-treatment Day 34.

Figure 4 Subject #4238-71160 Laboratory Data

Patient #GS-US-337-0102-4238-71160	Actual Treatment for Period 01: FDC tablet (SOF 400 mg/LDV 90 mg) once daily + RBV (12 weeks)
Study Site Identifier: 4238	Region: US
Country: USA	Investigator Identifier: 4238
Age: 74	Sex: M
Race: WHITE	Ethnicity: NOT HISPANIC OR LATINO
Baseline BMI (kg/m2): 28.79035	HCV Genotype: Genotype 1a
IL28B: TT	Cirrhosis: N
Cirrhosis Determination Method: Liver Biopsy	Reason Study Not Completed:
Reason Study Drug Not Completed:	Exposure to SOF/LDV (Days): 85
Exposure to RBV (Days): 85	Exposure to Any Study Regimen (Days): 85



Source: ADLB, ADSL Datasets (ION-1)

<u>Reviewer Comment</u>: I agree with the investigator's assessment that because ALT and AST were appropriately decreasing in response to HCV treatment, as expected, and bilirubin elevations occurred in the setting of RBV, these factors do not support a case of potential liver injury in the setting of LDV/SOF use.

● **Supportive Safety Data From Phase 1/2 LDV/SOF Trials**

In the phase 2 LDV/SOF trials, no cases of AST or ALT >3x ULN and bilirubin >2x ULN are identified.

One SAE of Grade 4 ALT elevation occurred in the phase 1 trial, GS-US-337-0128, a healthy volunteer DDI trial between LDV/SOF and abacavir/lamivudine (ABC/3TC).

- Subject #7832-1020 Elevated Liver Tests, Cholecystitis

31 year old man with screening HLA-B 5701 genotype (-) began LDV/SOF and after 10 days of dosing, laboratory tests were within normal limits, Day 11 began LDV/SOF + ABC/3TC coadministration and four days later had Grade 4 ALT, Grade 2 AST, Grade 1 alkaline phosphatase along with total bilirubin 2.3 mg/dL, primarily direct (1.6 mg/dL). Afebrile with Grade 1 constipation Day 10-17 and intermittent abdominal pain Day 10-15 reported. Study treatment was discontinued and additional work up revealed normal INR; no eosinophilia; negative hepatitis A and B serologies; negative ANA, serum mitochondrial antibody screen; serum copper, ceruloplasmin, alpha1-antitrypsin within normal limits. Ultrasound and CT scans supported evidence of gallstones. Peak ALT and AST Day 20, alkaline phosphatase and bilirubin Day 15. Bilirubin and alkaline phosphatase normalized by Day 20 and AST normalized by Day 25; however, ALT remained elevated at Grade 3. Day 29 experienced an SAE of Grade 3 cholecystitis (14 days after study drug discontinuation) with Grade 3 ALT and AST. Ultrasound revealed cholelithiasis with borderline gallbladder wall thickening and positive sonographic Murphy's sign. Liver enzymes normalized following a cholecystectomy. The events were considered related to study drugs by the investigator. Of note, this subject completed Day 10 PK assessments (LDV/SOF alone) which were unremarkable; however, because the subject discontinued, there are no data for the four-drug combination.

Table 55 Selected Laboratory Tests for Subject #7832-1020

Study Day	Alanine Aminotransferase (U/L)	Aspartate Aminotransferase (U/L)	Alkaline Phosphatase (U/L)	Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)
-1	14	23	52	0.6	0.18
10	13	18	50	0.9	0.3
15	655	145	199	2.3	1.6
18	637	234	153	1.5	0.7
20	1045	418	133	1	0.5
22	908	205	124	0.6	0.3
25	356	43	92	0.3	0.2
29	268	262	108	0.6	.
41	41	15	75	0.3	0.1

Source: ADLB GS-US-337-0128

Reviewer Comment: This case occurred in a healthy volunteer in the setting of LDV/SOF and ABC/3TC coadministration. Notably, liver-related laboratory parameters were normal following 10 days of LDV/SOF, became elevated only following five days after ABC/3TC was added, and ALT, AST elevations resolved after cholecystectomy. Based on the available data, I believe this subject's presentation is most likely due to pre-existing gallstones leading to cholecystitis. An ABC/3TC-related event due to the temporal relationship is an alternative possibility. 'Liver function test abnormalities' observed in clinical trials of abacavir are included in the Epzicom label, and isolated case reports of abacavir-induced hepatotoxicity in HLA-B 5701-negative subjects have been previously reported (Soni S 2008). Thus, this case does not satisfy all the elements of Hy's Law as alkaline phosphatase was elevated and an alternative etiology exists to explain the laboratory findings.*

● Supportive Safety Data From Phase 2 Trials with LDV in Combination with Other Investigational DAAs ± RBV ± PEG/RBV

Across six phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV enrolling 1224 HCV-infected subjects, of whom 1097 received LDV-containing treatment, nine cases (0.8%, 9/1097) meeting the modified Hy's Law laboratory screening criteria are identified, including subjects receiving protocol-specified LDV/VDV+PEG/RBV retreatment. None of these subjects had baseline cirrhosis.

LDV in Combination with VDV+TGV+RBV Regimen

Two cases occur with ALT or ALT >3x ULN and bilirubin 2x ULN in subjects receiving LDV/VDV/TGV+RBV.

- Subject #2761-6380 (GS-US-248-0120)

64 year old Caucasian man with baseline ALT 34 U/L, AST 29 U/L, bilirubin 1.2 mg/dL experienced combination of ALT >3x ULN (218 U/L) and bilirubin >2x ULN (2.6 mg/dL) on Day 71. Bilirubin began to increase Week 1 (2.4 mg/dL) and between Week 2-11 ranged 2.0-3.9 mg/dL associated with direct bilirubin 0.4-0.6 mg/dL. ALT, AST increased to Grade 2 and 1, respectively, Day 64 followed by the Day 71 Grade 3 elevations. Alkaline phosphatase was normal. Mild scleral icterus was reported. Study medication continued with Day 78 decreased ALT 153 U/L (Grade 2), AST 70 U/L (<Grade 1). On Day 83 the subject discontinued due to AEs of irritability, muscle atrophy and dyspepsia. Day 85 ALT decreased to Grade 1 (85 U/L), AST <Grade 1 (51 U/L) and bilirubin 1.0 mg/dL. Creatine kinase was within normal limits. The subject achieved SVR24.

- Subject #5664-6364 (GS-US-248-0120)

50 year old Caucasian woman with history including Graves' disease with baseline ALT 194 U/L (Grade 3), AST 159 U/L (Grade 2), bilirubin 0.6 mg/dL experienced combination of ALT >3x ULN (107 U/L) and bilirubin >2x ULN (2.8 mg/dL) on Day

55. Bilirubin began to increase Week 1 (1.4 mg/dL) and between Week 2 through 12 ranged 2.2-3.6 mg/dL associated with direct bilirubin 0.4-0.5 mg/dL. The Day 55 ALT increase was associated with Grade 2 AST (74 U/L) and normal alkaline phosphatase. No signs or symptoms of liver disease were reported. Mild peripheral edema was ongoing. Study medication continued and by Day 69 ALT, AST were <Grade 1 and remained so through trial completion. The subject achieved SVR24.

Reviewer Comment: These cases are confounded by the use of RBV and two additional investigational DAAs, VDV and TGV. RBV and VDV are known to increase bilirubin due to hemolysis and due to inhibition of OATP1B1 hepatic transporters, respectively, and are supportive of the primarily indirect bilirubin elevations observed in these cases. In preclinical studies of VDV, increases in bilirubin (both direct and indirect) in rats and monkeys, and increases in AST and ALT in rats have been observed. The Applicant states TGV has been implicated in ALT elevations. Subject #2761-6380 had aminotransferase elevations beginning Day 64 that were decreasing Day 78 while remaining on study treatment prior to discontinuing Day 83. Subject #5664-6364 had asymptomatic isolated transient aminotransferase elevations that normalized while study treatment continued. While the contribution of LDV cannot be fully excluded, the presence of these coadministered drugs are significant confounders and appear to be the more likely causal agent(s).

LDV in Combination with VDV + PEG/RBV Regimen

Two subjects satisfying the modified Hy's Law definition had ALT and/or AST decreasing from baseline, likely in response to HCV treatment, associated with increased bilirubin attributed to RBV and VDV and no action was taken with respect to study drug (Subject #3054-7004, GS-US-248-0124; Subject #2463-8229, GS-US-256-0148). One subject (#1126-1343, GS-US-248-0121) had baseline Grade 1 ALT with Day 15 increase to >3x ULN (172 U/L) associated with bilirubin 2.6 mg/dL, primarily indirect. Subsequently, liver enzymes normalized and bilirubin improved to 1.5 mg/dL while on treatment.

Three subjects had ALT, AST values that generally ranged between Grade 2-3 associated with Grade 2 bilirubin while treatment continued.

- Subject #4991-3871 (GS-US-248-0131)

32 year old Caucasian man received LDV/VDV/TGV+RBV for approximately 4 weeks with improving ALT and AST values from baseline and increased bilirubin (peak 5.2 mg/dL Week 1), primarily indirect, prior to stopping for lack of efficacy and initiating LDV/VDV+PEG/RBV the following day. On re-treatment regimen bilirubin ranged 1.9-3.2 mg/dL during the first 10 weeks of therapy. ALT and AST ranged Grade 2-3 with one Week 10 Grade 4 ALT (457 U/L) prompting PEG dose reduction with subsequent improvement to Grade 3. Study treatment continued. Post-treatment Day 33 bilirubin was normal, though ALT and AST remained >3x ULN.

Concomitant medications were notable for paracetamol which is an additional potential confounder. The subject achieved SVR24.

- Subject #0482-8253 (GS-US-256-0148)

57 year old Caucasian woman had baseline Grade 2 ALT (159 U/L) and AST (107 U/L). Bilirubin increased to 3.7 mg/dL Week 1, primarily indirect and ranged 2.5-3.9 mg/dL throughout treatment. ALT increased Week 2 (172 U/L, no value for AST) and ALT, AST ranged Grade 2-3 throughout treatment with peak values Week 12 (ALT 234 U/L, AST 217 U/L). No signs or symptoms of liver disease were reported. Liver enzymes and bilirubin normalized after treatment discontinuation. The subject achieved SVR24.

- Subject #1596-8126 (GS-US-256-0148)

40 year old Caucasian man had baseline Grade 2 ALT and AST, bilirubin 1.4 mg/dL. Bilirubin increased to 3.3 mg/dL Week 1, primarily indirect and ranged 2.0-3.3 mg/dL throughout treatment. ALT increased Week 4 to >3x ULN (141 U/L) associated with AST 77 U/L. ALT ranged 85-141 U/L between Weeks 4-16 on treatment, followed by normalization. No signs or symptoms of liver disease were reported. Bilirubin normalized after treatment discontinuation. The subject achieved SVR24.

One additional case is described in further detail:

- Subject #0526-1282 (GS-US-248-0121)

60 year old Black man with baseline bridging fibrosis and ALT 64 U/L, AST 73 U/L, bilirubin 0.4 mg/dL, alkaline phosphatase 48 U/L experienced combination of AST >3x ULN (327 U/L) and bilirubin >2x ULN (2.6 mg/dL) on Day 58. Bilirubin began to increase Week 1 (2.2 mg/dL) through Week 2 with direct bilirubin 0.5-0.6 mg/dL. RBV was stopped Day 21 due to anemia and subsequently bilirubin normalized Week 4-6 prior to increasing on Day 58 associated with direct bilirubin 1.2 mg/dL. AST began to increase Day 29 (Grade 1) with continued elevation peaking Day 58 (Grade 3) and associated with Grade 2 ALT (106 U/L) on that day. Alkaline phosphatase was 1.1x ULN (138 U/L), and noted to have nearly doubled from the preceding value of 76 U/L on Day 44. The narrative states jaundice was the only reported sign or symptom of liver disease. No new concomitant medications were reported. Study medication was discontinued Day 65 due to these events. Liver enzymes remained elevated post-treatment Day 6 with AST 460 U/L (Grade 4), ALT 111 U/L (Grade 2), bilirubin 8.1 mg/dL (Grade 4), direct bilirubin 4.4 mg/dL, prothrombin time normal. No additional diagnostic testing was performed. By post-treatment Day 29, liver enzymes normalized (AST 44 U/L, ALT 18 U/L), alkaline phosphatase was 69 U/L, and bilirubin improved to 1.4 mg/dL with direct bilirubin 0.8 mg/dL. The subject achieved SVR24.

Reviewer Comment: This case of aminotransferase and bilirubin elevation, with resolution following study medication (positive dechallenge) is supportive of a drug-related event; however, the concomitant use of VDV and PEG, and to a lesser

extent, RBV, confounds causality assessment. Marked elevations in ALT levels (5- to 10-fold above the upper limit of normal) have been reported in one percent of subjects during treatment and follow-up in hepatitis C trials for Pegasys. Transient elevations in ALT (2- to 5-fold above baseline) were observed in 10% of subjects treated with PegIntron, and were not associated with deterioration of other liver functions (Reference: USPI for Pegasys and PegIntron).VDV is known to increase bilirubin due to inhibition of OATP1B1 hepatic transporters. In preclinical studies, increases in bilirubin (both direct and indirect) in rats and monkeys, and increases in AST and ALT in rats have been observed. While the contribution of LDV cannot be fully excluded, the presence of these coadministered drugs are significant confounders.

The Applicant was queried for their assessment of cases satisfying the modified Hy's Law definition in the phase 2 LDV-containing development program. The response received July 3, 2014 states:

> In summary, subjects receiving VDV+RBV-containing regimens frequently experienced hyperbilirubinemia. Concomitant on-treatment increases in ALT or AST > 3x ULN were infrequent and were observed in the presence of Peg-IFN or TGV coadministration with LDV. These data, in the context of the LDV safety database with sofosbuvir, do not suggest LDV-related hepatotoxicity.

Reviewer Comment: The nine cases in the phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV are confounded by VDV use in all cases, an investigational DAA known to increase bilirubin due to inhibition of OATP1B1 hepatic transporters and with preclinical findings of increased liver enzymes. In addition, all cases include at least one additional confounding medication: RBV plus either TGV (an investigational non-nucleoside NS5B polymerase inhibitor) or PEG. I agree with the Applicant's assessment that the totality of the data does not suggest LDV-related hepatotoxicity in these phase 2 cases.

(2) Stopping Rules Utilized within LDV/SOF Phase 3 Trials

The phase 3 LDV/SOF protocols had the following liver-related stopping rules:

- Confirmed elevation of ALT or AST > 5x Day 1 (baseline) value or nadir
- Confirmed elevation of ALT >3x Day 1 (baseline) value and total bilirubin > 2x ULN
- Confirmed elevation of ALT >15x ULN

No subject in the phase 3 trials met these liver-related stopping rules during the on-treatment phase.

(3) Grade 3/4 Liver Enzyme Elevations within LDV/SOF Phase 3 Trials

Most ALT and AST graded laboratory elevations occurring in the LDV/SOF phase 3 trials are ≤Grade 2. The Grade 4 ALT and AST increase in the LDV/SOF 12 week arm

occur in Subject #0334-71474 (acute hepatitis) reviewed above. One Grade 4 increase in ALT and AST in the LDV/SOF+RBV 8 week arm (Subject #4308-73436, ION-3) occurred post-treatment Day 29 and is attributed to levofloxacin which was taken post-treatment Day 22-31 for sinus infection. On post-treatment Day 35 liver enzymes were <Grade 1 and the subject was asymptomatic. The investigator attributed the laboratory abnormalities to the concomitant medication levofloxacin.

Reviewer Comment: I agree with the investigator's assessment given the temporal association with levofloxacin use which has a labeled warning and precaution for hepatotoxicity and has labeled adverse reactions of increased hepatic enzymes.

In the phase 3 trials, treatment-emergent Grade 3 ALT or AST occurred in four subjects. Two cases are isolated events suspected to be laboratory error as the values were normal upon retesting within ≤3 days (Subject #7393-79346, LDV/SOF 24 Week, ION-2; Subject #4009-79336, LDV/SOF 12 Week, ION-2). Two additional subjects had isolated transient Grade 3 AST increases:

- An isolated transient Grade 3 increased AST was reported for one subject (Subject #0330-71328, ION-1) in the LDV/SOF 24 Week group with baseline AST 44 U/L that increased to a Grade 3 level (219 U/L) at Week 2 (Day 16) associated with Grade 2 ALT (189 U/L), normal bilirubin (0.6 mg/dL) and was within normal range at Week 4 and all subsequent visits. It is noted that heroin use was reported Day 13 which may be a contributory factor.
- Grade 3 increases in AST were reported in 1 subject in the LDV/SOF 24 Week group. Subject #0529-79314 had elevated AST values at screening, baseline, and Week 1 (51-79 U/L, Grade 1), with an isolated transient increase to 281 U/L (Grade 3) on Day 14. Upon retesting 7 days later, AST was 46 U/L (Grade 1), and then decreased and remained within the normal range through post-treatment Week 4.

Reviewer Comment: These isolated, transient liver enzyme increases, including one confounded by heroin use, do not raise significant concern for serious hepatotoxicity associated with LDV/SOF use.

Two other subjects had non-treatment emergent, post-baseline ALT elevations. The events are not captured in the laboratory table because Grade 3 ALT was present at baseline and thus not satisfying the treatment-emergent definition.

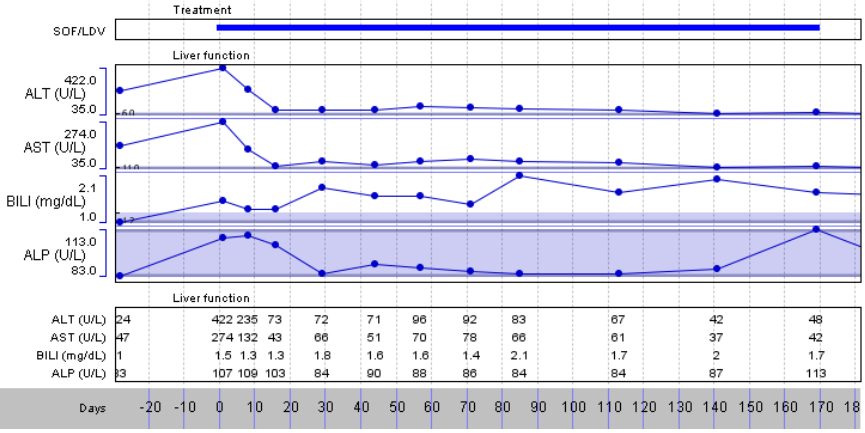
- Subject #6833-79354 (LDV/SOF 24 week, ION-2)

  65 year old Caucasian man without cirrhosis experienced Grade 3 ALT elevation Day 8 (235 U/L). Note, ALT had declined from a baseline value of 422 U/L and is considered to reflect response to HCV treatment. Total bilirubin was elevated at baseline (1.5 mg/dL) and mildly elevated on Day 8 (1.3 mg/dL). ALT, AST, and total bilirubin remained mildly elevated throughout treatment, albeit to a lesser extent (< 3x ULN for ALT and AST and < 2x ULN for bilirubin); direct bilirubin remained within normal range. No signs or symptoms of liver disease, including jaundice, were

reported. No additional diagnostic testing was performed to evaluate the laboratory abnormality. Grade 1 rash occurred Day 58 without associated eosinophilia ($0.1x10^3$/µl Day 54, 71). No new concomitant medications were reported ongoing at the time of the laboratory abnormality. The occurrence of ALT >5x ULN at baseline and on treatment were considered by the Applicant as a natural progression in ALT decline, with minor fluctuations, after initiating antiviral treatment. The study drugs were discontinued Day 169 after completing 24 weeks of treatment per protocol. The final ALT value was 35 U/L at the follow-up Week 4 visit on post-treatment Day 28.

Figure 5 Subject #6833-79354 Laboratory Data

Patient #GS-US-337-0109-6833-79354	Actual Treatment for Period 01: FDC tablet (SOF 400 mg/LDV 90 mg) once daily for 24 weeks
Study Site Identifier: 6833	Region: US
Country: USA	Investigator Identifier: 6833
Age: 65	Sex: M
Race: WHITE	Ethnicity: NOT HISPANIC OR LATINO
Baseline BMI (kg/m2): 27.382183	HCV Genotype: Genotype 1a
IL28B: CC	Cirrhosis: N
Cirrhosis Determination Method: Liver Biopsy	Reason Study Not Completed:
Reason Study Drug Not Completed:	Exposure to SOF/LDV (Days): 169
Exposure to RBV (Days): .	Exposure to Any Study Regimen (Days): 169



Source: ADLB, ADSL Datasets (ION-2)

Reviewer Comment: The initial liver enzyme pattern reflects response to antiviral treatment. The transient Grade 1 ALT and AST elevations between Week 8-10 are less well explained; however, the subject remained on treatment with normalization. The Grade 1-2 bilirubin fluctuation, primarily indirect, is also less well explained. LDV is primarily eliminated through biliary excretion which is supportive of a potential causal relationship. A recommendation is made to include bilirubin information in product labeling.

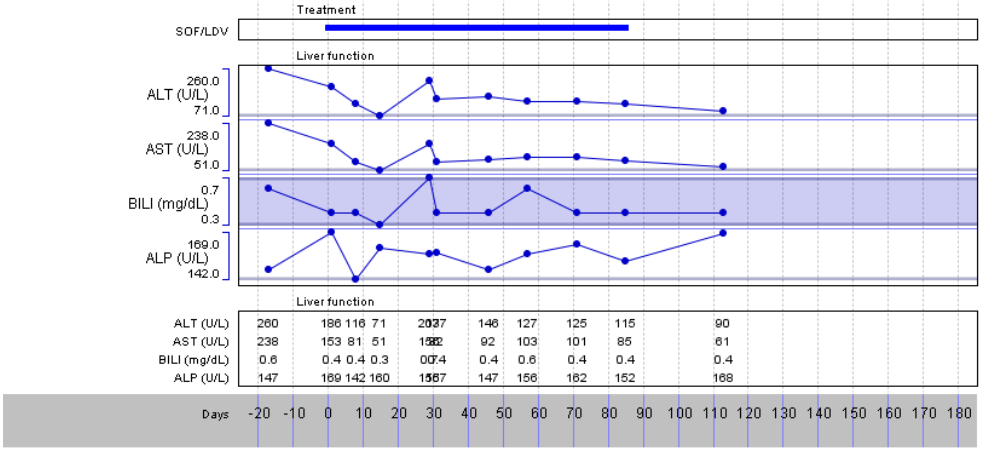
- Subject #3054-79014 (LDV/SOF 12 week, ION-2)

45 year old Hispanic woman with cirrhosis and prior PI+PEG/RBV failure experienced ALT >5X ULN Day 29 associated with AST 4.6x ULN and Alk phos 1.5x ULN. Total bilirubin was normal (peak 0.7 Day 29). ALT remained elevated throughout treatment, though to a lesser extent (i.e., <5x ULN). No signs or symptoms of liver disease, including jaundice, were reported. No additional

diagnostic testing was performed to evaluate the laboratory abnormality. No AEs were ongoing and no new concomitant medications were reported at the time of the laboratory abnormality. The elevated ALT was considered by the sponsor to be of unknown etiology. The study drugs were discontinued on 22 April 2013 (Day 85) after completing 12 weeks of treatment per protocol. The final ALT value was 90 U/L at the follow-up Week 4 visit on post-treatment Day 28. This subject achieved SVR12.

Figure 6 Subject #3054-79014 Laboratory Data

Patient #GS-US-337-0109-3054-79014	Actual Treatment for Period 01: FDC tablet (SOF 400 mg/LDV 90 mg) once daily for 12 weeks
Study Site Identifier: 3054	Region: US
Country: USA	Investigator Identifier: 3054
Age: 45	Sex: F
Race: WHITE	Ethnicity: HISPANIC OR LATINO
Baseline BMI (kg/m2): 31.445312	HCV Genotype: Genotype 1a
IL28B: CT	Cirrhosis: Y
Cirrhosis Determination Method: Liver Biopsy	Reason Study Not Completed:
Reason Study Drug Not Completed:	Exposure to SOF/LDV (Days): 85
Exposure to RBV (Days): .	Exposure to Any Study Regimen (Days): 85



Source: ADLB, ADSL Datasets (ION-2)

Reviewer Comment: This isolated >5x ULN increase in ALT with bilirubin remaining in the normal range occurred in a subject with cirrhosis, in the absence of clinical symptoms and while LDV/SOF continued which do not raise significant concern for serious hepatotoxicity associated with LDV/SOF use.

(4) Bilirubin Elevations within LDV/SOF Phase 3 Trials

Overall graded bilirubin elevations occur 4-7% across the LDV/SOF 8, 12 and 24 week durations with all but one reported event ≤Grade 2. A single subject receiving LDV/SOF had a Grade 3 increased total bilirubin; this subject had a history of Gilbert's syndrome. All other Grade 3 or 4 increases in total bilirubin occurred in RBV-treated subjects. No significant differences in ALT, AST or bilirubin graded laboratories are identified between the cirrhotic and non-cirrhotic LDV/SOF alone arms in ION-1 and ION-2.

Reviewer Comment: Inclusion of bilirubin laboratory data in the LDV/SOF product label is recommended. LDV is primarily eliminated through biliary excretion which is supportive of a potential causal relationship.

Summary of Hepatic Events

Based upon review of the available data, I do not believe a causal relationship between LDV/SOF use and hepatotoxicity is established at this time and thus do not believe labeling for hepatotoxicity is supported. We will continue to monitor closely in the postmarketing setting for any potential signals of hepatotoxicity. Bilirubin laboratory data is recommended to be included in the LDV/SOF product label.

Gallbladder Events

LDV is primarily eliminated through biliary excretion; therefore, an assessment of gallbladder-related events was performed. Preclinical data do not support formation of gallstones. In mice and rats, hepatobiliary findings including slight increased alkaline phosphatase, ALT, increased gallbladder weights without corresponding histopathology findings, and bile duct hyperplasia were detected at doses ~8-30 times the estimated human LDV exposure and were not considered adverse. No pertinent findings were detected in dogs.

In the phase 3 LDV/SOF trials, one case of treatment-emergent cholecystitis and two cases of common bile duct stone are reported (0.2%, 3/1952 subjects). Two of these cases occur in subjects with a prior history of cholelithiasis. Three non-treatment-emergent cases of cholecystitis occur between approximately 6 weeks and 4 1/2 months after trial completion, including two cases in subjects with a prior history of cholelithiasis. All reported events are considered unrelated to study drug. As background, it is noted that within the phase 3 population, 11.7% (229/1952 subjects) are reported to have a prior history of gallstones and/or cholecystitis (defined as presence of any of the following terms: cholecystitis, cholecystitis chronic, cholelithiasis, cholecystectomy, cholelithotomy).

- Subject #2012-71362 (LDV/SOF+RBV 12 Week, ION-1)
  41 year old Caucasian man experienced Grade 2 bile duct stone Day 41, associated with transient, isolated ALT increase to 191 U/L, alkaline phosphatase 119 U/L (>2x increase from Day 29), bilirubin 1.5 mg/dL. AST was normal. Study treatment continued, liver tests normalized and the event was considered not related to study drug.

- Subject #2130-73381 (LDV/SOF 12 Week, ION-3)
  43 year old Caucasian man with a history of cholelithiasis experienced Grade 3 common bile duct stone Day 2 (SAE) associated with abdominal pain that was present at randomization. Imaging revealed common bile duct stone with gallstones, without evidence of cholecystitis. Day 1 Alkaline phosphatase <Grade 1, ALT and

AST Grade 3, bilirubin Grade 4 (7.3 mg/dL). Endoscopic retrograde cholangiopancreatography and sphincterotomy were performed, removing a single common bile duct stone. The subject recovered and the following day was discharged home. ALT, AST normalized by Day 13, Bilirubin continued to improve with normalization Day 26. The event was considered not related to study drug by the investigator.
Reviewer Comment: I agree with the investigator's assessment. Occurrence on Day with presence of gallstones on imaging supports a pre-existing condition.

- Subject #4007-79145 (LDV/SOF+RBV 24 Week, ION-2)

55 year old Caucasian woman with a history of cholelithiasis experienced Grade 2 cholecystitis, initially presenting as abdominal pain, Day 120-128, which increased to Grade 3 Day 129 (latter SAE). Imaging studies detected cholelithiasis and gallbladder changes suggestive of cholecystitis. The subject underwent cholecystectomy and recovered Day 130. The event was considered not related to study drug by the investigator.

- Subject #4435-71818 (LDV/SOF 12 Week, ION-1) *Non-treatment emergent*

62 year old Caucasian woman with history of cholelithiasis experienced cholecystitis Day 220, approximately 4 1/2 months following treatment completion. She underwent cholecystectomy and recovered two days later. The event was considered not related to study drug by the investigator.

- Subject #5847-73044 (LDV/SOF 8 Week, ION-3) *Non-treatment emergent*

60 year old Caucasian man with experienced Grade 3 cholelithiasis (SAE) associated with acute abdominal pain on Day 100, approximately six weeks following treatment completion. Ultrasound detected blockage of the common bile duct due to a gallstone, and the subject underwent cholecystectomy. The event resolved Day 102 and was considered not related to study drug by the investigator.

- Subject #0529-79340 (LDV/SOF 12 Week, ION-2) *Non-treatment emergent*

56 year old Caucasian man with a history of cholelithiasis and gallbladder sludge experienced Grade 3 cholecystitis (SAE) Day 165, approximately 2 1/2 months following treatment completion, and underwent cholecystectomy. The event resolved Day 166 and was considered not related to study drug by the investigator.

The SUR includes one case of cholelithiasis associated with Grade 4 lipase.

- Subject #4021-88036 (LDV/SOF, GS-US-337-0121)

52 year old Caucasian man with history of cholelithiasis, intermittent right upper quadrant abdominal pain and baseline Grade 3 increased lipase. At Week 2, the subject had Grade 4 increased lipase (2135 U/L) coincident with Day 21 SAE of cholelithiasis. Underwent cholecystectomy and recovered Day 36. The event was considered not related to study drug by the investigator. Study drug administration was not interrupted. Lipase values remained elevated (≥ Grade 2) through Week 12,

the subject's most recent visit as of the cutoff date, although the narrative states lipase was returning to normal.

In the supportive phase 2 LDV/SOF trials, one case of cholelithiasis with biliary colic occurred Day 32 in a LDV/SOF+RBV-treated 66 year old female subject (Subject #1069-5588, ELECTRON) who has risk factors of gender and obesity. Study medications continued and this subject underwent cholecystectomy and recovered. In the supportive phase 2 trials with LDV in combination with other investigational DAAs ± RBV ± PEG/RBV one case occurs in a LDV+PEG/RBV-treated male subject (Subject #2108-8317, GS-US-256-0148) less than two days after study drug initiation with evidence of gallstone present on imaging.

In phase 1, a healthy volunteer (Subject #7832-1020) experienced increased liver enzymes, alkaline phosphatase, bilirubin 15 days after receiving daily LDV/SOF and 5 days after receiving LDV/SOF+ABC/3TC. Ultrasound showed cholelithiasis. All study drugs were stopped with some laboratory improvement; however, less than two weeks later the subject experienced cholecystitis and underwent cholecystectomy. Pathology of the gallbladder revealed chronic cholecystitis with cholelithiasis and no specific pathologic changes in the lymph node. LDV/SOF exposures Day 10 (prior to ABC/3TC) were not elevated, further drug levels were not measured (Please refer to Section 7.3.5 Hepatic Events for additional details).

Reviewer Comment: Overall, reported cases of cholecystitis and cholelithiasis are infrequent among subjects receiving LDV/SOF or LDV-containing regimens, with only three treatment-emergent cases occurring in the phase 3 LDV/SOF trials (0.2%). The case in a healthy volunteer has features suggesting pre-existing disease (e.g., cholelithiasis documented less than three weeks on study drug, lack of acute gallbladder pathology findings). LDV is excreted primarily via biliary excretion which may provide a possible causal relationship between LDV/SOF use and gallbladder-related events; however, these cases more likely represent background incidence of gallstones and cholecystitis. In the US population, the prevalence of gallstones in persons 40-60 years old ranges approximately 8-12% and 6-7% in women and men, respectively. Between 30-39 years, the prevalence of gallstones is 5.2% and 1.1% in women and men, respectively (Everhart JE 1999). In the HCV-infected population, a higher incidence of gallstones has been reported, particularly with factors such as cirrhosis, female sex, obesity and older age. In addition, among patients with cirrhosis and gallstones, female sex and advanced age have been identified as risk factors for developing symptomatic gallstone disease (Acalovschi M 2003; Acalovschi M 2009; Bini EJ 2005; Stroffolini T 2007). These factors are consistent with the observation that within the phase 3 LDV/SOF population, approximately 12% subjects are reported to have a prior history of gallstones and/or cholecystitis. The Applicant was queried for their assessment between LDV/SOF use and cholelithiasis, cholecystitis events. The response received July 3, 2014 includes their assessment that there is no evidence for LDV/SOF-related cholelithiasis and cholecystitis.

Thus, based on the currently available information, an obvious causal association between LDV/SOF use and cholelithiasis and/or cholecystitis is not identified at this time and I do not believe labeling for cholelithiasis and/or cholecystitis events is supported. Any potential signals will continue to be monitored in the postmarketing setting.

Myocardial Ischemia Events

A summary of myocardial ischemia events was requested to be included in the SUR. Of 3264 subjects evaluated, 9 subjects (0.3%) had myocardial ischemia events as listed in Table 56. The two myocardial ischemia SAEs considered related to study drug occur in the Japanese -0113 trial and are confounded by alternate causalities (e.g., suspected infection) and/or preexisting conditions (e.g., baseline RBBB, diabetes). The majority of the other reported cases have known or risk factors for preexisting coronary artery disease. Most subjects did not require LDV/SOF discontinuation.

Table 56 Subjects with Myocardial Ischemia Events in LDV/SOF Trials

Trial **Arm** **Subject ID**	**Dictionary-Derived Term**	**Start/Stop Day**	**SAE**	**Related**	**Action**	**Outcome**	**Cardiac RFs**
GS-US-337-0102							
LDV/SOF+RBV							
2130-71707	Myocardial Infarction, Cardiac Arrest, Ischemic Cardiomyopathy	PT Day 92	Yes	No	N/A	Resolved	No
Refer to Section 7.2.6 for narrative information							
GS-US-337-0108							
LDV/SOF							
0451-73265	Angina Pectoris	PT Day 13	No	No	N/A	Resolved	No
61 year old Caucasian woman with history including Graves' disease. Day 3 developed Grade 1 chest pain considered unrelated to study mediation which resolved Day 29 without medication. LDV/SOF treatment completed Day 86. On post-treatment Day 13 Grade 2 angina pectoris was reported. Received treatment with IV glyceryl trinitrate and began acetylsalicylic acid. The event resolved the same day and was considered unrelated to study medication.							
GS-US-337-0109							
LDV/SOF							
2493-79317	Angina Unstable	152 / 154	Yes	No	No Change	Resolved	Yes
65 year old man of African descent with history including coronary artery disease, hypertension, hyperlipidemia, stent placement to RCA (2005), and myocardial infarction (2006). Day 152 experienced sudden onset of unstable angina while exercising following three week history of intermittent angina. Cardiac enzymes and ECG did not indicate myocardial infarction. Nuclear stress test showed anteroapical ischemia. Received treatment with aspirin and Lopressor.							

Cardiac catheterization revealed 90% stenosis involving the proximal and mid left anterior descending artery. Coronary angioplasty with stent placement was performed with no complications. A repeat angiography showed residual stenosis just distal to the stenting. The unstable angina resolved and he was discharged home on Day 154. Discharge diagnosis was coronary atherosclerosis. Study medication continued and the investigator assessed the event as not related to the study drug.							
GS-US-337-0113 (safety data submitted with SUR: not part of original NDA)							
LDV/SOF+RBV							
8314-86263	Cardiac Arrest	63 / 64	Yes	Yes	N/A	Death	Yes
67 year old Asian man with history including cirrhosis, diabetes, right bundle branch block, pulmonary fibrosis, sarcoidosis, splenectomy. Day 63 experienced nausea, vomiting, diarrhea and fever. LDV/SOF+RBV discontinued. The following day, symptoms persisted and that evening he complained of inability to rise, loss of vision and stiffness, followed by loss of consciousness and cardiac arrest. Resuscitation failed and he was pronounced dead, no autopsy was performed. The investigator assessed the event to be related to LDV/SOF+RBV. The investigator reported, "Relationship between sudden death and investigation drugs seems to be low. Most probable explanation is viral GI infection and cardiac attack."							
8322-86046	Acute Myocardial Infarction	PT Day 9 / 40	Yes	Yes	N/A	Ongoing	Yes
71 year old Asian man with history including ex-smoker (10 cigarettes/day x 50 years until one year ago). Screening ECG with left ventricular hypertrophy and possible left atrial enlargement, abnormal Q waves in leads III and aVF assessed as normal variations. Baseline ECG with complete right bundle branch block (RBBB) and suggestion of inferior myocardial infarction. Completed study treatment and at Week 12 visit had decreased hemoglobin of 12.8 g/dL (screening 16.8 g/dL). Post-treatment Day 9 experienced acute myocardial infarction. Cardiac ultrasound revealed significant aortic valve insufficiency, decreased contractility near the basal aspect of the septum. Cardiac catheterization revealed 100% stenosis of left anterior descending artery, 99% stenosis in the right coronary artery. Angioplasty performed with stent insertion in the left anterior descending. During the procedure, intubated for decreased oxygenation. Subsequently treated for presumed aspiration pneumonia, extubated post-treatment Day 15. Repeat cardiac ultrasound with slight cardiac effusion; no valvular abnormality other than previously observed moderate aortic regurgitation. Post-treatment Day 37 underwent percutaneous coronary intervention with stent and dilatation of right coronary artery. Discharged post-treatment Day 40 after event of acute MI resolved. The investigator assessed the event related to LDV/SOF+RBV and commented that decreased hemoglobin caused by RBV may have been a contributing factor. The Applicant states the extensive coronary artery disease noted at the time of the event and the new RBBB at baseline suggests coronary artery disease had its onset prior to study enrollment.							
GS-US-337-0122 (safety data submitted with SUR: trial arm not part of original NDA)							
LDV/SOF+RBV							
1069-77012	Angina Pectoris	71 / 89	Yes	No	D/C RBV	Resolved with Sequelae	Yes
68 year old Caucasian man with history including myocardial infarction with coronary artery stenting (2000), hypertension, chest pain and moderate three vessel disease (2006), gastroesophageal reflux disease, hyperlipidemia, paroxysmal atrial fibrillation, ex-smoker (>15 years). Day 71 experienced chest pain and shortness of breath, ECG showed atrial fibrillation							

with transient lateral ST depression. Atrial fibrillation reverted spontaneously to sinus rhythm. RBV was permanently discontinued (Hgb 10.9 g/dL), LDV/SOF continued. Day 75 angiogram showed mild left anterior descending, severe obtuse marginal and severe diffuse right coronary artery disease with a normal EF. Day 84 underwent a coronary artery bypass x3. Day 89 the event of ischemic chest pain resolved with sequelae and the subject was discharged to cardiac rehabilitation. The investigator assessed the event as not related to study drugs.							
GS-US-337-0123 (safety data submitted with SUR: not part of original NDA)							
LDV/SOF+RBV							
1249-75309	Myocardial Infarction	PT Day 41	Yes	No	N/A	Resolved with Sequelae	Yes
65 year old man with history including diabetes, hypertriglyceridemia, immunosuppression (tacrolimus, mycophenolate mofetil), family history of MI. Post-treatment Day 41 experienced NSTEMI. Received two drug eluting stents to two culprit left descending artery lesions. Right coronary artery disease treated staged percutaneous coronary intervention. He was also noted to have congestive heart failure with EF 40% and anterioapical hypokinesis. The event was considered resolved with sequelae the same day, and the subject was discharged post-treatment Day 45. The investigator assessed the event as not related to study medication.							
GS-US-337-0125 (safety data submitted with SUR: not part of original NDA)							
LDV/SOF							
0773-80002	Acute Myocardial Infarction	19 / 21	Yes	No	nterrupt LDV/SOF 2 days	Resolved	Yes
60 year old Caucasian woman with history including hypertension, diabetes, hypercholesterolemia, atrial fibrillation, Sjogren's vasculitis, coronary artery disease, multiple myocardial infarctions, chest pain. Day 19 experienced NSTEMI associated with substernal chest pain. Cardiac catheterization showed single vessel disease with successful PTCA of circumflex, obtuse marginal. Echocardiogram EF 40-45%, severe inferior and lateral wall hypokinesis, trace mitral regurgitation thought to be likely ischemic, trace tricuspid regurgitation and Grade 1 diastolic dysfunction. Study drug interrupted Day 20-21. Discharged home Day 21 after recovered from the event. The investigator assessed the event as not related to study drug.							
GS-US-337-0133 (safety data submitted with SUR: not part of original NDA)							
LDV/SOF+GS-9669*							
2760-84272	Acute Myocardial Infarction	12 / 16	Yes	No	No Change	Resolved	Yes
61 year old man with history including hepatic steatosis, cirrhosis, diabetes, coronary artery disease, myocardial infarction, cardiac stent replacement, coronary artery bypass grafting, hypertension, alcohol use, illegal substance use-marijuana, smoker. Day 11 experienced chest pain with recurrence Day 12 and diagnosed with NSTEMI. Underwent cardiac angiogram times two for cardiac artery disease intervention and stent placement. Discharged Day 16 after the event was considered resolved. Study drugs continued and the investigator assessed the event as not related to study drugs.							

PT-post treatment
*GS-9669 is an investigational non-nucleoside NS5B inhibitor
Source: NDA 205834 Safety Update Report

Reviewer Comment: Less than 0.3% of >3200 LDV/SOF-treated subjects experienced myocardial ischemia events. Based upon the currently available data, a causal relationship between LDV/SOF use and myocardial ischemia is not established at this time and thus I do not believe labeling for myocardial ischemia is supported. Cases of myocardial ischemia will be monitored in the postmarketing setting.

Rash Events

Rash is reported with RBV use and an analysis of rash events was performed to evaluate a potential causal association with LDV/SOF-containing treatment. An analysis of rash events in the LDV/SOF phase 3 trials pooled the following terms: rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular (Table 57). The overall incidence of rash events (all cause) and treatment-related rash events is 8.8% and 6.5%, respectively. A lower percentage of treatment-related rash events occurs in the LDV/SOF pooled arms than in the RBV-containing pooled arms (2.9% versus 11.0%, respectively). All events are ≤Grade 2, no SAEs occur and no subject discontinued LDV/SOF due to a rash event.

Median time to onset is generally similar across treatment durations within the respective LDV/SOF and LDV/SOF+RBV groups. The RBV-containing arms have earlier median rash onset in the 8 and 12 week groups (26-28 days) compared with the other treatment groups (38-43 days). Three-quarters of events have onset within the first 8 weeks (75%, defined as onset ≤Study Day 63), and 91% have onset within the first 12 weeks (defined as onset ≤Study Day 98).

Table 57 Pooled Rash Events, Treatment-Emergent, LDV/SOF Phase 3 Integrated Safety Population

	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
All Grades, n (%)	4 (2%)	26 (5%)	23 (7%)	21 (10%)	45 (14%)	53 (16%)
Maximum Grade						
Grade 1, n (%)	3 (1%)	24 (4%)	21 (6%)	19 (9%)	40 (12%)	49 (15%)
Grade 2, n (%)	1 (<1%)	2 (<1%)	2 (1%)	2 (1%)	5 (2%)	4 (1%)
Related events, n (%)	2 (1%)	14 (3%)	15 (5%)[1]	18 (8%)	35 (11%)	43 (13%)
Time to onset of first event, days – median (range)[2]	38.5 (22-71)	43 (2-93)	38 (1-157)	28 (1-56)	26 (1-99)	40 (1-190)

[1]The calculated percentage is 4.6% (15/326 subjects)
[2]Includes subjects experiencing a rash event with available onset study day
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

The SUR reports one LDV/SOF+RBV discontinuation due to Grade 2 treatment-related morbilliform rash on Day 6 occurring in the Japanese trial, GS-US-337-0113. The rash resolved post-treatment Day 9.

The phase 1 and phase 2 LDV-containing trials were examined for notable rash events. One healthy subject discontinued study drugs due to maculopapular rash in the drug-drug interaction trial, GS-US-344-0102. This subject received darunavir/ritonavir (DRV/r) for 10 days. On Day 11 LDV was added and on the same day the subject developed a Grade 2 maculopapular rash. Study drugs were discontinued and the rash resolved. The investigator considered the event related to DRV/r.

Reviewer Comment: The investigator's assessment seems reasonable as DRV/r is labeled for rash events; however, LDV does have a temporal associated in this case and its relationship to the event cannot be entirely excluded.

One subject receiving LDV+PEG/RBV discontinued study drugs due to rash on Day 208. Three SAEs occurred in subjects receiving LDV+VDV (an investigational PI) +PEG/RBV, including two events considered related to study treatment (rash/leg ulcer, cutaneous rash/foot drop). Two subjects discontinued study treatment due to rash, both considered related to study treatment by the investigator (Grade 2 rash generalized, Grade 3 rash). The following notable event of cutaneous rash, foot drop is described further:

- Subject #4009-3727 Cutaneous rash, foot drop (GS-US-248-0131)

51 year old Caucasian man completed 4 weeks LDV+VDV+RBV and started LDV + VDV + PEG/RBV rescue treatment. Day 48 (Day 69 total therapy) experienced upper extremity rash associated with pruritus, treated with topical steroids. On Day 55 the skin eruption involved almost 60-70% of his body surface area without mucosal involvement, and study drugs were discontinued. Day 57 punch biopsy demonstrated spongiotic dermatitis with numerous eosinophils, suggestive of medication reaction. Other differential diagnoses included atopic dermatitis and hypersensitivity spongiotic dermatitis. Result to the direct immunofluorescent study of the skin biopsy sample was negative. Oral steroids were given Day 55-67 with some improvement. Day 69 experienced worsening of rash and was re-initiated on prednisone therapy. Concomitant medication sulindac/aspirin discontinued.

Day 74 he developed right foot paresthesia and motor dysfunction and diagnosed with neurosensory weakness with right foot drop and neurosensory alteration with polyneuritis. Electromyography of the right leg was abnormal with evidence of widespread demyelination and limited axonal compromise, consistent with an immune-mediated multifocal acquired demyelinating motor and sensory neuropathy.

The rash was slow to resolve, with episodes of improvement along with episodes of progression including one associated with oral ulcers. Day 80 skin biopsy of the left thigh showed subacute spongiosis with scattered dyskeratotic keratinocytes and a moderately dense superficial dermal perivascular and interstitial infiltrate of lymphocytes and eosinophils. This histologic finding was compatible with a drug hypersensitivity reaction; the density of inflammation and presence of perakeratosis makes erythema multiforme much less likely. Steroid treatment continued along with loratadine, topical steroids and UVB ultraviolet light. Right eyelid droop developed Day 103 which progressed over the next 2 weeks. Myasthenia gravis was excluded as a diagnosis and Horner's syndrome was suspected. The cutaneous rash resolved after 115 days (Day 162) and the right foot drop resolved after 179 days (Day 254).

Reviewer Comment: This serious case is confounded by PEG/RBV use which has a labeled warning and precaution for serious skin reactions and is the more likely the causative factor in this event. Peripheral neuropathy is a labeled warning and precaution for interferon use and interferon may be causal for the subject's neurologic events. VDV is an investigational HCV PI and numerous PIs have been associated with rash, some severe, which is an additional confounder.

The Applicant was queried for their assessment of rash events occurring in the LDV/SOF development program. Their response received May 21, 2014 is summarized in this section. They identify a greater frequency of rash events in subjects taking LDV/SOF+RBV (11.3%, 180/1595 subjects) compared with LDV/SOF without RBV (4.4%, 66/1514 subjects). The majority of the rash AEs are Grade 1 or Grade 2 and reported as not related to study drug. A search for events that are both clinically

significant (defined as Grade 3 or 4 AEs or SAEs) and treatment related identified no cases. The Applicant's assessment is "that the Phase 2 and Phase 3 data analysis suggests that LDV/SOF is unlikely to be a causal factor in cases of rash."

Reviewer Comment: In subjects receiving LDV/SOF, treatment-emergent, treatment-related rash events are infrequent (6.5% overall and 2.9% limited to the pooled LDV/SOF alone arms). No LDV/SOF duration treatment arm meets the treatment-emergent, treatment-related, all grade 5% cutoff for inclusion in the label. All rash events in the phase 3 trials are ≤Grade 2, and no SAEs or discontinuations due to rash event occur. The phase 1 event has an alternative etiology of DRV/r. SAEs in phase 2 LDV-containing program are confounded by concomitant use of PEG, RBV. Based on the totality of the available data, I agree with the Applicant's assessment that LDV/SOF is unlikely to be a causal factor in cases of rash and do not believe labeling for rash is supported at this time. Serious rash events will be monitored postmarketing.

Hypersensitivity, Anaphylaxis, Angioedema, Swollen Tongue Events

In the LDV/SOF phase 3 trials, one subject each experienced treatment-emergent events of hypersensitivity, anaphylactic reaction and swollen tongue. These cases are described in more detail:

- Subject #2024-71260 (LDV/SOF+RBV, ION-1) Hypersensitivity

  40 year old Caucasian man experienced Grade 1 allergic reaction on his hands Day 96-110 due to exposure to construction materials at work. Study medications continued and the event was not considered related to study drugs by the investigator.

- Subject #4078-73488 (LDV/SOF 8 weeks, ION-3) Anaphylaxis

  53 year old Caucasian man experienced life-threatening anaphylaxis post-treatment Day 9 with associated chest pain one hour after receiving injection of triamcinolone/lidocaine/Marcaine to his right elbow. Treated with IM epinephrine, diphenhydramine, methylprednisolone and improved. Later went to ER where had pruritic rash on torso, back and extremities in addition to tongue/lip swelling. Received famotidine and prednisone, work up for MI was negative. The following day anaphylaxis was reported as resolved and the subject was discharged. The event was not considered related to study treatment by the investigator.

  Reviewer Comment: I agree with the investigator's assessment as this event occurred while off LDV/SOF and one hour after receiving injection of triamcinolone/lidocaine/Marcaine.

- Subject #0521-73621 (LDV/SOF+RBV, ION-3) Swollen Tongue

  63 year old black/African American woman experienced Grade 1 swollen tongue on Day 5-11. The subject denied other symptoms (e.g., difficulty breathing, rash). Study

medication continued and the event was considered related to study treatment by the investigator.

An analysis of hypersensitivity events performed during the SOF NDA review did not demonstrate evidence of a causal relationship with SOF use. Additional exploration of hypersensitivity, anaphylaxis, angioedema and/or swollen tongue SAEs or discontinuation due to these AEs was performed in the LDV-containing phase 2 trials.

Supportive Safety Data from Phase 2 Trials with LDV in Combination with Other Investigational DAAs ± RBV ± PEG/RBV

LDV/VDV/TGV

- Subject #4435-3416 (GS-US-248-0131) Hypersensitivity (SAE)

56 year old African American man with a prior history of reaction to interferon/RBV (2010-2011: "rash to ribavirin which was treated with Benadryl on multiple occasions"). Day 39 experienced shortness of breath, generalized edema, itching and hives twice, transported to ER after each episode and treated with prednisone, famotidine and diphenhydramine. Day 40 LDV/VDV/TGV discontinued. Day 42 had recurrence of symptoms without shortness of breath. Treated with diphenhydramine and observed in ER. The narrative notes use of a new brand of ibuprofen. The event was assessed as related to study drugs.

LDV/VDV/RBV

- Subject #2075-4653 (GS-US-248-0132) Swollen tongue, Stomatitis

55 year old Caucasian man on Day 47 experienced Grade 1 stomatitis and Grade 1 swollen tongue, and study drugs were discontinued. Treated with diphenhydramine and the events resolved. The event was assessed as related to study drugs.

LDV/VDV/PEG/RBV

- Subject #3996-6368 (GS-US-248-0120) Angioedema

50 year old African American woman receiving concomitant lisinopril for HTN. Completed 4 weeks LDV/VDV/TGV/RBV and started LDV/VDV/PEG/RBV rescue treatment. Day 9 rescue therapy (Day 38 total therapy) experienced Grade 3 fatigue. Day 14 experienced Grade 3 angioedema (facial swelling) treated with diphenhydramine, prednisone and omeprazole. The narrative has conflicting information regarding study medication discontinuation Day 13 or 14 due to fatigue or angioedema.

- Subject #4488-1362 (GS-US-248-0121) Swollen tongue

55 year old American Indian/Alaska native man completed 6 weeks PEG/RBV and started LDV/VDV/PEG/RBV rescue treatment. Day 25 (Day 67 total therapy) experienced a swollen tongue, and LDV/VDV discontinued. The following day the event resolved. PEG/RBV continued for approximately 6 more weeks.

The Applicant was queried for their assessment of hypersensitivity, angioedema and swollen tongue cases. Their response received on May 21, 2014 is summarized in this section. The LDV/SOF phase 2 and 3 program, as well as all LDV phase 1 trials, were reviewed for preferred terms of Hypersensitivity, Drug Hypersensitivity, Angioedema, and Swollen tongue. Six identified treatment-emergent cases, including Subjects #2024-71260 and #0521-73621, associated with these terms are all considered non-serious. Of the additional four cases, the observed reaction was attributable to a medication or substance other than study drug in three cases (e.g., Bactrim). In the remaining case the subject was taking placebo. The Applicant concludes "no events of hypersensitivity, drug hypersensitivity, angioedema, or swollen tongue due to an allergic reaction to study drug have occurred that are attributable to SOF, LDV, or LDV/SOF FDC."

Reviewer Comment: Reported cases of hypersensitivity, angioedema and swollen tongue are confounded by use of concomitant medications such as PEG/RBV, which has a labeled warning and precaution for severe hypersensitivity reactions, and investigational DAAs. Phase 3 events are infrequent with alternative causal etiologies in the cases of anaphylaxis and hypersensitivity. Phase 2 events with LDV in Combination with Other Investigational DAAs ± RBV ± PEG/RBV generally have a time to onset <6 weeks and positive dechallenge suggesting a drug-related causal etiology, though these cases are confounded by concomitant VDV (investigational PI) use with/without TGV, PEG, RBV. Based on the totality of the available data, I do not believe a strong causal association between LDV/SOF and hypersensitivity, anaphylaxis, angioedema and swollen tongue events is established at this time and therefore does not does not support related labeling in my opinion. Such cases will be monitored in the postmarketing setting.

Fall and Fracture Events

A focused analysis of fall and fracture events was performed to evaluate a potential causal association with LDV/SOF-containing treatment due to eight SAEs reported in seven subjects from the phase 3 trials. In the LDV/SOF phase 3 trials, 23 subjects (1.2%) experienced treatment-emergent fall and fracture events: 12 subjects in LDV/SOF arms, 11 subjects in LDV/SOF+RBV arms. No event is considered related to study treatment by the investigator. The median time to onset is 64 days (Day 2-180). Seven subjects experienced SAEs (5 subjects in LDV/SOF arms; 2 subjects in LDV/SOF+RBV arms) and one subject discontinued due to AE (Subject #5847-73029 following road traffic accident). Of the non-SAE events, all are ≤Grade 2. Analysis for dizziness as a potential contributing event identified a single subject with ongoing dizziness at time of event (Day 62 Rib Fracture, Grade 2, not related). Alternative etiologies (e.g., fall on ice, motor vehicle accident caused by other driver, fall off horse, concomitant clonazepam or alcohol use) are provided for the SAEs and additional cases with narrative information.

Two additional subjects experienced non-treatment emergent fall or fracture SAEs (≥60 days post-treatment). In the phase 2 trials, one subject receiving LDV (30mg)/PEG/RBV experienced an SAE of fractured ankle Day 17 after slipping on ice. In the SUR, three additional SAEs of fall or fracture events are identified: one subject with highway accident, two subjects with falls, including one subject with decompensated cirrhosis and encephalopathy with resulting subdural hematoma, vertebral fracture, and seizure (Subject #0585-75241).

The Applicant was queried for their assessment of these cases, and their response received May 21, 2014 is summarized in this section. Their assessment following review of the LDV/SOF phase 2 and 3 program, as well as all LDV phase 1 trials for cases with preferred terms of Fall and Road traffic accident is "that no cases of fall or road traffic accident have occurred that are attributable to SOF, LDV, or LDV/SOF FDC."

Reviewer Comment: Based upon available narrative and dataset information, no consistent pattern of time to onset or associated events (e.g., dizziness) is identified, no event is considered related to study treatment by the investigator, and the events generally have an alternative etiology. No safety concern associated with LDV/SOF use and fall and fracture events is identified at this time and thus I do not believe labeling is needed.

Dizziness Events

One subject discontinued LDV/SOF due to dizziness; therefore a focused analysis of dizziness events was performed. In the phase 3 trials 5.5% (108 subjects) experienced treatment-emergent dizziness, with a lower percentage reported in the LDV/SOF pooled arms than in the RBV-containing pooled arms (4.4% versus 7.0%, respectively). Median time to onset is similar within the respective pooled LDV/SOF (11 days, range 1-157 days) and LDV/SOF+RBV groups (18 days, 1-192 days). Eighty percent of dizziness events have onset within the first 8 weeks (defined as onset ≤Study Day 63), and 92% have onset within the first 12 weeks (defined as onset ≤Study Day 98). Treatment-related dizziness occurs 3.5% overall, representing approximately two-thirds of all reported dizziness events (64%). All events are ≤Grade 2 and no SAEs occur. The case of discontinuation due to dizziness is described further:

- Subject #1302-71477 (LDV/SOF 24 week, ION-1) Dizziness and Throat Tightness
  61 year old Caucasian woman with cirrhosis experienced Grade 1 dizziness Day 71, considered unrelated to study drug, and Grade 1 throat tightness/neck pain Day 87, considered related to study drug. These events led to study drug interruption Day 136-139, followed by permanent discontinuation Day 157, primarily due to the subject's concerns of dizziness impeding driving. Both events resolved 14 days after stopping LDV/SOF treatment (positive dechallenge). The subject believes the throat tightness/neck pain was due to tendonitis.

Reviewer Comment: Based on the available information, an obvious serious safety concern between LDV/SOF use and dizziness is not identified at this time and I do not believe labeling for dizziness is indicated. The single Grade 1 case leading to discontinuation is noted, and additional cases will be monitored postmarketing.

Chest Pain Events

A focused analysis of chest pain events was performed due to five SAEs of chest pain or non-cardiac chest pain reported in the phase 3 trials. In the phase 3 trials, 2.3% subjects experienced chest pain events defined as preferred terms of chest pain, chest discomfort, non-cardiac chest pain. More events occur in the RBV-containing arms (2.8%) compared with the LDV/SOF alone arms (1.9%). The majority of subjects (93%) experienced ≤Grade 2 event, and most are not considered treatment-related by the investigator (69%). Five SAEs are reported, none considered related to study drugs. All cases had negative evaluations for myocardial ischemia and the investigators' assessments for alternative etiologies (e.g., musculoskeletal strain, GERD) seem reasonable. One case led to study drug discontinuation, and the event was believed to be due to viral myocarditis secondary to a viral infection as described further:

- Subject #1039-71100 (LDV/SOF ION-1) Chest Pain
  27 year old Caucasian woman experienced chest pain Day 59 one week following presumed viral infection. Work up for myocardial infarction and pulmonary embolism unrevealing. Study drug was discontinued. Day 60 the chest pain resolved. An infectious disease specialist was consulted and believed the subject's shortness of breath and chest pain were due to viral myocarditis secondary to upper respiratory tract infection. The investigator assessed the event as unrelated to the study drug or study procedure but rather related to the intercurrent illness of viral infection.

The Applicant was queried for their assessment of chest pain-related events, and their response received May 21, 2014 identified one additional treatment-related SAE:

- Subject #4421-86034 (LDV/SOF+RBV, GS-US-337-1118) Chest Pain
  68 year old man with prior SOF+PEG/RBV treatment failure experienced a prodrome of chest pain for a couple of weeks, and hospitalization Day 34 with persistent chest pain. Cardiac and pulmonary embolism workups negative. The subject was informed that the pain might be due to a hiatal hernia or gallbladder issue and was discharged the following day. In the absence of a definitive diagnosis and given the temporal relationship, the investigator assessed this event as related to study drug. However, subsequently (Day 110) the subject had gangrenous cholecystitis, for which a cholecystectomy was performed. This second SAE is considered to provide a likely alternative explanation for this subject's chest pain.

The Applicant's assessment is "that the Phase 2 and Phase 3 data analysis suggests that LDV/SOF is unlikely to be a causal factor in cases of chest pain or chest discomfort".

Reviewer Comment: Based on the available data, no obvious safety concern is identified associated with LDV/SOF use and chest pain at this time and I do not believe labeling for chest pain is indicated.

7.4 Supportive Safety Results

The supportive safety results have been integrated in pertinent sections of this review.

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events

Treatment-emergent AEs met one of the following criteria:

- AEs with onset dates on or after the start of treatment and up to 30 days after the discontinuation of all the study drugs
- Continuing AEs diagnosed prior to the start of treatment and worsening in severity grade, nonserious AEs at baseline which became serious, or AEs resulting in treatment discontinuation after the start of treatment.

AEs related to study drug are defined using clinical judgment and considerations of:

- A temporal relationship between the AE onset and administration of investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies
- The AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product
- In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge

The AE tables in this section are derived from FDA analyses of pooled phase 3 pivotal trial data. An overall presentation of AEs without regard to causality is included, with subsequent AE analyses focusing on treatment-related AEs. The LDV/SOF phase 3 trials were neither placebo- nor active-controlled; therefore, use of investigator-causality assessment is used to define adverse drug reactions, acknowledging the bias that is introduced by excluding events from the rate calculation based on the judgment of individual investigators.

A summary of all grade, treatment-emergent AEs reported in ≥5% subjects in any group is provided in Table 58. The most frequently reported AEs ≥10% in any LDV/SOF group without RBV are fatigue (21-24%), headache (14-24%), nausea (7-11%) and diarrhea (7-10%). The most frequently reported AEs ≥10% in any LDV/SOF+RBV group are fatigue (35-40%), headache (23-30%), nausea (17-18%), irritability (9-13%), insomnia (12-20%), rash (9-13%), cough (6-13%), anemia (8-10%), dyspnea (5-10%) and pruritus (7-10%).

Table 58 Treatment-Emergent Adverse Events, All Cause, All Grade, by Preferred Term (≥5% of subjects in any treatment group), LDV/SOF Phase 3 Integrated Safety Population

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
#Subjects with AE (%)	145 (67%)	390 (72%)	265 (81%)	165 (76%)	280 (85%)	300 (91%)
Fatigue	45 (21%)	116 (22%)	79 (24%)	75 (35%)	124 (38%)	132 (40%)
Headache	30 (14%)	113 (21%)	79 (24%)	54 (25%)	75 (23%)	99 (30%)
Nausea	15 (7%)	61 (11%)	36 (11%)	38 (18%)	57 (17%)	57 (17%)
Insomnia	11 (5%)	41 (8%)	30 (9%)	26 (12%)	63 (19%)	66 (20%)
Diarrhea	15 (7%)	40 (7%)	33 (10%)	13 (6%)	23 (7%)	31 (9%)
Arthralgia	9 (4%)	32 (6%)	27 (8%)	11 (5%)	27 (8%)	28 (9%)
Constipation	9 (4%)	23 (4%)	21 (6%)	13 (6%)	16 (5%)	13 (4%)
Rash[1]	3 (1%)	23 (4%)	21 (6%)	19 (9%)	32 (10%)	43 (13%)
Irritability	3 (1%)	22 (4%)	21 (6%)	29 (13%)	30 (9%)	36 (11%)
Back Pain	6 (3%)	21 (4%)	16 (5%)	9 (4%)	8 (2%)	23 (7%)
Dizziness	6 (3%)	21 (4%)	20 (6%)	13 (6%)	18 (5%)	30 (9%)
Pruritus	2 (1%)	21 (4%)	10 (3%)	16 (7%)	32 (10%)	30 (9%)
Myalgia	7 (3%)	20 (4%)	20 (6%)	8 (4%)	18 (5%)	22 (7%)
Nasopharyngitis	3 (1%)	19 (4%)	16 (5%)	4 (2%)	14 (4%)	23 (7%)
Cough	3 (1%)	18 (3%)	21 (6%)	12 (6%)	37 (11%)	41 (13%)
Asthenia	1 (<1%)	15 (3%)	22 (7%)	4 (2%)	23 (7%)	29 (9%)
Decreased Appetite	5 (2%)	14 (3%)	9 (3%)	6 (3%)	16 (5%)	13 (4%)
Muscle Spasms	3 (1%)	14 (3%)	11 (3%)	11 (5%)	22 (7%)	24 (7%)
Vomiting	6 (3%)	12 (2%)	6 (2%)	7 (3%)	12 (4%)	21 (6%)
Dyspepsia	3 (1%)	11 (2%)	16 (5%)	5 (2%)	15 (5%)	14 (4%)
Anxiety	5 (2%)	9 (2%)	16 (5%)	10 (5%)	16 (5%)	23 (7%)
Anemia	2 (1%)	2 (<1%)	1 (<1%)	17 (8%)	34 (10%)	33 (10%)
Dyspnea	0	4 (1%)	8 (2%)	11 (5%)	34 (10%)	24 (7%)
Dry Skin	1 (<1%)	3 (1%)	6 (2%)	3 (1%)	17 (5%)	23 (7%)
Dyspnea Exertional	0	4 (1%)	2 (1%)	4 (2%)	14 (4%)	17 (5%)
Upper Respiratory Tract Infection	1 (<1%)	13 (2%)	13 (4%)	7 (3%)	12 (4%)	16 (5%)

[1]Rash is defined as the single "Rash" MedDRA preferred term in this table.
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

A summary of all grade, treatment-emergent, treatment-related AEs reported in ≥5% subjects in any group is provided in Table 59. The most frequently reported treatment-

related AEs ≥10% in any LDV/SOF group without RBV are fatigue (13-18%) and headache (11-17%). The most frequently reported AEs ≥10% in any LDV/SOF+RBV group are fatigue (32-35%), headache (18-21%), nausea (13-15%), insomnia (10-17%), irritability (8-11%), rash (8-10%) and anemia (8-10%).

Table 59 Treatment-Emergent, Treatment-Related Adverse Events, All Grade, by Preferred Term (≥5% of subjects in any treatment group), LDV/SOF Phase 3 Integrated Safety Population

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF +RBV 8 Week	LDV/SOF +RBV 12 Week	LDV/SOF +RBV 24 Week
Total Subjects	215	539	326	216	328	328
#Subjects with AE (%)	82 (38%)	237 (44%)	165 (51%)	133 (62%)	229 (70%)	255 (78%)
Headache	23 (11%)	76 (14%)	57 (17%)	42 (19%)	59 (18%)	69 (21%)
Fatigue	34 (16%)	70 (13%)	58 (18%)	70 (32%)	112 (34%)	115 (35%)
Nausea	13 (6%)	39 (7%)	29 (9%)	33 (15%)	43 (13%)	48 (15%)
Insomnia	7 (3%)	29 (5%)	18 (6%)	21 (10%)	55 (17%)	55 (17%)
Pruritus	2 (1%)	16 (3%)	8 (2%)	15 (7%)	31 (9%)	23 (7%)
Diarrhea	9 (4%)	15 (3%)	22 (7%)	8 (4%)	19 (6%)	18 (5%)
Asthenia	1 (<1%)	14 (3%)	15 (5%)	4 (2%)	21 (6%)	24 (7%)
Dizziness	5 (2%)	13 (2%)	11 (3%)	11 (5%)	12 (4%)	17 (5%)
Irritability	2 (1%)	13 (2%)	14 (4%)	23 (11%)	25 (8%)	29 (9%)
Arthralgia	8 (4%)	11 (2%)	11 (3%)	8 (4%)	15 (5%)	17 (5%)
Rash[1]	2 (1%)	11 (2%)	13 (4%)	17 (8%)	25 (8%)	34 (10%)
Anemia	0	0	1 (<1%)	17 (8%)	33 (10%)	33 (10%)
Cough	0	4 (1%)	6 (2%)	8 (4%)	23 (7%)	23 (7%)
Dyspnea	0	3 (1%)	4 (1%)	11 (5%)	31 (9%)	21 (6%)
Dry Skin	1 (<1%)	2 (<1%)	3 (1%)	2 (1%)	15 (5%)	20 (6%)
Dyspnea Exertional	0	2 (<1%)	0	3 (1%)	12 (4%)	17 (5%)

[1]Rash is defined as the single "Rash" MedDRA preferred term in this table.
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

RBV-Containing versus Non-RBV-Containing LDV/SOF Regimens

RBV-containing arms have increased AEs and treatment-related AEs, relative to non-RBV-containing arms of the same duration (Tables 58 and 59). An exploratory analysis pooling the RBV-containing and non-RBV-containing arms demonstrates the following treatment-related AEs occur in ≥10% RBV-containing arms and with ≥5% increased incidence compared with the non-RBV-containing arms: fatigue (34% versus 15%), headache (19% versus 14%), insomnia (15% versus 5%), nausea (14% versus 8%), anemia (10% versus <1%). In addition, irritability, rash, pruritus, dyspnea and cough are also increased in the RBV-containing regimens (Table 60).

Table 60 Treatment-Emergent, Treatment-Related Adverse Events, All Grade, by Preferred Term (≥5% of subjects in any treatment group), LDV/SOF Phase 3 Integrated Safety Population: Pooled LDV/SOF+RBV versus LDV/SOF Arms

Dictionary-Derived Term	LDV/SOF arms	LDV/SOF+RBV arms
Total Subjects	1080	872
#Subjects with AE (%)	484 (45%)	617 (71%)
Fatigue	162 (15%)	297 (34%)
Headache	156 (14%)	170 (19%)
Insomnia	54 (5%)	131 (15%)
Nausea	81 (8%)	124 (14%)
Anemia	1 (<1%)	83 (10%)
Irritability	29 (3%)	77 (9%)
Rash	26 (2%)	76 (9%)
Pruritus	26 (2%)	69 (8%)
Dyspnea	7 (1%)	63 (7%)
Cough	10 (1%)	54 (6%)
Asthenia	30 (3%)	49 (6%)
Diarrhea	46 (4%)	45 (5%)
Arthralgia	30 (3%)	40 (5%)
Dizziness	29 (3%)	40 (5%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2, ION-3)

Reviewer Comment: The addition of RBV to LDV/SOF results in an increased incidence of AEs and increased need for dose modification or interruption. A treatment option without RBV would provide a safer, more tolerable and simplified regimen. As noted in Section 6, the addition of RBV does not significantly increase efficacy in the various studied HCV GT 1 populations. Therefore, the review team does not believe the benefit-risk assessment supports a labeling recommendation for LDV/SOF+RBV regimens in the intended patient population (i.e., patients with HCV GT 1 infection who do not have evidence of decompensated cirrhosis and/or who are not post-liver transplantation).

LDV/SOF Analyses

As stated above, because the review team does not believe the benefit-risk assessment supports a labeling recommendation for LDV/SOF+RBV regimens in the intended patient population (i.e., patients with HCV GT 1 infection who do not have evidence of decompensated cirrhosis and/or who are not post-liver transplantation), safety analyses of treatment duration and of events occurring in the cirrhotic and non-cirrhotic populations are limited to the LDV/SOF arms.

(1) HCV GT 1 Treatment-Naïve, Non-cirrhotic Population

(b) (4)

The ION-3 SVR12 and relapse rate data in this

population support consideration of a 12 week LDV/SOF duration as outlined in Section 6. An analysis was performed to explore the safety considerations for (b) (4) LDV/SOF treatment (b) (4) in the HCV GT 1 treatment-naïve non-cirrhotic population. The LDV/SOF 12 week arms in non-cirrhotic subjects are pooled from the ION-1 and ION-3 trials based upon comparison of demographic and baseline characteristics from these two trials. Compared with ION-3, ION-1 enrolled fewer black/African American subjects (12.9% versus 19.4-20.9%), more Hispanic/Latino subjects (12.4% versus 6.1-6.5%), more non-US subjects (42.7% versus 0%) and subjects with lower BMI (median 25.9 versus 27.1 kg/m^2).

Reviewer Comment: ION-1 and ION-3 treatment-naïve, non-cirrhotic population demographic and baseline characteristics differences are acknowledged. For this exploratory safety analysis, I believe these differences do not substantively alter the conclusions (b) (4) *and therefore allow pooling of these trials.*

A total of 215 subjects received treatment in the LDV/SOF 8 Week arm (ION-3), and 394 subjects received treatment in the LDV/SOF 12 Week arm (pooled ION-1 and ION-3). Differences between AEs and treatment-related AEs in the LDV/SOF 8 and 12 week arms are <10%. Grade 3 or 4 AEs, SAEs, and AEs leading to LDV/SOF discontinuation are low and are similar between the durations (Table 61).

Table 61 Overall Summary of Adverse Events in the HCV Genotype 1 Treatment-Naïve, Non-Cirrhotic Population, LDV/SOF Arms (ION-1 and ION-3 Integrated Safety Population)

	LDV/SOF 8 Week	LDV/SOF 12 Week
Total Number of Subjects	215	394
Number of Subjects (%)		
Any AE	145 (67%)	290 (74%)
Treatment-related AE	82 (38%)	184 (47%)
Serious AE	4 (2%)	6 (2%)
Treatment-related SAE	0	0
Grade 3 or 4 AE	2 (1%)	10 (3%)
Treatment-related Grade 3 or 4 AE	0	0
AE Leading to Permanent D/C from LDV/SOF	0	2 (<1%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-3)

Analysis of all grade treatment-emergent, treatment-related AEs identifies headache (13%), fatigue (13%), nausea (8%) and insomnia (5%) as events occurring ≥5% in the 12 week arm (Table 62). These events have similar incidence as observed in the 8 week arm.

Table 62 Treatment-Emergent, Treatment-Related Adverse Events, All Grade ≥5% in the HCV Genotype 1 Treatment-Naïve, Non-Cirrhotic Population, LDV/SOF Arms (ION-1 and ION-3 Integrated Safety Population)

Dictionary-Derived Term	LDV/SOF 8 Week	LDV/SOF 12 Week
Total Subjects	215	394
#Subjects with AE (%)	82 (38%)	184(47%)
Headache	23 (11%)	52 (13%)
Fatigue	34 (16%)	50 (13%)
Nausea	13 (6%)	32 (8%)
Insomnia	7 (3%)	19 (5%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-3)

Overall Grade ≥3 events are low, with no events considered related to LDV/SOF. Four subjects in the 8 week arm (diabetes inadequate control, hypertension, anaphylactic reaction, colitis/lower gastrointestinal hemorrhage) and six subjects in the 12 week arm (abdominal pain/bile duct stone/jaundice, chest pain, intestinal perforation due to rectal trauma, road traffic accident, squamous cell carcinoma of the lung, hypoglycemia) experienced SAEs, none were considered treatment-related and there is no clustering of SAE events between the two durations. Two subjects discontinued LDV/SOF in the 12 week arm:

- Subject #0380-73346 experienced Grade 1 arthralgia with onset Day 9
- Subject #0331-73239 experienced Grade 3, SAE of squamous cell carcinoma of the lung with onset Day 43.

Comparison of Safety Profile Between 8 and 12 Week Treatment Windows

Protocol definitions for treatment-emergent events included events occurring up to 30 days following study drug discontinuation. In examining the 8 versus 12 week treatment durations from a safety perspective, an interest was in determining if new AEs occur between Weeks 8-12. In other words, is there a different safety profile for the LDV/SOF 12 week duration than for the 8 week duration in the HCV GT 1 treatment-naïve, non-cirrhotic population necessitating incorporation into benefit-risk considerations for dosing recommendations? To address this question, the following definitions for Treatment Window based upon protocol defined study visit windows are used:

- Week 8: Day 56. Study window extends to Day 63
- Event ≤Week 8 defined as occurring ≤Day 63
- Event >Week 8 defined as occurring >Day 63

For ≤Week 8 group, the LDV/SOF 8 and 12 week durations from ION-1 and ION-3 are combined. The >Week 8 group is limited to the LDV/SOF12 week duration as all subjects from the Week 8 group would be off treatment; therefore, the denominator changes and some events occurring in the 8 week arms during the 30 day post-treatment window period will not be captured in this “>Week 8” analysis.

Fatigue, headache and nausea are the most common treatment-emergent, treatment-related AEs occurring overall in the pooled LDV/SOF 8 and 12 week arms. The majority of events occurred within the first eight weeks as shown in Table 63.

Table 63 Pooled ION-1 and ION-3 LDV/SOF 8 and 12 Week Arms: Treatment-Emergent, Treatment-Related Adverse Events, All Grade ≥5% in the HCV Genotype 1 Treatment-Naïve, Non-Cirrhotic Population (ION-1 and ION-3 Integrated Safety Population) [1]

Dictionary-Derived Term	Treatment-Emergent Events		
	Total	Occurring ≤Week 8	Occurring >Week 8
Total Subjects	609	609	394
#Subjects with AE (%)	266 (44%)	257 (42%)	26 (7%)
Fatigue	84 (14%)	83 (14%)	2 (1%)
Headache	75 (12%)	71 (12%)	5 (1%)
Nausea	45 (7%)	44 (7%)	1 (<1%)

[1] Only one event per treatment window is captured; however, if a second event occurred in the >Week 8 window, that event is also captured. Thus not all rows will add up to the total.
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-3)

Reviewer Comment: These analyses do not identify a negative safety consequence for extending LDV/SOF treatment from 8 to 12 weeks in the HCV GT 1 treatment-naïve, non-cirrhotic population.

(2) HCV GT 1 Cirrhotic and Non-Cirrhotic Population

(b) (4)

The SVR12 and relapse rate data from the phase 3 LDV/SOF-containing trials support a 24 week LDV/SOF duration in the treatment-experienced cirrhotic population, and consideration of a 24 week duration in the HCV GT 1 treatment-experienced, non-cirrhotic population with poor baseline predictors (see Section 6). To identify if there are unique safety considerations in the cirrhotic population and/or with extending to a LDV/SOF 24 week treatment duration, an analysis was performed by pooling the ION-1 and ION-2 trials. Pooling these trials is supported by the facts that baseline cirrhosis presence/absence was one of the stratification factors in the randomization in both trials, and these trials had the same randomization ratio (i.e., evenly to each treatment duration arm). Compared to ION-1, ION-2 subjects enrolled more men (68% versus 62%), black/African American subjects (19% versus 13%), cirrhotics (20% versus 16%), IL28B non-C/C (88% versus 75%) and subjects with baseline HCV RNA ≥ 800,000 IU/mL (90% versus 78%).

Reviewer Comment: ION-1 and ION-2 population demographic and baseline characteristics differences are acknowledged. For this exploratory safety analysis, I

believe these differences do not substantively alter the conclusions regarding LDV/SOF 12 versus 24 week duration and therefore allow pooling of these trials.

Table 64 presents an overall summary of AEs in the HCV GT 1 cirrhotic and non-cirrhotic population. Subjects with cirrhosis have a similar incidence of treatment-emergent AEs, treatment-related AEs, SAEs, Grade ≥3 AEs compared to subjects without cirrhosis. Among the cirrhotic population, more treatment-emergent AEs, treatment-related AEs, SAEs and Grade ≥3 AEs occur in the LDV/SOF 24 week group compared with the 12 week group. Similar findings are observed between the non-cirrhotic LDV/SOF 12 and 24 week groups.

Table 64 Overall Summary of Adverse Events in the HCV Genotype 1 Cirrhotic and Non-Cirrhotic Population, LDV/SOF Arms (ION-1 and ION-2 Integrated Safety Population)

	Cirrhosis		No Cirrhosis	
	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF 12 Week	LDV/SOF 24 Week
Total Subjects	56	55	265	270
Number of Subjects (%)				
Any AE	39 (70%)	46 (84%)	201 (76%)	218 (81%)
Treatment-related AE	21 (38%)	25 (45%)	122 (46%)	140 (52%)
Serious AE	0	5 (9%)	1 (<1%)	19 (7%)
Treatment-related SAE	0	1 (2%)	0	3 (1%)
Grade 3 or 4 AE	1 (2%)	6 (11%)	5 (2%)	25 (9%)
Treatment-related Grade 3 or 4 AE	1 (2%)	1 (2%)	1 (<1%)	8 (3%)
AE Leading to Permanent D/C from LDV/SOF	0	0	0	4 (1%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2)

Table 65 shows all grade treatment-emergent, treatment-related AEs in the cirrhotic and non-cirrhotic populations. Compared to the non-cirrhotic population, cirrhotic subjects in the LDV/SOF 12 week arm have >2% more fatigue, muscle spasms and arthralgia; however, this difference is not present when comparing the 24 week durations between these groups. More rash events occur in the cirrhotic LDV/SOF 24 week arm compared with the non-cirrhotic LDV/SOF 24 week arm. Among the cirrhotic population, analysis of all grade treatment-emergent, treatment-related AEs identified nausea, rash and dizziness as events occurring >2% in the 24 week arm compared to the 12 week arm. All rash events are ≤Grade 2 and study drug continued in all subjects.

Table 65 Treatment-Emergent, Treatment-Related Adverse Events, All Grade ≥5% in the HCV Genotype 1 Cirrhotic and Non-Cirrhotic Populations, LDV/SOF Arms (ION-1 and ION-2 Integrated Safety Population)

Dictionary-Derived Term	Cirrhosis		No Cirrhosis	
	LDV/SOF 12 Week	LDV/SOF 24 Week	LDV/SOF 12 Week	LDV/SOF 24 Week
Total Subjects	56	55	265	270
#Subjects with AE (%)	21 (38%)	25 (45%)	122 (46%)	140 (52%)
Headache	8 (14%)	8 (15%)	46 (17%)	49 (18%)
Fatigue	9 (16%)	7 (13%)	33 (12%)	51 (19%)
Nausea	1 (2%)	5 (9%)	21 (8%)	24 (9%)
Rash	0	4 (7%)	8 (3%)	9 (3%)
Irritability	2 (4%)	3 (5%)	6 (2%)	11 (4%)
Insomnia	4 (7%)	3 (5%)	15 (6%)	15 6%)
Dizziness	1 (2%)	3 (5%)	7 (3%)	8 (3%)
Muscle Spasms	3 (5%)	1 (2%)	2 (1%)	2 (1%)
Arthralgia	3 (5%)	0	1 (<1%)	11 (4%)
Diarrhea	0	0	12 (5%)	22 (8%)
Asthenia	2 (4%)	0	11 (4%)	15 (6%)

Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2)

Within the cirrhotic population, overall Grade ≥3 events were low, with only two events considered related to LDV/SOF:

- Subject #0334-71474 Acute Hepatitis (LDV/SOF 12 week). This case occurred approximately four weeks post-treatment and is discussed in detail in Section 7.4.2.
- Subject #5667-71227 Mesenteric Vein Thrombosis (LDV/SOF 24 week). Please see Section 7.3.2 for details.

No SAEs are reported in the LDV/SOF12 week cirrhosis group, and five subjects experienced SAEs in the LDV/SOF 24 week group (cellulitis, lower limb fracture, mesenteric vein thrombosis/abdominal discomfort, upper gastrointestinal hemorrhage, urinary tract infection). Only the event of mesenteric vein thrombosis was considered treatment-related. No subjects discontinued LDV/SOF due to an AE.

Comparison of Safety Profile Between 12 and 24 Week Treatment Windows

Protocol definitions for treatment-emergent events included events occurring up to 30 days following study drug discontinuation. In examining the 12 versus 24 week treatment durations from a safety perspective, an interest was in determining if new AEs occurred during Weeks 12-24. The following definitions for Treatment Window based upon protocol defined study visit windows are used:

- Week 12: Day 84. Study window extends to Day 98
- Event ≤Week 12 defined as occurring ≤Day 98

- Event >Week 12 defined as occurring >Day 98

For ≤Week 12 group, the LDV/SOF 12 and 24 week durations from ION-1 and ION-2 are combined. The >Week 12 group is limited to the LDV/SOF 24 week duration as all subjects from the Week 12 group are off treatment; therefore, the denominator changes and some events occurring in the 12 week arms during the 30 day post-treatment window period will not be captured in this ">Week 12" analysis.

Within the cirrhotic population, fatigue, headache, insomnia, nausea and irritability are the most common treatment-emergent, treatment-related AEs occurring overall in the pooled LDV/SOF 12 and 24 week arms, and all events occur within the Week 12 treatment window (Table 66). Events occurring outside the Week 12 window were all ≤Grade 2 and include memory impairment, malaise, rash and edema/depression, with no event occurring in more than one subject.

Within the non-cirrhotic group, the majority of treatment-emergent, treatment-related events occur within the Week 12 window. Events occurring outside the Week 12 window in ≥2% subjects include fatigue and headache.

In summary, events occurring >12 weeks are not concerning and do not preclude extending treatment duration to 24 weeks, regardless of underlying cirrhosis status.

Table 66 Pooled ION-1 and ION-2 LDV/SOF 12 and 24 week arms: Treatment-Emergent, Treatment-Related Adverse Events, All Grade ≥5% in the HCV Genotype 1 Cirrhotic and Non-Cirrhotic Population, LDV/SOF Arms (ION-1 and ION-2 Integrated Safety Population) [1]

Dictionary-Derived Term	Cirrhosis			No Cirrhosis		
	Total	≤Week 12	>Week 12	Total	≤Week 12	>Week 12
Total Subjects	111	111	55	535	535	270
#Subjects with AE (%)	46 (41%)	46 (41%)	4 (7%)	262 (49%)	257 (48%)	30 (11%)
Fatigue	16 (14%)	15 (14%)	0	84 (16%)	82 (15%)	6 (2%)
Headache	16 (14%)	16 (14%)	0	95 (18%)	91 (17%)	5 (2%)
Insomnia	7 (6%)	7 (6%)	0	30 (6%)	29 (5%)	1 (<1%)
Nausea	6 (5%)	6 (5%)	0	45 (8%)	45 (8%)	0
Irritability	5 (5%)	5 (5%)	0	17 (3%)	17 (3%)	1 (<1%)
Diarrhea	0	0	0	34 (6%)	32 (6%)	4 (1%)
Asthenia	2 (2%)	2 (2%)	0	26 (5%)	26 (5%)	3 (1%)

[1]Only one event per treatment window is captured; however, if a second event occurred in the >Week 12 window, that event is also captured. Thus not all rows will add up to the total.
Source: Integrated Datasets, ADAE, ADSL (ION-1, ION-2)

Reviewer Comment: These analyses do not identify a negative safety consequence for extending LDV/SOF treatment from 12 to 24 weeks in either the HCV GT 1 cirrhotic or non-cirrhotic populations.

7.4.2 Laboratory Findings

This section summarizes the reported laboratory findings for the three phase 3 trials. Liver laboratory data is included in Section 7.3.5 Hepatic Events.

Hematology Test Abnormalities

Anemia is the most common cause of RBV dose reduction. Hemoglobin (hgb) values of <10 g/dL and <8.5 g/dL are the values recommended in the approved RBV package inserts for RBV dose-reduction and discontinuation, respectively. Erythropoiesis-stimulating agents such as epoetin alfa used to treat anemia were prohibited medications from 28 days prior to the Day 1 (baseline) visit through the end of treatment in all phase 3 trials.

The number of subjects with hemoglobin <10 g/dL (the level that recommended RBV dose reduction per protocol) and <8.5 g/dL (the level that recommended RBV dose discontinuation per protocol) at any post baseline visits is summarized in Table 67.

Table 67 Hemoglobin Laboratories <10 and <8.5 g/dL, LDV/SOF Phase 3 Integrated Safety Population

	No RBV			RBV-Containing		
Lowest Hemoglobin Value	**LDV/SOF 8 Week**	**LDV/SOF 12 Week**	**LDV/SOF 24 Week**	**LDV/SOF +RBV 8 Week**	**LDV/SOF +RBV 12 Week**	**LDV/SOF +RBV 24 Week**
Total Subjects in Analysis*	215 n (%)	538 n (%)	325 n (%)	214 n (%)	328 n (%)	328 n (%)
Hemoglobin (g/dL)						
<10 g/dL	0	1 (<1%)	0	11 (5%)	22 (7%)	25 (8%)
<8.5 g/dL	0	0	0	0	1 (<1%)	2 (1%)

*N based on number of subjects with post-baseline hemoglobin measurement
Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

More subjects in the LDV/SOF + RBV treatment groups had lowest hgb values <10 g/dL and 8.5 g/dL compared with the LDV/SOF treatment groups. The three subjects receiving LDV/SOF + RBV with post-baseline hgb <8.5 g/dL discontinued RBV, and one of these subjects received red blood cell transfusions due to hgb of 6.9 g/dL at Week 4 and 7.4 g/dL at Week 8. No other subjects received red blood cell transfusions in the phase 3 trials.

A single subject receiving LDV/SOF without RBV had a hgb <10 g/dL. This subject (Subject #3054-73011) in the ION-3 LDV/SOF 12 Week group had baseline hgb of 12.3 g/dL and on treatment hgb values ranged 11.1-12.4 g/dL. Post-treatment Week 4 had a Grade 2 hgb of 9.4 g/dL. This event was also considered a Grade 1 AE of anemia, and was not considered related to study drug by the investigator.

Table 68 presents hematology laboratory data from the integrated phase 3 trials. Few ≥Grade 3 hematologic laboratories occur across the LDV/SOF arms.

Table 68 Hematology Laboratory Data, LDV/SOF Phase 3 Integrated Safety Population

Laboratory Parameter Maximum Toxicity Grade	**LDV/SOF 8 Week**	**LDV/SOF 12 Week**	**LDV/SOF 24 Week**	**LDV/SOF +RBV 8 Week**	**LDV/SOF +RBV 12 Week**	**LDV/SOF +RBV 24 Week**
Total Number of Subjects in Analysis	215 n (%)	539 n (%)	326 n (%)	216 n (%)	328 n (%)	328 n (%)
Hemoglobin (g/dL)						
Grade 1 (10.0 to 10.9 g/dL OR any decrease from Baseline 2.5 to <3.5 g/dL)	3 (1%)	13 (2%)	18 (6%)	53 (25%)	116 (35%)	108 (33%)
Grade 2 (9.0 to <10.0 g/dL OR any decrease from Baseline 3.5 to <4.5 g/dL)	0	4 (1%)	4 (1%)	30 (14%)	75 (23%)	65 (20%)
Grade 3 (7.0 to <9.0 g/dL OR any decrease from Baseline ≥4.5 g/dL)	0	3 (1%)	0	14 (6%)	19 (6%)	40 (12%)
Grade 4 (<7.0 g/dL)	0	0	0	0	1 (<1%)	0
Leukocytes ($x10^3$/uL)						
Grade 1 (2000 to 2500/mm^3)	1 (<1%)	4 (1%)	2 (1%)	4 (2%)	7 (2%)	4 (1%)
Grade 2 (1500 to <2000/mm^3)	0	0	3 (1%)	0	1 (<1%)	1 (<1%)
Lymphocytes ($x10^3$/uL)						
Grade 1 (600 to 650/mm^3)	0	3 (1%)	3 (1%)	3 (1%)	6 (2%)	8 (2%)
Grade 2 (500 to <600/mm^3)	0	2 (<1%)	1 (<1%)	1 (<1%)	7 (2%)	6 (2%)
Grade 3 (350 to <500/mm^3)	0	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)
Grade 4 (<350/mm^3)	0	0	0	0	2 (1%)	1 (<1%)
Neutrophils ($x10^3$/uL)						
Grade 1 (1000 to 1300/mm^3)	3 (1%)	8 (1%)	10 (3%)	3 (1%)	11 (3%)	5 (2%)

Grade 2 (750 to <1000/mm^3)	1 (<1%)	3 (1%)	6 (2%)	3 (1%)	4 (1%)	1 (<1%)
Grade 3 (500 to <750/mm^3)	0	2 (<1%)	3 (1%)	1 (<1%)	0	0
Platelets (x10^3/uL)						
Grade 1 (100,000 to <125,000/mm^3)	2 (1%)	20 (4%)	17 (5%)	2 (1%)	7 (2%)	12 (4%)
Grade 2 (50,000 to <100,000/mm^3)	0	11 (2%)	13 (4%)	0	6 (2%)	9 (3%)
Grade 3 (25,000 to <50,000/mm^3)	0	2 (<1%)	3 (1%)	0	0	0

Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

In phase 2 trials of two investigational DAAs administered in combination with PEG/RBV, three cases of pancytopenia occurred, including one case of LDV given with VDV+PEG/RBV. Subsequently, all treatment was stopped in subjects receiving an investigational PI (e.g., VDV) combined with a second DAA+PEG/RBV, as all pancytopenia cases met this definition. Within the LDV/SOF program, no cases of pancytopenia are identified.

Hemoglobin

The majority of ≥Grade 3 hgb values occur in the LDV/SOF+RBV arms, with the exception of three subjects in LDV/SOF 12 week arm. These events are graded as Grade 3 due to the change from the subjects' baseline hgb values, and not due to a decline <9 g/dL.

- Subject #2111-71148 (ION-1): 37 year old man with baseline hgb 16.3 g/dL. An isolated Week 8 value of 11.3 g/dL (decrease 5 g/dL from baseline) was reported. No clinical AEs were reported at the time of this event. By Week 10 hgb increased to 15.5 g/dL without any intervention while continuing LDV/SOF treatment.
- Subject #0334-73614 (ION-3): 44 year old woman with baseline hgb 17.4 g/dL. An isolated post-treatment Week 4 value 12.5 g/dL (decrease 4.9 g/dL from baseline) was reported. No clinical AEs were reported at the time of this event. By post-treatment Week 12 hgb increased to 14.6 g/dL.
- Subject #5501-73503 (ION-3): 51 year old man with baseline Hgb 16.8 g/dL. An isolated Week 4 value 11.5 g/dL (decrease 5.3 g/dL from baseline) was reported. By Week 6 hgb increased to 16.5 g/dL without any intervention while continuing LDV/SOF treatment. No clinical AEs were recorded at the time of this event. Subsequently Grade 2 fatigue occurred Day 37 that did not resolve despite later increase in hgb.

Reviewer Comment: In the absence of RBV, hgb values <10 g/dL are infrequent (<0.1%, 1/1080 subjects) in LDV/SOF treated subjects. In addition, the three Grade 3 events (0.3%, 3/1080 subjects) reported in LDV/SOF treated subjects are isolated and improved without intervention; therefore, based on the phase 3 data, I do not believe hgb laboratories need to be labeled.

Neutrophils

Decreased neutrophil counts ≥Grade 3 occur in <1% overall. All ≥Grade 3 decreased neutrophil counts are isolated and/or occur in subjects with abnormal baseline values. No relevant infection-related AEs occur in association with any of these neutrophil decreased and no ≥Grade 3 decreases in other hematologic parameters occur.

Platelet Count

In the phase 3 trials, entry criteria allowed subjects with platelet counts ≥ 50,000/mm^3 in ION-1 and ION-2 trials, and >90,000/mm^3 in ION-3.

A total of 2.3% ≥Grade 2 thrombocytopenia (44/1952 subjects) occurs in the LDV/SOF±RBV treatment arms (2.9% LDV/SOF arms, 1.7% LDV/SOF+RBV arms), and all subjects remained on study treatment. Of the subjects with treatment-emergent ≥Grade 2 thrombocytopenia, 66% have baseline compensated cirrhosis. No thrombocytopenia is reported in the 8-week arms, noting these arms are from ION-3 where all subjects were non-cirrhotic.

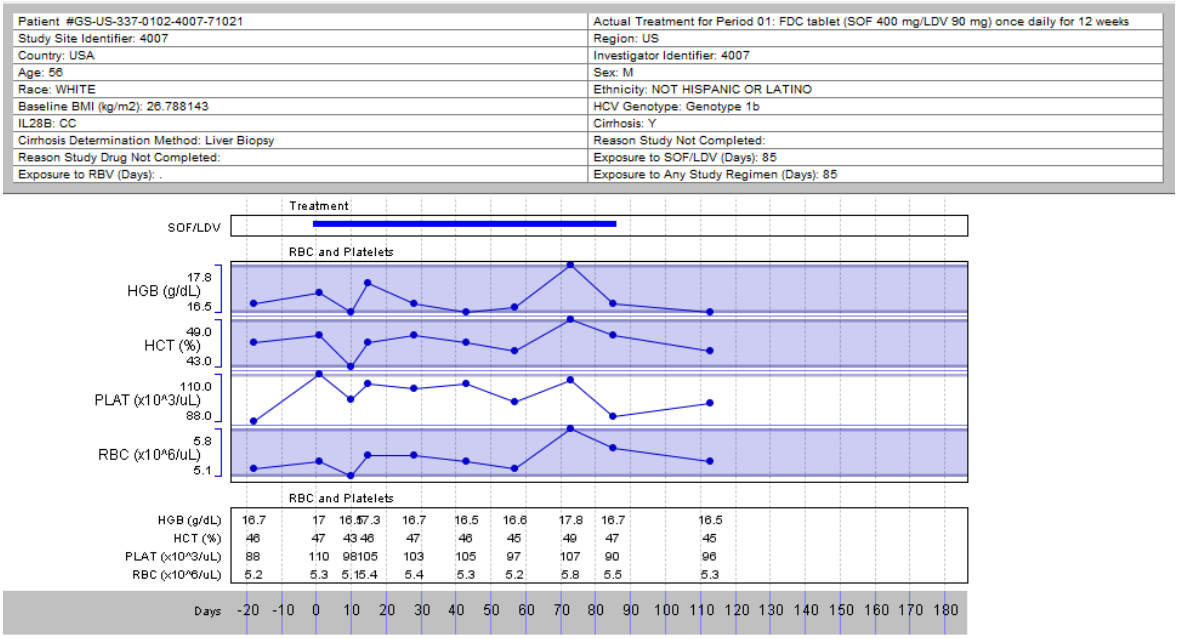
No Grade 4 thrombocytopenia is reported. Grade 3 thrombocytopenia occurs only in the LDV/SOF arms, and is <1% overall (5 subjects). One subject had an isolated Grade 3 platelet count Week 6 without reported AEs that was followed by normal count Week 8. The remaining four subjects are cirrhotic and had shift from baseline Grade 2 to Grade 3 platelet count. One subject with Grade 3 platelets experienced a gastrointestinal bleeding event.

- Subject #2760-79085 (LDV/SOF 24 Week, ION-2): 50 year old Caucasian man with cirrhosis and a history of Grade 2 esophageal varices, portal hypertension and splenomegaly had baseline platelets of 83,000/mm^3 (Grade 2). Note, prior to study this subject is reported to have received eltrombopag, though was not receiving the medication at study entry. Throughout the treatment course, platelet counts ranged 44,000-110,000/mm^3 with Grade 3 values occurring at Weeks 4 and 6. A Grade 3 SAE of upper gastrointestinal hemorrhage occurred Day 55, followed by initiation of eltrombopag Day 56. By post-treatment Week 4 the platelet count was 80,000/mm^3.

Reviewer Comment: No other subjects received eltrombopag during the phase 3 trials based upon review of ION-1, ION-2, ION-3 ADCM datasets.

Most subjects with Grade 2 thrombocytopenia had shift from baseline Grade 1 to Grade 2 platelet count (87%, 34/39 subjects). Of the remaining subjects, 4/5 had baseline platelet counts between 119,000-127,000/m^3. Most Grade 2 platelet decreases are either isolated or are fluctuations within a generally stable range. Below is a figure to illustrate this observed pattern of platelet fluctuation from Subject #4007-71021 (LDV/SOF 12 Week, ION-1) where screening and baseline platelet counts were 88,000/mm^3 and 110,000/mm^3, respectively, followed by on-treatment platelet range 90,000-107,000/mm^3.

Figure 7 Subject #4007-71021 Laboratory Data



Source: ADLB, ADSL Datasets (ION-1)

In summary, ≥Grade 2 thrombocytopenia occurring with LDV/SOF use in the phase 3 trials is low, 2.3%, occurs predominantly in subjects with baseline cirrhosis and did not lead to study treatment discontinuation. In addition, the majority of subjects with ≥Grade 2 thrombocytopenia have abnormal baseline values experiencing a single grade increase on treatment. Most subjects experienced either an isolated decrease or fluctuations within a generally stable on-treatment platelet range.

Reviewer Comment: Discussions regarding labeling for thrombocytopenia are ongoing. Based on review of the available data, it does not appear there is a strong causal association with LDV/SOF use and thrombocytopenia; however, a rationale for inclusion in the product label is to make prescribers aware of the occurrence of thrombocytopenia within the clinical trials, particularly in those with baseline cirrhosis.

Additional Grade 3 or 4 Laboratories

Table 69 displays additional ≥Grade 3 laboratories occurring in >1 subject. Subjects with ≥Grade 3 hyperglycemia had a medical history of diabetes. Grade 3 or 4 INR occurred in a total of seven subjects (0.4%, 7/1952 subjects). Four subjects were receiving anticoagulant therapy, two subjects had transient Grade 3 elevations at Week 24 (ION-2, LDV/SOF+RBV 24 Week) which returned to baseline levels by post-treatment Week 4, and one subject had Grade 3 elevation at Week 12 (ION-3, LDV/SOF 12 Week) which is attributed to a hemolyzed sample.

Table 69 Additional Laboratories with ≥Grade 3 Event in >1 Subject, LDV/SOF Phase 3 Integrated Safety Population

Laboratory Parameter Maximum Toxicity Grade	**LDV/SOF 8 Weeks**	**LDV/SOF 12 Week**	**LDV/SOF 24 Week**	**LDV/SOF +RBV 8 Week**	**LDV/SOF +RBV 12 Week**	**LDV/SOF +RBV 24 Week**
Total Number of Subjects in Analysis	215 n (%)	539 n (%)	326 n (%)	216 n (%)	328 n (%)	328 n (%)
Prothrombin Intl. Normalized Ratio						
Grade 3 (>2.0 to 3.0 x ULN)	0	1 (<1%)	2 (1%)	0	1 (<1%)	2 (1%)
Grade 4 (>3.0 x ULN)	1 (<1%)	0	0	0	0	0
Glucose (mg/dL) - Hyperglycemia						
Grade 3 (>250 to 500 mg/dL)	3 (1%)	9 (2%)	10 (3%)	1 (<1%)	3 (1%)	4 (1%)

Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

Renal Events

In the LDV/SOF phase 3 program, subjects with an eGFR <60 mL/min at screening were excluded; therefore, no clinical data on these subjects are available. Subjects with mild renal impairment were included with 31% of subjects having an eGFR <90 mL/min at baseline. No cases of renal failure or renal impairment occur in the pivotal trials. No Grade 3 or 4 events of elevated creatinine are reported as displayed in Table 70.

Table 70 Creatinine Laboratory Data, LDV/SOF Phase 3 Integrated Safety Population

Creatinine Maximum Toxicity Grade	**LDV/SOF 8 Week**	**LDV/SOF 12 Week**	**LDV/SOF 24 Week**	**LDV/SOF +RBV 8 Week**	**LDV/SOF +RBV 12 Week**	**LDV/SOF +RBV 24 Week**
Total Number of Subjects in Analysis	215 n (%)	538 n (%)	325 n (%)	214 n (%)	328 n (%)	328 n (%)
Grade 1 (>1.5 to 2 mg/dL)	3 (1%)	9 (2%)	4 (1%)	1 (<1%)	8 (2%)	9 (2%)
Grade 2 (>2 to 3 mg/dL)	0	0	1 (<1%)	0	1 (<1%)	0

Source: Integrated Datasets, ADLB, ADSL (ION-1, ION-2, ION-3)

Safety Update Report

Nine cases of renal failure are reported in subjects with either decompensated liver disease and/or are post-liver transplantation as listed in the Table 71. All cases of renal failure occur in subjects with cirrhosis or who are post-liver transplantation. These subjects have risk factors for development of renal failure including evidence of volume depletion (7/9 subjects), use of concomitant medications associated with renal toxicity (e.g., calcineurin inhibitor, ACE inhibitor, diuretics) and pre-existing renal insufficiency.

Table 71 Cases of Renal Failure Reported in the Safety Update Report

Trial Treatment Arm Subject ID	Dictionary-Derived Term	Start/ Stop Day	Related	Action	Peak Creatinine	Reported Outcome	Support for Prerenal Etiology
GS-US-337-0123, LDV/SOF+RBV							
Group 3, Post-OLT, F0-F3							
5969-75346	Acute Renal Failure	69 / 73	No	D/C RBV	2.18	Resolved	Yes
63 year old Caucasian man with history including hepatocellular carcinoma , ascites, liver transplant, chronic right pleural effusion, immunosuppression (tacrolimus). Baseline creatinine 1.1. Week 1 diagnosed with nephrolithiasis. Subsequently, pleural effusion required 1.5-2L thoracentesis 1-2 times per week associated with rising creatinine. Day 69 underwent thoracentesis, creatinine noted to be 2.17, BUN 69 and admitted for acute renal failure. RBV discontinued Day 70. Ultrasound showed echogenic renal cortices suggesting medical renal disease. Nephrology consultation indicated acute on chronic kidney injury secondary to multiple thoracenteses and hepatorenal syndrome (HRS)-type pathophysiology. Discharged Day 73 (creatinine 2.18) with diagnoses including suspected cirrhosis with portal hypertension, hepatic hydrothorax, acute kidney injury with suspected stable HRS and right pleural effusion possibly related to hepatic hydrothorax. The investigator's plan was to consider transjugular intrahepatic portosystemic shunt for the hepatic hydrothorax and to work him up for a repeat liver transplant.							
1516-75332	Acute Renal Failure	82 / 96	No	No Change	1.9	Resolved	No
58 year old woman of African descent with history including liver transplant, diabetes, hypertension, hypothyroid, chronic renal insufficiency, immunosuppression (tacrolimus, prednisone). Baseline creatinine 1.3. Day 82 creatinine 1.9. The following day admitted with acute renal insufficiency and anemia. Renal ultrasound normal. Etiology of elevated creatinine attributed to recent increase in lisinopril/HCTZ, and this drug was discontinued. The following day the event of acute renal insufficiency was considered resolved. Day 89 RBV was discontinued. Day 95 creatinine was 1.2.							
5267-75329	Acute Renal Failure	72 / 75	No	Dose Reduce RBV	4.39	Resolved	Yes
57 year old Caucasian man with history including liver transplant, hypertension, immunosuppression (mycophenolate mofetil, cyclosporine). Day 72 admitted with three days diarrhea and diagnosis of acute renal failure in setting of suspected C. difficile or enteritis. Creatinine 4.39 mg/dL, BUN 68 mg/dL. RBV interrupted (Day 72-76). Received intravenous fluids, metronidazole. Day 75 creatinine 1.48. Stool cultures negative and final diagnosis was worsening diarrhea and viral gastroenteritis. Discharged Day 76 after events resolved.							
5627-75328	Renal Failure	1 / 13	No	Dose Reduce RBV	24	Resolved	No
No narrative provided in SUR (not SAE). History includes chronic kidney disease. Baseline creatinine 3.27 mg/dL. Creatinine decreased to 1.83 and 1.39 mg/dL at Week 1 and 2, respectively. The AE was considered resolved Day 13.							
0519-	Acute Renal	PT Day	No	D/C	3.6	Resolved	Yes

75312	Failure	2 / PT Day 4		LDV/SOF, RBV			
57 year old man of African descent with history including liver transplantation, diabetes mellitus, chronic kidney disease, hypertension. Day 6 experienced nausea/vomiting with diarrhea occurring Day 7. The following day study drugs were discontinued. Day 10 (post-treatment Day 2) went to ER with continued symptoms, diagnosed with acute renal failure and diarrhea. Creatinine 3.6. Treated with intravenous fluids, ceftriaxone (for possible urinary tract infection). Discharged Day 12 (post-treatment Day 4) after events resolved, creatinine 1.6.							
Group 2, Pre-Transplant, CPT C							
0522-75211	Acute Renal Failure	22 / 29	No	Dose Reduce RBV	2.37	Resolved	Yes
55 year old Caucasian man with history including CPT C cirrhosis, hepatic encephalopathy, ascites, portal hypertension, esophageal varices, splenomegaly, history of SBP, listed for liver transplant with the Model of End-Stage Liver Disease (MELD) score of 28, peptic ulcer disease. Prior to study drug initiation hospitalized for Strep viridans bacteremia/SBP, paracentesis removed 2L fluid. Day 16 creatinine 2.7 (baseline 0.99). Day 22 diagnosed with acute kidney injury associated with epigastric discomfort and approximately 3-4 week history of worsening abdominal pain/nausea. Day 23 creatinine 2.37. Workup notable for amylase 190, lipase 129, though imaging without evidence of acute pancreatitis. Renal function improved with hydration and diuretic discontinuation, Day 26 creatinine 1.07. Workup for abdominal symptoms included EGD showing gastric ulcers in the antrum. Discharged Day 29 after events resolved. The subject's history of abdominal pain/nausea may have led to decreased fluid intake precipitating the event. Response to hydration while study drugs continued support a prerenal etiology.							
0200-75240	Acute Renal Failure	16 / 17	No	nterrupt LDV/SOF, D/C RBV	1.49	Resolved	Yes
64 year old man of African descent with history including CPT C cirrhosis, ascites, encephalopathy, GERD, diabetes. Baseline creatinine 1.3. Day 16 diagnosed with acute renal failure (creatinine 1.49) associated with nausea/vomiting. Held study treatment and diuretics. Renal function improved with intravenous fluids, antiemetics. Day 17 creatinine 1.09 and the subject was discharged. LDV/SOF treatment resumed Day 17, and RBV was discontinued.							
1249-75217	Acute Renal Failure	24 / 29	No	No Change	1.27	Resolved	Yes
61 year old Caucasian woman with history including CPT C cirrhosis, ascites, hepatic encephalopathy (MELD 24), SBP, hydrothorax, oral/esophageal candidiasis, odynophagia, dysphagia. Day 24 hospitalized with worsening dysphagia, dehydration. Creatinine 1.27. The increased creatinine and dehydration considered due to dysphagia and inability to eat or drink. Day 25 EGD unchanged. Renal function improved with intravenous albumin and interruption of diuretics. Discharged Day 26, and the subject was considered recovered Day 29. No follow up creatinine provided in the narrative.							
GS-US-337-0122 (ELECTRON 2), LDV/SOF							
Cohort 3, Group 1, CPT B							
1069—77214	Acute Renal Failure	43 / 55	No	No Change	172 µmol/L (RR 60-105	Resolved	Yes

					μmol/L)		
55 year old Caucasian man with history including end stage liver disease, CPT B cirrhosis, ascites, diabetes who experienced acute renal failure Day 43 following three day history of nausea/vomiting. Diagnosed with hepatic encephalopathy and hepatorenal syndrome. Received intravenous fluids, albumin and Telipressin. Day 46 creatinine improved to 111 μmol/L. Discharged Day 55 after events resolved.							

PT – post-treatment

Reviewer Comment: Based upon the lack of renal failure cases and lack of ≥Grade 3 creatinine elevation in the phase 3 LDV/SOF program, and due to the confounding comorbidities, evidence suggesting prerenal etiology and/or concomitant medication use in the SUR cases, a causal relationship between LDV/SOF use and renal failure is not supported at this time. In addition, no preclinical renal signal is identified and no SOF-related renal toxicity was identified in the SOF NDA Clinical Review. Cases of renal failure will be monitored in the postmarketing setting.

7.4.3 Vital Signs

In the phase 3 trials, no notable changes in pulse were observed in the LDV/SOF arms. The RBV-containing arms had a slight increase in pulse from baseline with median increase <5 beats per minute, and generally returned to baseline by post-treatment Week 4.

No notable changes from baseline in mean systolic blood pressure or diastolic blood pressure were observed in the phase 3 trials. A total of 2.5% subjects in the phase 3 trials experienced hypertension or blood pressure increased. No treatment-emergent, treatment-related hypertension events ≥Grade 3 were reported. Two SAEs of hypertension occurred (Subject #7751-71496, ION-1 LDV/SOF+RBV 12 weeks, Day 61-62; Subject #4326-73477, ION-3 LDV/SOF 8 weeks, Day 12-15). Common to both cases were an underlying medical history of hypertension, concomitant use of antihypertensives, continuation of study drugs while the event resolved, and investigator assessment were that the events were not related to study drug. I concur with the investigator assessment.

The Applicant was queried regarding hypertension events. Their assessment of the phase 2 and 3 LDV/SOF development program in a response received May 21, 2014 did not identify clinically significant (defined as Grade 3 or 4 AEs or SAEs) and treatment-related hypertension cases. They reference the SIRIUS trial where hypertension events were all ≤Grade 2 and similar between the LDV/SOF (7/77 subjects) and placebo groups (4/78 subjects).

Reviewer Comment: No obvious safety signal associated with LDV/SOF use and hypertension is identified at this time.

7.4.4 Electrocardiograms (ECGs)

The effect of LDV 120 mg twice daily for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 60 healthy subjects (GS-US-344-0109). The data were reviewed by the FDA Interdisciplinary Review Team (IRT) for QT Studies. Please refer to their consultation for complete details. The IRT Review Team concluded:

> No significant QTc prolongation effect of ledipasvir 120 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between ledipasvir 120 mg and placebo of the corrected QT calculated using population correction (ΔΔQTcN) at different time-point was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcN for moxifloxacin was greater than 5 ms.
>
> In this randomized, partially-blinded, placebo- and positive-controlled, 3 period single-and multiple-dose crossover study, 60 healthy subjects received ledipasvir 120 mg twice a day (BID), placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 72.

Table 72 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ledipasvir 120 mg BID and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcN (ms)	90% CI (ms)
Ledipasvir 120 mg BID	12	1.5	(-0.8, 3.8)
Moxifloxacin 400 mg*	12	9.7	(7.5, 12.0)

*Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 time points is 6.8 ms.
Source: FDA Interdisciplinary Review Team (IRT) for QT Studies, GS-US-344-0109 Review, Table 1

> The supratherapeutic dose (120 mg) produces mean Cmax values of about 3-fold the mean Cmax for the therapeutic dose (90 mg) at steady state. These concentrations are above those for the predicted worst case scenario (double the exposure after co-administration with P-gp inhibitors) and show that at these concentrations there are no detectable prolongations of the QT-interval. Increase in ledipasvir exposure by CYP-based drug- drug interactions is likely, but no data are available at this time. Hepatic or renal impairment may also increase ledipasvir concentrations; however, exposure data in patients with hepatic or renal impairment are not available.

Reviewer Comment: At the supratherapeutic dose of 120mg twice daily, LDV does not prolong QTc to any clinically relevant extent. One subject discontinued from the trial due to an exacerbation of pre-existing hematuria considered unrelated to study drug.

ECGs were performed at prespecified intervals in the phase 3 trials. Three subjects had single ECGs with a notable change from baseline deemed clinically significant:

- Subject #0521-71003 (LDV/SOF 12 Week, ION-1)
  30 year old woman experienced Week 1 ECG change deemed to be clinically significant: new onset, incomplete right bundle branch block. The subject was asymptomatic and continued on study drug. Subsequent ECGs showed the same result, however the investigator considered those as not clinically significant.

- Subject #2689-71058 (LDV/SOF 24 Week, ION-1)
  63 year old man with a history of hypertension experienced Week 12 ECG change deemed to be clinically significant: possible inferior infarct (age undetermined). The subject was evaluated by a cardiologist and was noted to have intermittent palpitations via 24-hour Holter monitoring and poorly controlled blood pressure. The investigator did not consider this finding to be related to the drug and suggested it could be due to the subject's uncontrolled blood pressure. The subject remained otherwise asymptomatic and continued on study drug.

- Subject #0334-73434 (LDV/SOF+RBV 8 Week, ION-3)
  55 year old man experienced Week 8 ECG change deemed to be clinically significant: new onset myocardial strain. Subsequent ECGs on the same day showed extensive T wave changes possibly due to myocardial ischemia. The subject was asymptomatic, and was specifically noted to not have any chest pain or shortness of breath. The ECGs were reviewed by an expert cardiologist who concluded that "the change in repolarization observed was clinically relevant and myocardial ischemia or pericarditis should be excluded". Consequently, a stress echocardiogram was done 4 days later which was normal with no signs of ischemia or pericarditis. An ECG performed approximately a week later showed that T waves had reverted to normal (no longer inverted). This was reported as a Grade 2 AE of myocardial strain on post-treatment Day 1 which resolved without action on post-treatment Day 5. The investigator considered this event related to study drug.

Reviewer Comment: The overall rate of subjects experiencing a single ECG deemed clinically significant is low. The subject with ECG showing myocardial strain had a negative stress echocardiogram, and the ECG reverted to normal without intervention. No obvious safety signal is identified associated with LDV/SOF use and ECG changes at this time.

7.4.5 Special Safety Studies/Clinical Trials

The SUR includes safety data from 120 subjects with decompensated cirrhosis (CPT B and C) with no liver transplant [20 subjects ELECTRON-2 (CPT B only), 100 subjects SOLAR-1], and an additional 107 subjects who had a liver transplant (SOLAR-1), of whom 41 had decompensated cirrhosis (CPT B and C). In this population based on submitted data to date, treatment with LDV/SOF±RBV has low discontinuation rates (<5%). Of the 81 SAEs reported (in 48 subjects), 11 are considered related to study drug, specifically RBV, by the investigator: 8 SAEs of anemia, and 1 SAE each of acute renal failure, hepatic encephalopathy, and portal vein thrombosis.

Reviewer Comment: The investigators' causality assessments seem reasonable in the cases of anemia, a known adverse reaction with RBV use. The cases of hepatic encephalopathy and portal vein thrombosis more likely explained by the subjects' advanced liver disease. Note, the SUR SOLAR-1 narratives do not report any case of acute renal failure considered related to study drug, as reflected in Table 71.

Additional safety information pertaining to the SOLAR-1 trial is summarized in this section. GS-US-337-0123 (SOLAR-1) is a phase 2, multicenter, open-label trial evaluating the efficacy and safety of LDV/SOF+RBV treatment for 12 or 24 weeks in HCV GT 1 and 4-infected subjects with advanced liver disease or who are post-liver transplant, including those with decompensated cirrhosis. Safety data from 307 subjects are summarized using the following categories:

- Subjects with decompensated cirrhosis (CPT B and C): Cohort A, Groups 1, 2
- Liver transplant subjects with F0 to F3 fibrosis: Cohort B, Group 3
- Liver transplant subjects with compensated (CPT A) and decompensated cirrhosis (CPT B and C): Cohort B, Groups 4, 5, and 6
- Liver transplant subjects with aggressive recurrent disease after transplant with fibrosing cholestatic hepatitis: Cohort B, Group 7

Approximately three-quarters of subjects (74%, 227/307 subjects) were on study treatment at the time of the SUR data cut: >90% Cohort A had received study drug for at least 6 weeks, >90% Cohort B had received study drug for at least 2 weeks. No subject had received study drugs more than 16 weeks. Seventy subjects (23%) have completed study treatment; the remaining subjects discontinued study treatment early as follows below.

- Four subjects with decompensated cirrhosis (Cohort A) discontinued study treatment early (4.0%, 4/100 subjects):
- Two subjects died (Subjects #5969-75231 and #6927-75149, please see below for narrative information)
- One subject discontinued study treatment early due to a nonserious AE of hepatic encephalopathy, and one subject had a liver transplant

- Two liver transplant subjects with F0 to F3 fibrosis (Cohort B, Group 3) discontinued study treatment early (1.8%, 2/112 subjects):

- One subject withdrew consent
- One subject discontinued due to nonserious AEs of ALT and AST increased

Subject #3055-75304 is a 57 year old man with a history including liver transplant February 2012 complicated by several episodes of rejection, plasma cell hepatitis diagnosed by liver biopsy, and significant depression. At screening, the subject was non-cirrhotic. Started LDV/SOF+RBV on 26 September 2013. At that time, baseline ALT 12 U/L, AST 18 U/L, total bilirubin 0.7 mg/dL. Due to increased depression, lamotrigine was started on Day 8. On Day 15, ALT declined to a nadir of 6 U/L. Subsequently, by Day 43, ALT increased to 72 U/L (1.7 × ULN, Grade 1) and AST increased from a nadir of 14 U/L to 82 U/L (2.3 × ULN, Grade 1). Study drugs were discontinued on Day 54 (18 November 2013) when ALT and AST elevations were confirmed as being >10 x nadir (stopping criterion). Lamotrigine was also discontinued at this time. The investigator considered the event ALT and AST increased as being related to study drugs. Following discontinuation of LDV/SOF+RBV and lamotrigine, ALT and AST values trended downwards through post-treatment Day 17; but subsequently increased on post-treatment Day 31 to ALT 110 U/L (2.6x ULN) and AST 138 U/L (3.8x ULN) followed by decrease post-treatment Day 59 to ALT 92 U/L (2.1x ULN) and AST 105 U/L (2.9x ULN) and normalization post-treatment Day 87 to ALT 27 U/L and AST 24 U/L. Total bilirubin was within the normal range at baseline and remained within the normal range throughout the study except for a single elevated value of 2.3 mg/dL (1.9 × ULN) on Day 8 (03 October 2013), with a direct bilirubin value of 0.6 mg/dL on the same date. HCV RNA remained undetectable, excluding HCV relapse as a potential etiology. The subject was taking numerous medications, including the following:

- Concomitant medications ongoing at baseline included amlodipine, omeprazole, docusate sodium and lactulose, zolpidem tartrate, hydroxyzine and clindamycin, oxycodone hydrochloride tramadol, gabapentin, fluconazole (pulmonary coccidiomycosis), acetylsalicylic acid (hepatic arterial flow), ropinirole (neuropathy), tacrolimus and mycophenolate mofetil (immunosuppression).
- New concomitant medications ongoing at the time of the AE included pseudoephedrine (26 September 2013–continuing), lamotrigine 12.5 mg QD (depression/anxiety; 04 October 2013–18 November 2013), and salbutamol sulfate (12 October 2013–10 April 2014).

The Applicant was queried for their assessment of this case, and their response received June 18, 2014 is included below:

> This subject experienced an increase in ALT and AST 10x above baseline/nadir values which required treatment discontinuation per protocol stopping rules. However, these elevations were mild in magnitude (72 U/L and 82 U/L) and not accompanied by increases in total bilirubin. These elevations were temporally associated with the initiation of lamotrigine. Furthermore, given the transient reduction in liver enzymes following treatment discontinuation and subsequent elevation of both lamotrigine and LDV/SOF+RBV, it is also possible that an

alternate etiology such as mild rejection or plasma cell hepatitis was responsible for these findings. A liver biopsy was not performed as part of his evaluation as the elevations were not deemed clinically meaningful…. In conclusion, polypharmacy in the setting of lamotrigine use, as well as the possibility of mild rejection or plasma cell hepatitis, confound the ability to determine the role of study drugs in this mild episode of abnormal ALT/AST elevation.

Reviewer Comment: I believe the Applicant's assessment is reasonable. The liver enzyme elevations were ≤Grade 2 without increases in bilirubin. This case has several confounders and/or alternative etiologies including temporal association with lamotrigine use (which has labeled events of AST increase, ALT increase), history of plasma cell hepatitis and possible mild rejection. AST and ALT did not normalize following LDV/SOF+RBV and lamotrigine discontinuation (negative dechallenge), lending support for an alternative etiology. It should be noted this event occurred in a post-liver transplant subject, and it is possible the LDV/SOF safety profile may be different in the post-transplant population compared with what has been characterized in the submitted phase 3 trials supporting the LDV/SOF application where an obvious causal association between LDV/SOF use and liver enzyme elevations has not been currently identified.

- Four liver transplant subjects with either compensated cirrhosis (one subject) (Cohort B, Group 4) or decompensated cirrhosis (three subjects) (Cohort B, Group 5) discontinued study treatment early (4.3%, 4/92 subjects):
- Two subjects with decompensated cirrhosis died (Subjects #1086-75511 and 0451-75523, please see below for narrative information)
- One subject with compensated cirrhosis discontinued study treatment early due to a nonserious AE of dyspnea, and one subject with compensated cirrhosis withdrew consent

- No liver transplant subjects with fibrosing cholestatic hepatitis (Cohort B, Group 7) have discontinued study treatment early. Note, only three subjects had been randomized at the time of the SUR data cut.

Eight deaths are reported, including the four deaths associated with trial discontinuation.

- Subject # 6927-75149 (Cohort A, Group 1: LDV/SOF+RBV 24 Weeks): Gastric hemorrhage, septic shock

53 year old woman with decompensated cirrhosis (CPT B) died of gastric hemorrhage and septic shock 62 days after the first dose of study drug; the subject's underlying cirrhosis and its known complications of variceal hemorrhage and portal hypertensive gastropathy may provide an alternative explanation for the event. The death was considered unrelated to study drug by the investigator.

- Subject # 5969-75231 (Cohort A, Group 2: LDV/SOF+RBV 24 Weeks): Septic shock

58 year old woman with decompensated cirrhosis (CPT C) died of septic shock 52 days after the first dose of study drug; the event was associated with complications of sepsis related to recurrent spontaneous bacterial peritonitis. The death was considered unrelated to study drug by the investigator.

- Subject #0200-75242 (Cohort A, Group 2: LDV/SOF+RBV 12 Weeks): Oliguric renal failure

57 year old woman with decompensated cirrhosis (CPT C) experienced shortness of breath Day 61 and was found to have gram negative rods cultured from a pleural effusion, treated with vancomycin. The subject was described as clinically stable with normal renal function. Three days later required intubation and developed oliguric renal failure. The subject died Day 67. The death was considered unrelated to study drug by the investigator.

- Subject #0200-75243 (Cohort A, Group 2: LDV/SOF+RBV 12 Weeks) Multi-organ failure, septic shock

59 year old man with decompensated cirrhosis (CPT C) died of multi-organ failure and septic shock 16 days after a liver transplant and 37 days after the first dose of study drug. Per the case narrative, study drug was discontinued the day prior to liver transplant. The death was considered unrelated to study drug by the investigator.

- Subject #3055-75425: (Cohort B, Group 4: LDV/SOF+RBV 12 Weeks) Progressive Multifocal Leukoencephalitis (PML)

67 year old man post-liver transplant on immunosuppression with tacrolimus with cirrhosis (CPT A) reported exacerbation of intermittent instability with abnormal gait on Day 23, symptoms that predate initiation of study drug therapy. On Day 40 this subject was diagnosed with PML (positive JC virus PCR from cerebral spinal fluid). The subject died of PML Day 80. The death was considered unrelated to study drug by the investigator. The subject's underlying immunosuppression status-post liver transplant was considered likely to have played a role in JC virus reactivation.

- Subject #1086-75511: (Cohort B, Group 5: LDV/SOF+RBV 24 Weeks): Thoracic aorta aneurysm dissection

69 year old man post-liver transplant with decompensated cirrhosis (CPT B) died of thoracic aorta aneurysm dissection 52 days after the first dose of study drug. The death was considered unrelated to study drug by the investigator.

- Subject #0451-75523: (Cohort B, Group 5: LDV/SOF+RBV 12 Weeks) Gastrointestinal Bleeding

44 year old man post- liver transplant receiving immunosuppression with tacrolimus, mycophenolate mofetil with decompensated cirrhosis (CPT B) experienced significant hematemesis Day 57 associated with hypotension, leading to fluid resuscitation, intubation and ICU admission. The hospital course was complicated by ascites requiring repeated paracenteses, possible pneumomediastinum. The

subject died on Day 59. The death was considered unrelated to study drug by the investigator. In the setting of underlying cirrhosis, gastrointestinal bleeding was considered likely related to portal hypertension (associated with esophageal varices and/or gastropathy).

- Subject #1516-75527: (Cohort B, Group 5: LDV/SOF+RBV 24 Weeks) Splenic Vein Thrombosis, Hepatic Abscess, Sepsis, Hemolytic Anemia

62 year old man post-liver transplant receiving immunosuppression with tacrolimus with decompensated cirrhosis (CPT B) experienced new onset fatigue and weakness Day 50. Work-up revealed splenic vein thrombosis, hepatic abscess with enterococcus faecalis bacteremia/sepsis and hemolytic anemia. Treatment included RBV discontinuation, antibiotic therapy, packed red blood cells, fresh frozen plasma. The subject died Day 76 with cause of death reported as hepatic cirrhosis and complications of cirrhosis. The death was considered unrelated to study drug by the investigator. The events are considered most likely due to the risks of thrombosis and infection associated with advanced liver disease and post-transplant immune suppression.

Reviewer Comment: This decompensated liver disease/post-transplant population has known associated comorbidities and is overall a sicker population compared with the population enrolled in the phase 3 trials. Overall there is no clustering of events and the increased incidence of AEs, SAEs and deaths does not raise concern at this time. Reports of anemia occur in the setting of RBV use, a known side effect of this medication. The data are used to support labeling recommendations in patients with severe hepatic impairment. Will monitor future safety information in this population and review the complete trial data when it is submitted to the Division. Submission of the complete SOLAR-1 data to provide further assessment of safety data is recommended as a postmarketing commitment.

7.4.6 Immunogenicity

LDV/SOF is comprised of two small molecules, not peptides; therefore, development of immunogenicity directed against LDV/SOF was not specifically evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only the LDV 90 mg/SOF 400 mg QD dose was used in the pivotal phase 3 trials and is the proposed dose for use if the marketing application is approved.

7.5.2 Time Dependency for Adverse Events

Three different LDV/SOF treatment durations were explored in the phase 3 trials. No notable differences in the side effect profile were identified among the 8 week versus 12 week versus 24 week treatment durations as described in Section 7.4.1.

7.5.3 Drug-Demographic Interactions

- AUC and Cmax of LDV are 77% and 58% higher, respectively, in women than in men. After correcting for weight differences, women have ~40% higher exposure compared with men. No clinically relevant PK differences have been observed between men and women for SOF and GS-331007.

- Population PK analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposures of LDV, SOF or GS-331007.

- Population PK analysis in HCV-infected subjects showed that within the age range (19 to 80 years) analyzed, age did not have a clinically relevant effect on the exposures of LDV, SOF or GS-331007.

Safety data in the pivotal phase 3 safety population based on demographic characteristics such as age, gender, race and region are briefly discussed in this section.

Age

There was no upper age limit entry criterion in the phase 3 trials. An age cutoff of 65 years is selected to evaluate safety events in elderly subjects. Approximately 8% subjects in the phase 3 trials were ≥65 years old (152 subjects, range 65-80 years).

In the pooled LDV/SOF groups, no notable differences occur between the percentages of subjects aged ≥65 years with treatment-related AE (49%, 34 subjects) or Grade 3 or 4 AE (7%, 5 subjects) and subjects <65 years (61% and 6%, respectively). The most common treatment-related AEs occurring in LDV/SOF-treated subjects ≥65 years are fatigue (23%, 16 subjects) and headache (11%, 8 subjects), consistent with what is observed in the <65 years population.

In the pooled RBV-containing groups, higher percentages of subjects aged ≥65 years experienced treatment-related AEs (86%, 48 subjects) and Grade 3 or 4 AEs (13%, 7 subjects) compared with subjects aged <65 years (82% and 5%, respectively). Additionally, in subjects receiving LDV/SOF+RBV, AEs leading to study drug modification or interruption were reported at an approximately 2.5-fold higher incidence in subjects aged ≥65 years (38%, 21 subjects) compared with subjects <65 years (14%). The most common treatment-related AEs occurring in LDV/SOF+RBV-treated

subjects ≥65 years are fatigue (48%, 27 subjects), anemia (25%, 14 subjects), nausea (18%, 10 subjects) and insomnia (16%, 9 subjects). Treatment-related anemia is reported at a higher incidence in subjects aged ≥65 years (25%) compared with subjects aged <65 years (10%).

Gender

Approximately 40% (777 subjects) of the phase 3 population were women. In the pooled LDV/SOF groups, women have higher percentage of treatment-related AEs compared with men (54% versus 39%, respectively). No notable differences occur between the percentages of women with Grade 3 or 4 AEs (5%) and men (4%). The only treatment-related AE that occurs ≥5% more in women than in men is headache (19% versus 12%, respectively).

In the pooled RBV-containing groups, modestly higher percentages of women experienced treatment-related AEs and AEs leading to study drug modification or interruption (73% and 15%, respectively) compared with men (69% and 12%, respectively). Grade 3 or 4 AEs were similar between the women and men (5% in each group). Treatment-related anemia was reported in 11% women and 8% men. This numerical trend of greater anemia in women receiving RBV-containing treatment compared with men may be explained by generally lower pretreatment hemoglobin levels (mean 13.8 g/dL versus 15.2 g/dL, respectively) and by lower median BMIs which may contribute to higher overall RBV exposures from the weight-based RBV dosing.

Reviewer Comment: Although women have higher LDV exposures compared with men, no clinically significant safety differences are identified between genders.

Race

Approximately 16% (308 subjects) of the phase 3 trial population were black/African American. In the pooled LDV/SOF groups, black/African American subjects have similar/lower percentage of treatment-related AEs (49%, 59 subjects) and Grade 3-4 AEs (4%, 5 subjects) compared with non-black/African American subjects (62% and 6%, respectively).

In the pooled RBV-containing groups, black/African American subjects experienced similar/lower percentages of treatment-related AEs (68%, 66 subjects), Grade 3 or 4 AEs (5%, 5 subjects) and AEs leading to study drug modification or interruption (16%, 16 subjects) compared with non-black/African American subjects (68%, 6% and 16%, respectively). Treatment-related anemia was reported in 11% black/African American and non-black/African American groups.

Region

ION-1 is the only multinational LDV/SOF pivotal phase 3 trial within this application. Approximately 40% enrolled ION-1 subjects were European, compared with approximately 60% US subjects. In the pooled LDV/SOF groups, US subjects have lower percentage of treatment-related AEs (47%) compared with European subjects (57%), and similar percentages of Grade 3 or 4 events (5% US vs 6% Europe). The only treatment-related AE with ≥5% between the two groups is asthenia (0% US vs 16% Europe).

In the pooled RBV-containing groups, US subjects experienced similar percentages of treatment-related AEs (72%) and Grade 3 or 4 AEs (7%) compared with European subjects (78% and 5%, respectively). More AEs leading to drug modification or interruption occurred in US subjects (20%) than in European subjects (12%).

7.5.4 Drug-Disease Interactions

Please refer to NDA 204671 for details regarding SOF and renal impairment, hepatic impairment interactions.

Renal Impairment

LDV PK was studied with a single LDV 90 mg dose in HCV-negative subjects with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault) in GS-US-344-0108. No clinically relevant differences in LDV PK were observed between healthy subjects and subjects with severe renal impairment. As noted in Section 4.4.3, no SOF dose recommendation can be given for patients with severe renal impairment or ESRD due to high SOF exposures.

As discussed in Section 4.4.3, LDV/SOF was not specifically studied in subjects with renal impairment. Since LDV increases SOF AUC by ~2.3-fold, SOF AUC could be up to 4.5-fold higher in patients with mild or moderate renal impairment receiving LDV/SOF if the effects on SOF AUC are additive. Phase 3 population PK analysis found subjects with baseline mild renal impairment (31.4%, 612/1952 subjects, defined as baseline eGFR 60 to <90 mL/min) had ~17% higher SOF AUC_{tau} compared to subjects with baseline normal renal function. This SOF AUC increase is lower than observed in non-HCV-infected subjects, suggesting the impact of LDV/SOF on SOF exposure in patients with mild and moderate renal impairment may be lower in HCV-infected patients.

In the pooled phase 3 LDV/SOF group without RBV, the percentages of subjects with any treatment-emergent AE, ≥Grade 3 AE, and AEs leading to study drug modification or interruption is similar for subjects with an eGFR ≥90 mL/min (74.2%, 4.2%, and 0.5%, respectively) and subjects with an eGFR <90 mL/min (73.8%, 4.5%, and 0.6%, respectively). The most common AEs in each of the two groups are similar (fatigue,

headache, nausea) and no AE occurs with >5% proportion difference in the eGFR <90 mL/min group compared with the eGFR >90 mL/min group.

Based on these data, it will be recommended that LDV/SOF can be administered to patients with mild or moderate renal impairment. No LDV/SOF dose recommendation can be given for patients with severe renal impairment or end stage renal disease due to increased SOF and GS-331007 exposures and lack of established safety and efficacy information in this population.

Hepatic Impairment

LDV PK was studied with a single LDV 90 mg dose in HCV-negative subjects with severe hepatic impairment (Child-Pugh Class C) in GS-US-344-0101. LDV plasma exposure (AUC_{inf}) was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function. Ledipasvir C_{max} was ~35% lower in subjects with severe hepatic impairment. Population PK analysis in HCV-infected subjects with compensated cirrhosis from phase 2 and 3 trials indicated that cirrhosis had no clinically relevant effect on LDV exposure. Assessment of phase 3 LDV/SOF safety information in subjects with compensated cirrhosis is included in Section 7.4.1.

As discussed in Section 4.4.3, PK data from 33 HCV-infected subjects with moderate and severe hepatic impairment enrolled in ongoing GS-US-337-0122 and GS-US-337-0123 trials, including 8 post-liver transplant subjects, demonstrates ~2.7-fold and ~3.2-fold increase in AUC_{tau} and C_{max}, respectively, for subjects with Child-Pugh Class B, and ~2.8-fold increase in AUC_{tau} and C_{max} for subjects with Child-Pugh Class C, compared to 1845 non-cirrhotic subjects enrolled in phase 2 and 3 trials.
Section 7.4.5 contains safety information in subjects with decompensated cirrhosis and/or who are post-liver transplantation from GS-US-337-0123 (SOLAR-1).
Submission of the complete SOLAR-1 data to provide further assessment of safety data is recommended as a postmarketing commitment.

Based on the combined PK and available safety information, it will be recommended that LDV/SOF can be administered to patients with mild, moderate or severe hepatic impairment, noting that safety and efficacy of LDV/SOF have not been established in patients with decompensated cirrhosis.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review for detailed assessment of the Phase 1 drug-drug interaction trials and labeling considerations. This section summarizes notable findings.

Drugs that are P-gp inducers (e.g., rifampin, St. John's wort) should not be used with LDV/SOF as they may significantly decrease LDV and SOF plasma concentrations and may lead to a reduced therapeutic effect.

Coadministration with drugs that inhibit P-gp and/or BCRP may increase LDV and SOF plasma concentrations without increasing GS-331007 plasma concentration. Review of submitted data from subjects taking P-gp inhibitors including azithromycin, erythromycin, verapamil, ketoconazole, amiodarone and fluvoxamine in phase 2 and 3 LDV/SOF trials indicates ~1.3-1.7-fold higher LDV exposures (overall and by gender) compared to subjects not on P-gp inhibitors. No SAEs occur in these 12 subjects. Submitted data from subjects receiving SOF and cyclosporine (doses 75 to 225 mg) indicate increases in SOF exposure are lower than observed in phase 1 drug-drug interaction trials where 600 mg cyclosporine dose used. Therefore, clinically used cyclosporine doses may not be associated with substantial increases in SOF exposure. Based on the available data, the review team recommends LDV/SOF may be coadministered with P-gp and/or BCRP inhibitors.

Because LDV is an inhibitor of P-gp and methadone is a P-gp substrate, a safety analysis was conducted in HCV-infected subjects receiving methadone. Baseline methadone use was 2.3% in ION-1 (20/865 subjects), 1.4% in ION-2 (6/440 subjects) and 2.0% in ION-3 (13/647 subjects). Among LDV/SOF±RBV-treated subjects receiving concomitant methadone in the phase 3 trials (N=39 subjects), the most common AEs occurring ≥10% (>3 subjects) are fatigue (33%), nausea (23%), headache (15%), back pain (13%), rash (13%), diarrhea (10%), insomnia (10%), irritability (10%) and myalgia (10%). The majority of these events were Grade 1. Grade 1 dizziness is reported in two subjects.

Reviewer Comment: The identified AEs in subjects receiving methadone are similar to the AEs identified in the general LDV/SOF phase 3 population.

Simeprevir is not recommended to be coadministered with LDV/SOF. LDV 30 mg once daily dose increased simeprevir Cmax and AUC by 161% and 169%, respectively due to P-gp inhibition.

LDV/SOF coadministered with efavirenz/emtricitabine/tenofovir reduced LDV AUC and Cmax ~34%. In addition, tenofovir AUC, Cmax and Ctau increase 98%, 79% and 163%, respectively. Interim safety data from subjects receiving LDV/SOF and efavirenz/emtricitabine/tenofovir in the CO-US-337-1116 and GS-US-337-0115 trials were submitted to inform labeling decisions regarding coadministration of these agents on July 1, 2014 and July 7, 2014, respectively. These data remain under review at the time of this Clinical NDA Review.

There are insufficient data to make dosing recommendation for LDV/SOF coadministration with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased exposure of tenofovir.

LDV solubility decreases as pH increases; therefore, drugs that increase gastric pH are expected to decrease LDV exposure. Decreased LDV exposure (~42% to 48% lower AUC and Cmax) occurred with proton pump inhibitor (PPI), omeprazole, 2 hours prior to LDV. LDV absorption was not affected with simultaneous or 12 hour staggered dosing with famotidine (H2-receptor antagonist). Recommended LDV/SOF dosing with PPI and H2-receptor antagonists remains under review at this time.

Coadministration of SOF and oral contraceptives increase ethinyl estradiol C_{max} ~40% and AUC ~20%. No significant changes occur in PK with LDV and oral contraceptive coadministration. Labeling of LDV/SOF coadministration with oral contraceptives is not finalized at the time of this review, with considerations factoring in the recommended LDV/SOF treatment durations.

No dose adjustment is needed for LDV/SOF and the following drugs based on review of available PK and drug-drug interaction data: abacavir, atazanavir/r, cyclosporine, darunavir/r, emtricitabine, lamivudine, methadone, raltegravir, rilpivirine, tacrolimus, tenofovir (excluding tenofovir when used as part of elvitegravir/cobicistat/emtricitabine/tenofovir as noted above), or verapamil.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The maximum LDV/SOF trial duration (approximately 36 weeks for ION-2 LDV/SOF±RBV 24 week arms) limits assessment of neoplastic events in LDV/SOF-treated subjects. In the pivotal phase 3 trials, ten subjects experienced an event within the SOC of Neoplasms, Benign, Malignant and Unspecified: basal cell carcinoma (2), squamous cell carcinoma (hand), skin papilloma, neuroma, pituitary tumor, hepatocellular carcinoma, pancreatic ductal carcinoma, squamous cell carcinoma of the lung, squamous cell carcinoma (sinonasal mass). Several events occurred within 12 weeks of LDV/SOF exposure and/or in subjects with pre-existing symptoms making a LDV/SOF causal etiology unlikely: pituitary tumor (Subject #0380-73282 Day 75, unintentional weight loss 3 months prior to trial initiation), pancreatic ductal adenocarcinoma (Day 149, pancreatic lesions detected 3 months prior to trial initiation), squamous cell carcinoma of the lung (Day 43, prior history of lung adenocarcinoma), squamous cell carcinoma (sinonasal mass, Day 102, pre-existing nasal congestion and runny nose >1 year, chronic sinusitis). Case of hepatocellular carcinoma (Subject #5847-79051) occurred in subject with underlying cirrhosis approximately four months after completing therapy without achieving SVR12.

Reviewer Comment: No clustering of any particular malignancy is noted and most cases occurred in subjects with pre-existing symptoms. Cirrhosis is a known risk factor for hepatocellular carcinoma.

7.6.2 Human Reproduction and Pregnancy Data

Based upon preclinical data, LDV/SOF is currently proposed to be labelled as Pregnancy Category B.

In all clinical trials conducted to date with SOF, LDV, or LDV/SOF, pregnant and breastfeeding women were excluded. RBV is known to be genotoxic and teratogenic, and all phase 3 LDV/SOF trials included RBV-containing regimens. Women of childbearing potential enrolled in trials were required to use two effective methods of birth control. In addition, urine pregnancy testing was performed at regular intervals as defined in each protocol. Pregnancy, once determined, was a condition for required withdrawal of the subject from the trial.

There have been six pregnancies reported in clinical trials in the LDV/SOF clinical development program. These are briefly described below:

ION-1: two pregnancies, one pregnancy in the female partner of a male subject

- Subject #0472-71514 in the LDV/SOF+RBV 24 Week group had a pregnancy confirmed on Day 29. Contraception included condoms and contraceptive medication. Spermicide had been prescribed but was not in use. The subject had an induced abortion on Day 43.
- Subject #2012-71373 in the LDV/SOF 24 Week group discontinued treatment Day 71 due to pregnancy. The subject's IUD was removed after a salpingitis diagnosis while on treatment. The investigator considered that the pregnancy was due to IUD removal and subject report of a condom breakage. The subject had an induced abortion on post-treatment Day 14.
- Subject #3060-71150 in the LDV/SOF 12 week group's female partner was pregnant at the trial onset and while the male subject received LDV/SOF for approximately 2.5 months. The mother delivered a full-term healthy female infant via cesarean delivery.

ION-3: one pregnancy in a female partner of a male subject

- Subject #4435-73554 in the LDV/SOF 12 week group discontinued study drugs on 05 September 2013, and his female partner had her last menstrual period on an unspecified date in September 2013. The pregnancy was reported to be due to inconsistency in use of condoms as contraception. Prenatal tests and ultrasounds have not performed at the time of reporting. The pregnancy is ongoing with an estimated date of delivery of June 2014.

P7977-0523 (Part 4, Groups 12 and 13 and Part 6, Groups 16 to 18; 20, and 21): one pregnancy

- Subject #1069-5561 in the LDV/SOF 12 week group (Group 18) had pregnancy confirmed Day 57 and elected to interrupt the pregnancy by induced abortion. The narrative states contraceptive failure of condoms occurred. The subject completed study treatment.

GS-US-337-0101: one pregnancy (Cohort 1, LDV+SOF)

- Subject #2687-1025 had a confirmed pregnancy Day 16 after having negative pregnancy tests Days -9, -1 and 7. She reported a spontaneous abortion on Day 25 that resolved on Day 104, the day of a scheduled dilation and curettage procedure.

The SUR reports four additional pregnancies. Two nontreatment-emergent pregnancies were reported from the LDV/SOF phase 3 trials.

- Subject #0482-71851 (LDV/SOF, ION-1) a 36 year old woman became pregnant approximately 3 months after the last dose of study drug, and experienced a spontaneous abortion at approximately week 8 of the pregnancy. The investigator assessed the event as not related to study drug, with an alternative causality of natural causes. The event was considered resolved with no sequelae.
- Subject #2493-73099 (LDV/SOF, ION-3) a 25 year old woman had last menstrual period approximately 3 months after the last dose of study drug and on an unknown date, the subject became pregnant. The pregnancy was ongoing at the time of the SUR report.

One pregnancy occurred in GS-US-337-0122 (Subject #5868-77114). One pregnancy occurred in CO-US-337-0117 (Subject # FDCNV02). Please refer to Section 7.7 for additional details.

7.6.3 Pediatrics and Assessment of Effects on Growth

The agreed initial Pediatric Study Plan (PSP) was previously submitted to IND 115268 (SN0119), dated January 2, 2014. A copy of the Agreed Initial PSP and the FDA Agreed PSP letter, dated January 3, 2014, are included with the original NDA. The Applicant has requested a waiver of pediatric studies in children < 3 years of age and a deferral for submission of pediatric data in children aged 3 to (b) (4) years. This request will be discussed at the FDA Pediatric Review Committee meeting scheduled August 6, 2014.

LDV/SOF has only been administered in adults, and therefore no clinical assessment of effects on growth has been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is limited experience with overdosage of LDV/SOF. Regarding the individual components, the highest documented multiple LDV dose is the supratherapeutic dose of 120 mg twice daily for 10 days administered to 59 healthy subjects in GS-US-344-0109. As reported by the Applicant, AEs were similar in frequency and severity to those reported in the placebo groups.

The highest documented SOF dose is a single supratherapeutic dose of SOF 1200 mg administered to 59 healthy subjects in P7977-0613 where AEs were similar in frequency and severity to those reported in the placebo and SOF 400 mg treatment groups.

No specific antidote is available for LDV/SOF overdose. The Applicant notes hemodialysis is unlikely to result in significant removal of LDV since LDV is highly bound to plasma protein. Hemodialysis can remove the predominant circulating metabolite of SOF, GS-331007, with an extraction ratio of 53%.

LDV/SOF is not expected to have abuse or dependence potential. Elevations in liver enzymes and HCV RNA levels can occur with virologic failure (e.g., relapse).

7.7 Additional Submissions / Safety Issues

The Applicant provided responses to FDA's Information Requests during the course of the review cycle. Pertinent information provided from these responses is integrated throughout this review in relevant sections.

The Applicant submitted the Safety Update Report (SUR) on May 5, 2014 (90 days after the original NDA submission as was previously agreed). The report provides available updated safety data from ongoing LDV/SOF-containing trials (13 Gilead-sponsored clinical trials and 2 non-Gilead-sponsored trials) as well as a summary of myocardial ischemia events (reviewed in Section 7.3.5). The data presented by the Applicant is cumulative from the initiation of the clinical trials to the SUR data cutoff dates.

This section summarizes the SUR data provided from phase 2 and 3 trials not included with the original NDA submission, with references to pertinent narratives integrated into other sections of this review. These trials are: GS-US-337-0113, GS-US-337-0121 (SIRIUS), GS-US-337-0122 (ELECTRON-2) Part A LDV/SOF groups, GS-US-337-0125, GS-US-337-0131, GS-US-337-0133 (LONESTAR-3), GS-US-337-1118, CO-US-337-0116 (ERADICATE; National Institute of Allergy and Infectious Diseases [NIAID]-sponsored Study IND 117444), and CO-US-337-0117 (SYNERGY; NIAID-sponsored Study IND 116585). The SOLAR-1 trial safety data are discussed separately in Section 7.4.5 Special Safety Studies/Clinical Trials.

GS-US-337-0113

This phase 3, randomized, multicenter, open-label trial evaluates LDV/SOF±RBV 12 weeks in HCV GT 1 treatment-naive and treatment-experienced Japanese subjects, with or without compensated cirrhosis. HCV GT 1 treatment-naïve and treatment-experienced subjects randomized 1:1 to LDV/SOF for 12 weeks or LDV/SOF+RBV for 12 weeks. Overall, 22% of enrolled subjects have compensated cirrhosis.
Of the 341 subjects who received at least one dose of study drug, 311 subjects (91.2%) were still on study treatment at the time of the data cut; 28 subjects (8.2%) completed study treatment. Two subjects (0.6%) discontinued study treatment early: one subject discontinued due to an AE (morbilliform rash, Subject #8355-86317 LDV/SOF+RBV, see Section 7.3.5 Rash Events) and one subject died (cardiac arrest, Subject #8314-86263 LDV/SOF+RBV, see Section 7.3.5 Myocardial Ischemia Events).

One non-fatal SAE is reported:

- Subject #8317-86021 (LDV/SOF 12 Weeks)
  67 year old Asian man categorized as non-cirrhotic experienced Day 71 Grade 3 esophageal varices hemorrhage (SAE). LDV/SOF was interrupted for one day. The subject was hospitalized, received a blood transfusion, and an emergency variceal ligation was performed. The event resolved the same day and was considered unrelated to study drug by the investigator.

No other SAEs of interest (including death), ≥Grade 3 AEs, or AEs leading to permanent discontinuation of study drug were reported. No subjects had Grade 4 laboratories reported. No subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

GS-US-337-0121 (SIRIUS)

This phase 2, randomized, multicenter, double-blind, placebo-controlled trial evaluates LDV/SOF+RBV 12 weeks or LDV/SOF 24 weeks in HCV GT 1 treatment-experienced, cirrhotic subjects. Eligible subjects were required to have not achieved SVR following treatment with at least one PEG/RBV regimen followed by at least one PI+PEG/RBV regimen. Subjects randomized 1:1 to LDV/SOF (+ placebo) for 24 weeks or placebo for 12 weeks (deferred treatment) followed by LDV/SOF+RBV for 12 weeks. The SUR includes data for the first 12 week period, comparing placebo to LDV/SOF.

Of the 155 subjects who received at least one dose of study drug, all subjects were continuing study drug treatment with the exception of one subject (0.6%) in the placebo group, who discontinued study treatment early due to an AE (Grade 4 hepatic decompensation, SAE).

Similar percentages of subjects had at least one AE in the LDV/SOF group (84.4%) and placebo group (83.3%). More subjects in the LDV/SOF group compared with the

placebo group had headache (35.1% vs 20.5%), fatigue (16.9% vs 3.8%) and irritability (10.4% vs 2.6%). More subjects in the placebo group compared with the LDV/SOF group had pruritus (17.9% vs 5.2%).

No deaths were reported. Three subjects had ≥Grade 3 AEs, two in the LDV/SOF group (both Grade 3: cholelithiasis, headache) and one in the placebo group (Grade 4 hepatic decompensation). Four subjects had an SAE, three in the LDV/SOF group (cholelithiasis, cranial nerve infection due to herpes simplex virus, road traffic accident) and one in the placebo group (bacterial arthritis/hepatic decompensation). None of these SAEs were considered related to study drug by the investigator.

One subject who received LDV/SOF had a Grade 4 lipase laboratory abnormality associated with SAE of cholelithiasis (Subject #4021-88036, please see Section 7.3.5 for additional details). No subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

Reviewer Comment: Unlike the pivotal phase 3 trials, this trial includes a placebo group which allows for comparison with LDV/SOF, noting these data have not been independently reviewed by the Division and come from a trial conducted in France which may limit generalizability to the US population. Headache and fatigue have the largest treatment differences between the LDV/SOF and placebo groups, events that are captured in the currently proposed LDV/SOF label.

GS-US-337-0122 (ELECTRON-2)

This phase 2, multicenter, open-label trial is described in Section 5.3. The SUR includes safety data for subjects in Part A Cohorts 1 (Group 1), 2 (Groups 1-4), and 3 (Group 1) as follows:

- Cohort 1: HCV GT 1 subjects who were previously treated in P7977-0523 (ELECTRON) and did not achieve SVR. Receive LDV/SOF+RBV for 12 weeks.
- Cohort 2:
  - Groups 1 and 2: HCV GT 1 treatment-experienced subjects with advanced fibrosis or compensated cirrhosis randomized 1:1 to receive LDV/SOF+ RBV for 12 weeks, or LDV/SOF+GS-9669 500 mg QD for 12 weeks.
  - Groups 3 and 4: HCV GT 3 treatment-naïve subjects randomized 1:1 to LDV/SOF for 12 weeks or LDV/SOF+RBV for 12 weeks.
- Cohort 3: HCV GT 1 CPT B treatment-naive or treatment-experienced subjects to receive LDV/SOF for 12 weeks.

Overall, 44.7% of subjects had cirrhosis, including 14.2% with decompensated (CPT B) cirrhosis. Of the 141 subjects who received at least one dose of study drug, 137 subjects (97.2%) completed study drug treatment. Four subjects (2.8%) discontinued study treatment early: two subjects were noncompliant with study drug, one subject

discontinued study treatment early due to an AE (perforated sigmoid diverticulitis), and one subject was lost to follow-up.

No deaths were reported. Five subjects had ≥Grade 3 AEs. No individual Grade 3 or 4 AE is reported in >one subject. One Grade 4 AE was reported which is also an SAE.

- Subject #1069-77012 Pericardial Effusion

  This subject had a Grade 4 AE of pericardial effusion post-treatment Day 20 as a sequela of coronary artery bypass graft surgery (see summary in Section 7.3.5 Myocardial Ischemia Events). The event was considered unrelated to study drug by the investigator and resolved on post-treatment Day 33.

Five subjects had Grade 3 AEs: angina pectoris, renal colic, abdominal pain, perforated sigmoid diverticulitis, and upper abdominal pain. Each of these Grade 3 AEs was serious with the exception of renal colic, which was considered nonserious. The Grade 3 SAE of perforated sigmoid diverticulitis (Subject #5868-77124) led to the permanent discontinuation of LDV/SOF, please refer to Section 7.3.5 Gastrointestinal Events for case details.

Seven subjects experienced SAEs (Cohort 2 Group 1, LDV/SOF+RBV: angina pectoris/pericardial effusion; Cohort 2, Group 2 LDV/SOF: abdominal pain, abdominal pain upper, diverticular perforation, choroidal effusion/lens dislocation; Cohort 3, Group 1 LDV/SOF: acute renal failure, squamous cell carcinoma of the tongue). Note, SAEs of choroidal effusion/lens dislocation, angina pectoris and acute renal failure are discussed in Section 7.3.5 Ocular and Myocardial Ischemia Events and Section 7.4.2 Renal Failure Events, respectively. Two SAEs (Subject #5868-77113 abdominal pain, Subject #5868-77150 upper abdominal pain), both in Cohort 2, Group 3, are considered related to study drug by the investigator. Please refer to Section 7.3.5 Gastrointestinal Events for case details.

Two subjects had Grade 4 laboratories: increased lipase and decreased lymphocytes. The event of increased lipase is summarized below:

- Subject #5868-77015 Elevated Lipase (Cohort 2, Group 2)

  This subject had baseline Grade 2 increased lipase that remained elevated through Week 10, yet at the Week 12 visit, lipase values decreased to within the reference range. Post-treatment Week 4, Grade 4 increase in lipase (444 U/L), follow-up visits at 35 and 55 days after the last dose of study drug showed decreasing lipase values (210 U/L and 82 U/L, respectively). The subject was asymptomatic

No subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

One pregnancy is reported (Subject #5868-77114, LDV/SOF), occurring approximately 5 1/2 months after last dose of study drug. At the time of the SUR, the status of the current pregnancy was reported as continuing.

GS-US-337-0125

This single center, open-label trial evaluates LDV/SOF for 12 weeks in subjects with nosocomial HCV GT 1 infection. A total of five subjects have received at least one dose of study drug, one of whom was still on study treatment at the time of the data cut. No subjects had discontinued study treatment early. One subject experienced an SAE of myocardial infarction (Subject #0773-80002), please refer to Section 7.3.5 Myocardial Ischemia Events for case details. No deaths, ≥Grade 3 AEs, Grade 4 laboratories or on-treatment liver-related laboratory abnormalities were reported.

GS-US-337-0131

This multicenter, open-label, international trial (Korea and Taiwan) evaluates LDV/SOF 12 week treatment in HCV GT 1 treatment-naive and treatment-experienced subjects. Overall 18.2% subjects have cirrhosis. A total of 44 subjects have received at least one dose of study drug, all of whom were still on study treatment at the time of the data cut. No subjects had discontinued study treatment early. No SAEs (including death), ≥Grade 3 AEs or Grade 4 laboratories occurred. No subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

GS-US-337-0133 (LONESTAR-3)

This phase 2, randomized, single center, open-label trial evaluates LDV/SOF+RBV or GS-9669 (250 mg or 500 mg, an investigational non-nucleoside NS5B inhibitor) for 8 weeks in HCV GT 1 treatment-naive and treatment-experienced subjects with compensated cirrhosis. Of the 100 subjects who received at least one dose of study drug, 98 subjects (98.0%) completed study drug treatment and one subject was still on study treatment at the time of the data cut. One subject (Subject #2760-84468) in the LDV/SOF+GS-9669 250 mg 8 Week group discontinued study treatment early due to an SAE (cardiomyopathy, Subject #2760-84468), please refer to Section 7.2.6 for case details. No deaths were reported. One additional subject experienced an SAE of myocardial infarction (Subject #2760-84272), please refer to Section 7.3.5 Myocardial Ischemia Events for case details. Grade 4 lipase was reported at Week 8 in one subject (Subject #2760-84096, LDV/SOF+GS-9669) who had Grade 4 lipase at screening with fluctuating on-treatment values. The subject was asymptomatic and post-treatment Week 2 lipase normalized. No other Grade 4 laboratories were reported and no subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

GS-US-337-1118

This phase 2, multicenter, open-label trial evaluates LDV/SOF±RBV for 12 or 24 weeks in HCV GT 1 subjects who participated in a prior Gilead-sponsored HCV treatment trial. In Group 1, subjects who failed a prior SOF+PEG/RBV regimen receive LDV/SOF+RBV for 12 weeks. In Group 2, subjects who failed a prior LDV/SOF±RBV regimen receive

LDV/SOF for 24 weeks. Safety data are only available for Group 1 subjects. A total of 51 subjects have received at least one dose of LDV/SOF+RBV, all of whom were still on study treatment at the time of the data cut. No subjects had discontinued study treatment early. Overall, 29.4% subjects have compensated cirrhosis. No deaths were reported. One subject experienced a Grade 3 SAE of chest pain (Subject #4421-86034), please refer to Section 7.3.5 Chest Pain Events for case details. No other SAEs, Grade 3 or 4 AEs were reported. One subject (Subject #5369-86040) experienced Grade 4 increased bilirubin on Day 15. This subject had baseline Grade 2 bilirubin, and repeat bilirubin on Day 26 decreased to Grade 3. ALT, AST and direct bilirubin were normal. RBV dose was reduced in response to the bilirubin elevation. No subject experienced ALT or AST >3x ULN with bilirubin >2x ULN while on treatment.

Non-Gilead-Sponsored Phase 2 Trials

CO-US-337-0116 (ERADICATE, HCV/HIV-1 GT 1 treatment-naïve subjects) and CO-US-337-0117 (SYNERGY, HCV treatment-naïve and treatment-experienced null responder subjects) are evaluating LDV/SOF-containing regimens. No deaths were reported. One subject (LDV/SOF+VDV) in SYNERGY experienced an SAE of vertigo that resolved after one day and was considered not related to study drug by the investigator as symptoms predated study drug initiation.

One pregnancy was reported in SYNERGY during the reporting period. Subject #FDCNV02 is a female aged 32 years who received LDV/SOF had last menstrual period approximately one month after study drug completion. The following month the subject was determined to be pregnant. On an unspecified date, the subject electively terminated the pregnancy. No induced abortion complications were reported.

Reviewer Comment: No new safety signal of concern associated with LDV/SOF use is identified based on review of the submitted SUR safety data.

8 Postmarket Experience

SOF received US approval December 2013. During the approximately seven months since approval, no labeling changes have occurred due to an identified postmarketing safety signal. In collaboration with the Office of Surveillance and Epidemiology, monitored SOF postmarketing safety events include cardiomyopathy, cardiac failure, liver failure, deaths, creatine kinase-related events, hypersensitivity events, renal failure, pancreatitis, pancytopenia, hypothyroidism, increased INR, accidental overdose.

9 Appendices

9.1 Literature Review/References

Links to the referenced websites are provided throughout the review and additional references are noted below.

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9.2 Labeling Recommendations

The proposed Package Insert (PI or label) is being reviewed by all disciplines. Labeling discussions are ongoing and the recommendations have not been finalized at the time of this review. Please refer to Cross Discipline Team Leader Memo by Dr. Kim Struble for detailed labeling recommendations. Some of the key recommendations under consideration by the clinical review team are outlined below:

Dosing and Administration

- RBV coadministration is not recommended with LDV/SOF. RBV does not substantially impact overall SVR12 or relapse rates, and is associated with greater safety events compared with LDV/SOF alone regimens.
- The review team currently recommends the following dosing and administration in the HCV GT 1 population based upon the rationale outlined in Sections 6 and 7. Considerations for the below recommendations factor in optimizing treatment success with the LDV/SOF regimen, minimizing development of NS5A and/or NS5B substitutions which may negatively impact future retreatment options, and the acceptable LDV/SOF safety profile:
    - Treatment Naïve, non-cirrhotic: LDV/SOF 12 weeks with consideration for 8 weeks in certain treatment-naïve patients without cirrhosis. Section 14 Clinical Studies is referenced to present ION-3 relapse rate differences between the 8 and 12 week durations based upon HCV RNA above or below 6 million IU/mL.
    - Treatment Naïve, cirrhotic: LDV/SOF 12 weeks
    - Treatment-Experienced, non-cirrhotic: LDV/SOF 12 or 24 weeks. 24 weeks can be considered for treatment-experienced patients without cirrhosis and with baseline factors associated with a lower response to HCV treatment. Section 14 Clinical Studies is referenced to present ION-2 relapse rate differences between 12 and 24 week durations based upon presence of baseline NS5A resistance associated polymorphisms and IL28B genotype.
    - Treatment-Experienced, cirrhotic: LDV/SOF 24 weeks

Adverse Reactions

- Presentation of adverse reactions, all grade, occurring in ≥5% subjects receiving LDV/SOF for 8, 12 or 24 weeks.
- Recommend inclusion of depression and suicidal ideation language and inclusion of creatine kinase language for consistency with the Sovaldi label.
- Inclusion of bilirubin laboratory data is recommended. Overall graded bilirubin elevations occur 4-7% across the LDV/SOF 8, 12 and 24 week durations with all but one reported event ≤Grade 2. LDV is primarily eliminated through biliary excretion which is supportive of a potential causal relationship.
- Overall ≥Grade 2 thrombocytopenia occurs in 2.3% of subjects in the phase 3 trials, predominantly in subjects with cirrhosis. Discussions regarding labeling for thrombocytopenia are ongoing.
- Information on additional less common adverse events may be added to the PI based upon clinical significance.

Clinical Pharmacology

- Labeling has not been finalized regarding dosing with H2-receptor antagonists, proton-pump inhibitors, oral hormonal contraceptives or tenofovir-containing products.

The final PI will be available at the time of approval.

9.3 Advisory Committee Meeting

N/A

Attachment 1

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205834

Submission Date(s): February 10, 2014

Applicant: Gilead Sciences

Product: ledipasvir/sofosbuvir fixed dose combination

Reviewer: Sarah Connelly, MD

Date of Review: February 11, 2014

Covered Clinical Study (Name and/or Number): GS-US-337-0102, GS-US-337-0108, GS-US-337-0109

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 123 Principal Investigators, 551 Sub-Investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): One: a sub-investigator at a single site later became a full-time Gilead employee, and was no longer an investigator for any Gilead-sponsored trials.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 15 Principal Investigators and 5 Sub-Investigators		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: 15 Principal Investigators and 5 Sub-Investigators Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) not		

checked		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*[i]. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. The Form FDA 3455 for each investigator was provided.

Overall, the number of investigators with a financial interest is low, approximately 3%. Due to the multicenter nature of these trials, the potential bias by any one investigator is minimized. Moreover, the efficacy endpoints are determined using objective measurements of HCV-RNA PCR by central laboratories and hence should not be vulnerable to bias on the part of the investigator.

The trials are open label and there is the potential for non-laboratory adverse event reporting bias. To mitigate this bias, a Clinical Research Associate (CRA) worked on behalf of the Applicant to 100% verify the source documents and evaluate whether investigators under- or over-reported the incidence of AEs.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

[i] http://www fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf, accessed February 11, 2014.

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

/s/

SARAH M CONNELLY
07/10/2014

KIMBERLY A STRUBLE
07/10/2014

Medical Officer's Review of NDA 205834
Consult Request from
Division of Antiviral Products

NDA 205834	**Submission Date: 2/27/14**
SDN-003	**Consult Receipt Date: 3/12/14**
	Review Date: 5/16/14
Sponsor/Applicant:	Gilead Sciences, Inc.
Drug:	ledipasvir/sofosbuvir fixed-dose combination tablets
Pharmacologic Category:	Hepatitis C NS5A inhibitor/HCV nucleotide analog NS5B polymerase inhibitor

Comments/Special Instructions:

NDA 205834 has been submitted for the fixed dose combination product with ledipasvir (LDV, a hepatitis C NS5A inhibitor under IND (b) (4)) and sofosbuvir (SOF, a hepatitis C NS5B inhibitor under IND 106739) for the treatment of chronic hepatitis C genotype 1 infection in adults. The IND for this fixed dose product is under IND 115268. Preclinical studies demonstrate LDV, which absorbs UV light, accumulates in the uveal tract of the eye in pigmented (but not albino) rats and the Applicant concluded that LDV is not phototoxic. The Applicant also conducted a single dose phototoxicity study in mice.

After considering Gilead's response and available LDV data, it is our contention that significant uncertainty regarding the potential for ocular phototoxicity with LDV exists. Thus, we are not convinced that available data provide an adequate assessment of ocular phototoxicity risk and believe this risk should be further evaluated. Therefore, we plan to request Gilead conduct an in-vitro 3T3 NRU phototoxicity test with LDV.

In response to a request from the Division, the Applicant provided a clinical summary of all eye disorder adverse events in LDV containing trials. Within the LDV/SOF Phase 3 program, the Applicant reports no Grade 3 or 4 AEs or serious adverse events (SAEs) within the Eye Disorder SOC were observed, the total incidence of Eye Disorder AEs was 4.3% and the incidence of Eye Disorders AEs was similar irrespective of treatment duration (8 versus 12 versus 24 weeks). Review of Gilead Drug Safety and Public Health (DSPH) database, which includes all reported SAEs (Phase 1-3) in which LDV was administered, identified three cases within the SOC of Eye Disorders (and no relevant cases from the Investigations SOC):

--- Uveal effusion syndrome followed by trauma and subluxation of lens: assessed as not related
--- Iritis/vitritis: subsequently downgraded to non-serious status
--- Eye pruritus: erroneously reported as serious

(b) (4)

The EDR link
Module 1
Section 1.11 Information Not Covered Under Modules 2 through 5
1.11.2 Safety Information Amendment
EDR Location: \\cdsesub1\evsprod\nda205834\0001\m1\us\111-info-amendment\safety.pdf

The Division requests DTOP review the applicant's submission and provide feedback on the nonclinical assessment and planned request along with clinical findings in relation to the nonclinical findings. Please comment if any of these findings warrant labeling.

Background:

Gilead Sciences (Gilead) has submitted a new drug application for sofosbuvir (SOF, GS-7977) and ledipasvir (LDV, GS-5885) together as an oral fixed-dose combination (FDC) tablet (400 mg/90 mg) for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection. Sofosbuvir is a novel nucleotide nonstructural protein 5B (NS5B) polymerase inhibitor that inhibits HCV RNA replication in vitro and has demonstrated high rates of sustained virologic response (SVR) when given with ribavirin (RBV) or pegylated interferon (Peg-IFN) + RBV to subjects with chronic genotype 1, 2, 3, or 4 HCV infection. Sofosbuvir has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults in the United States (NDA 204671) December 6, 2013), Canada, and European Union (EU) (tradename Sovaldi®). Ledipasvir is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype 1a and 1b HCV infection.

The proposed indication for SOF/LDV is for the treatment of chronic genotype 1 HCV infection in adults. The recommended oral dose of SOF/LDV is one 400 mg/90 mg tablet once daily with or without food. The proposed SOF/LDV treatment durations are (b) (4)

Sofosbuvir does not absorb ultraviolet light; ledipasvir does absorb ultraviolet light.

Nonclinical Evaluation of the Ocular Phototoxicity Potential of LDV

As described in the original ledipasvir/sofosbuvir (LDV/SOF) NDA (SN0000), LDV was considered non-phototoxic when administered as a single dose up to 300 mg/kg to hairless mice (Study TX-256-2015). Although low levels of [^{14}C]-LDV-derived radioactivity persisted longer in the uveal tract of pigmented rats, there was no marked difference in distribution to pigmented and non-pigmented skin, suggesting that LDV does not selectively associate with melanin-containing tissues The repeat dose toxicity studies with LDV included ophthalmic observations, and microscopic evaluation of the eyes and optic nerves. In the 26-week rat and 39-week dog studies, there were no visual abnormalities noted during ophthalmic observations by a veterinary

ophthalmologist, and no microscopic changes were detected in the eyes or optic nerves at exposures up to 7-fold above the mean LDV AUC with the LDV/SOF fixed-dose combination (FDC). Based on the absence of effects observed in the in vivo phototoxicity study and the absence of ophthalmic changes in the chronic toxicity studies, the potential for ocular phototoxicity is considered low, and no other phototoxicity studies.

Reviewer's Comments:

The purpose of TX-256-2015 was to evaluate the phototoxic potential of ledipasvir (GS-5885-02) at doses up to 300 mg/kg when administered once via oral gavage to female Crl:SKH1-hr hairless mice before exposure to radiation from a xenon lamp (to simulate sunlight). For phototoxic potential, GS-5885-02 was compared with 8-MOP, a known phototoxicant.

No skin reactions indicative of phototoxicity occurred at doses up to 300 mg/kg GS-5885 followed by a single UVR exposure (30 minutes ±5 minutes) at approximately 4 hours after dosing. Mice administered positive control article (8-MOP) had skin findings consistent with phototoxicity, validating the assay.

Clinical Data

An analysis of adverse events (AEs) in the clinical database for the system organ class (SOC) Eye Disorders was performed for completed and ongoing Phase 2 and 3 clinical studies in which LDV has been administered. The incidence of Eye Disorders AEs in the Phase 1 studies was not evaluated, given the current stage of LDV/SOF development and the limited duration of exposure to LDV in the Phase 1 studies.

Table 1 presents the incidence of Eye Disorders AEs observed in the Phase 2 and 3 studies containing LDV as well as relevant non-LDV-containing reference studies. The small number of HCV-infected subjects in the Phase 2 studies and the presence or absence of Peg- IFN in the regimen likely account for the differences in the incidence rates observed between them.

In the sofosbuvir (SOF; Sovaldi®) Phase 3 program, 5.3% of subjects experienced an AE in the Eye Disorders SOC. As evidenced by the similar incidence of Eye Disorder AEs (4.3%) in the LDV/SOF Phase 3 program, the addition of LDV to SOF did not affect the number of subjects experiencing Eye Disorder AEs (Table 1). Furthermore, in the LDV/SOF Phase 3 program, no Grade 3 or 4 AEs or serious adverse events (SAEs) within the eye disorder SOC were observed. The incidence of eye disorders AEs was similar irrespective of treatment duration (8 versus 12 versus 24 weeks). In addition, evaluation of LDV/SOF PK in subjects with and without Eye Disorder AEs within the LDV/SOF Phase 3 program revealed similar plasma exposures of LDV in both groups (Table 2).

Reviewer's Comments:

Similar incidence of ocular adverse events does not rule out potentially new serious events.

Table 1. Incidence of Adverse Events in the SOC Eye Disorders in Phase 2 and 3 Ledipasvir-Containing and Relevant Reference Studies

Study[a]	Regimen	SOC Eye Disorders Adverse Events
P7977-1231	PEG + RBV	13.6% (33/243)
GS-US-248-0121	PEG + RBV	15.7% (19/121)
	30 mg LDV + VDV + PEG + RBV	13.8% (17/123)
GS-US-256-0148	30 mg LDV + PEG + RBV	15.5% (18/116)
	30 mg LDV + VDV + PEG + RBV	15.9% (37/232)
GS-US-256-0124	30 mg LDV + VDV + PEG + RBV	16.0% (26/163)
GS-US-248-0120	30 mg LDV + VDV + TGV + RBV	13.0% (6/46)
	90 mg LDV + VDV + TGV + RBV	10.6% (10/94)
GS-US-248-0131[b]	90 mg LDV + VDV + TGV + RBV (Arm 1)	8.8% (5/57)
GS-US-248-0132[b]	90 mg LDV + VDV + TGV + RBV (Arm 1)	22.2% (12/54)
GS-US-337-0118 (LONESTAR)	LDV/SOF +/- RBV	0.0% (0/100)
P7977-0523 (ELECTRON, Part 6)	LDV/SOF +/- RBV	8.8% (6/68)
GS-US-337-0122 (ELECTRON 2, Cohort 2, Groups 3 and 4)	LDV/SOF +/- RBV	3.9% (2/51)
SOF ISS (FISSION, POSITRON, FUSION)	SOF + RBV (12-16 Weeks)	5.3% (35/664)
LDV/SOF ISS (ION-1, ION-2, ION-3)	LDV/SOF + RBV (8, 12, or 24 Weeks)	4.4% (38/872)
	LDV/SOF (8, 12, or 24 Weeks)	4.3% (46/1080)

a Non-LDV-containing studies or groups (shaded rows) are included for reference.
b Only Arm 1 data are presented, as a majority of subjects dropped out of Arms 2 and 3 of these studies due to lack of efficacy.

Table 2. LDV PK Parameters by Presence or Absence of Adverse Events in the Eye Disorders System Organ Class in HCV-Infected Subjects Following Administration of LDV/SOF in the Phase 3 Studies

Mean (%CV) LDV PK Parameter	Subjects with Eye Disorders AEs (N = 84)	Subjects without Eye Disorders AEs (N = 1861)
AUC_{tau} (ng•h/mL)	8790 (65.2)	8540 (60.3)
C_{max} (ng/mL)	366 (52.7)	364 (51.3)

Source: Adhoc Table 6454.1
Data are shown to 3 significant figures.

Reviewer's Comments:

The safety analysis set for this NDA (Studies GS-US-337-0102, GS-US-337-0109, GS-US-337-0108) containing all treatment –emergent adverse events, Table 5.1, was reviewed. Listing 1,

containing All Adverse Events, Safety Analysis Set (Studies GS-US-337-0102, GS-US-337-0109, GS-US-337-0108), was also reviewed.

No clinically significant ocular adverse events were identified by individual line review of all adverse events in the safety analysis set. No additional serious ocular adverse events were identified.

Gilead Sciences, Inc.
SOF/LDV ISS

Table 5.1: All Treatment-Emergent Adverse Events
Safety Analysis Set

	SOF/LDV			SOF/LDV+RBV		
	8 Weeks	12 Weeks	24 Weeks	8 Weeks	12 Weeks	24 Weeks
	GS-US-337-0108 (ION-3) (N=215)	GS-US-337-0108 (ION-3) GS-US-337-0109 (ION-2) GS-US-337-0102 (ION-1) (N=539)	GS-US-337-0109 (ION-2) GS-US-337-0102 (ION-1) (N=326)	GS-US-337-0108 (ION-3) (N=216)	GS-US-337-0109 (ION-2) GS-US-337-0102 (ION-1) (N=328)	GS-US-337-0109 (ION-2) GS-US-337-0102 (ION-1) (N=328)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event	145 (67.4%)	390 (72.4%)	265 (81.3%)	165 (76.4%)	280 (85.4%)	300 (91.5%)
Number (%) of Subjects Experiencing Any Treatment-Emergent Adverse Event by System Organ Class And Preferred Term						
EYE DISORDERS	6 (2.8%)	25 (4.6%)	15 (4.6%)	13 (6.0%)	12 (3.7%)	13 (4.0%)
VISION BLURRED	0	7 (1.3%)	2 (0.6%)	3 (1.4%)	4 (1.2%)	3 (0.9%)
DRY EYE	1 (0.5%)	0	6 (1.8%)	2 (0.9%)	4 (1.2%)	2 (0.6%)
CONJUNCTIVITIS	0	4 (0.7%)	2 (0.6%)	1 (0.5%)	1 (0.3%)	0
EYE PRURITUS	0	2 (0.4%)	3 (0.9%)	0	2 (0.6%)	0
LACRIMATION INCREASED	0	4 (0.7%)	1 (0.3%)	0	0	1 (0.3%)
VISUAL ACUITY REDUCED	0	1 (0.2%)	2 (0.6%)	0	0	2 (0.6%)
VISUAL IMPAIRMENT	1 (0.5%)	2 (0.4%)	0	1 (0.5%)	1 (0.3%)	0
CATARACT	1 (0.5%)	3 (0.6%)	0	0	0	0
EYE PAIN	0	0	0	3 (1.4%)	0	0
PHOTOPSIA	1 (0.5%)	0	0	0	1 (0.3%)	1 (0.3%)
EYE HAEMORRHAGE	0	1 (0.2%)	0	0	1 (0.3%)	0
EYE IRRITATION	0	0	1 (0.3%)	1 (0.5%)	0	0
EYE SWELLING	0	0	0	2 (0.9%)	0	0
OCULAR HYPERAEMIA	1 (0.5%)	1 (0.2%)	0	0	0	0
VITREOUS DETACHMENT	0	0	0	1 (0.5%)	0	1 (0.3%)

Note: Adverse events are mapped according to MedDRA Version 16.0.
Note: Subjects are counted once for each system organ class, and once for each AE preferred term.
Note: Data included to last dose date of any study drug + 30 days.

Data Extracted: GS-US-337-0102 (ION-1): 26Nov2013, GS-US-337-0109 (ION-2): 06Dec2013, GS-US-337-0108 (ION-3): 17Dec2013.
Source: .../version1/prog/t-ae.sas v9.2 18DEC2013:23:30

A review of the Gilead Drug Safety and Public Health (DSPH) database, which includes all SAEs reported from all studies (Phase 1-3) in which LDV was administered, identified three cases within the SOC of Eye Disorders (and no relevant cases from the Investigations SOC): uveal effusion syndrome followed by trauma and subluxation of lens; iritis/vitritis; and eye pruritus. The event of eye-pruritus was erroneously reported as serious, and the event of iritis/vitritis was subsequently downgraded to non-serious status. The single remaining serious case (uveal effusion syndrome) was assessed as not related to LDV/SOF by the investigator.

Reviewer's Comments:

The two relevant ocular SAE narratives were reviewed and are summarized below. Neither narrative event appears to represent a treatment-related event; specifically, neither appears to represent a phototoxicity-related event.

Case Number: 2012-0052520
Iritis, Vitritis

This 67-year-old female patient with chronic hepatitis C infection was enrolled in GS-US-248-0120. The patient's medical history was significant for hypertension (2004), chronic cough (1978) and aortic valve insufficiency.

On 20 March 2012, the patient reported awareness of painless "floaters" in right eye, which had begun 12 days prior. The patient had an ophthalmology examination on 20 March 2012 and she was found to have anterior and posterior uveitis (iritis and vitritis) in both eyes, which the patient initially described as pain, decreased vision and light sensitivity. She was placed on prednisolone every two hours in the right eye and Cyclogyl twice a day. The investigator planned to have a rapid plasma reagin (RPR) test performed on the patient, to rule out syphilis.

On 04-May-2012, the patient condition was reported to be resolving and she was being weaned off the steroid eye drops. On 17-May-2012, the site reported that the patient's symptoms have resolved off study drugs.

Case Number: 2013-0079963
Right eye uveal effusion syndrome, Right eye lens subluxation

This 40 year old female patient with hepatitis C was enrolled in study GS-US-337-0122.

On 19 July 2013, the patient presented with a three day history of blurred vision in the right eye. Right eye was not red or painful. There was no discharge, no diplopia, photophobia, or floaters. Visual acuity of the right eye was 6/60 improving to 6/24 on pinhole. Left eye was 6/6. An ophthalmologist made a diagnosis of right eye uveal effusion syndrome. The ophthalmologist recommended close monitoring with no specific intervention.

On (b) (6)*, the patient was assaulted, being struck in the face, fist versus right eye. She presented with extensive periorbital bruising and visual blurring. She was referred for specialist ophthalmic assessment and findings were of a right eye lens subluxation.*

On (b) (6)*, the patient was hospitalized. She underwent right vitrectomy, lensectomy, laser and air-gas exchange.*

Gilead Conclusions

The lack of phototoxicity observed in the in vivo phototoxicity study (TX-256-2015) and the absence of any observations of visual abnormalities or microscopic changes in the eyes or optic nerves in the chronic oral toxicity studies in Sprague-Dawley rats (TX-256-2008) and Beagle dogs (TX-256-2009) indicate that LDV has low potential for ocular toxicities.

The clinical studies conducted to date demonstrate no evidence for a causative relationship between administration of LDV and eye disorder AEs. The incidence of eye disorder AEs in subjects receiving LDV/SOF±RBV was similar to the incidence of eye disorder AEs in subjects receiving SOF+RBV; the AEs were almost entirely mild or moderate in severity; no duration effect was observed with longer treatment (8 versus 12 versus 24 weeks); and the systemic exposures of LDV were comparable in subjects with and without eye disorders. Gilead will continue to monitor the AEs reported in ongoing studies for any change in this assessment of the potential for ocular phototoxicity of LDV.

Summary Reviewer's Comments and Recommendations:

1. We agree that LDV has low potential for ocular toxicities based on the information provided.

2. Human adverse event reporting has identified no clinically significant ocular adverse events.

3. No additional clinical monitoring, other than continued ocular adverse event collection, is recommended at this time.

4. We have no suggested revisions to the product labeling.

William M. Boyd, M.D.
Clinical Team Leader
Division of Transplant and Ophthalmology Products

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

/s/

WILLIAM M BOYD
05/23/2014

WILEY A CHAMBERS
05/23/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205834 **Applicant:** Gilead Sciences, Inc. **Stamp Date:** 2/10/2014

Drug Name: ledipasvir/sofosbuvir **NDA/BLA Type:** Original NDA Submission/NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS (Module 5.3.5.3.iss) has a link to the Clinical Summary of Safety (Module 2.7.4), and separately has pertinent tables, figures and line listings.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			The ISE (Module 5.3.5.3.ise) has a link to the Clinical Summary of Efficacy (Module 2.7.3), and separately has pertinent tables, figures and line listings.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview (Module 2.5), Section 6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Dose, duration and regimen were explored in the following Phase 2 Trials: **Sofosbuvir:** Refer to NDA 204671 for 400 mg QD dosage selection. **Ledipasvir:** **Study Number**: **GS-US-248-0120** **Study Title**: *A Phase 2 Randomized, Open-Label Study of GS-5885 Administered Concomitantly with GS-9451, Tegobuvir and Ribavirin (RBV) to Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection* This Phase 2 trial evaluated the safety, tolerability and antiviral efficacy of LDV 30 mg or 90 mg once daily (QD) doses, administered with tegobuvir (TGV, an HCV NS5B non-nucleoside polymerase inhibitor), vedoprevir (VDV, GS-9451, an HCV polymerase inhibitor) and RBV in treatment-naïve subjects with chronic HCV genotype (GT) 1 infection. Used 30 mg tablets (b) (4) Sample Size: 140 Group 1 (n = 46): LDV 30 mg QD +TGV 30 mg BID +VDV 200 mg QD +RBV (weight-based) BID x 24 weeks Group 2* (n = 94): LDV 90 mg QD +TGV +VDV +RBV x 12 or 24 weeks. *Subjects with very rapid virologic response (vRVR; HCV RNA < LLOQ at Week 2) and HCV RNA < LLOQ maintained through Week 10 re-randomized (1:1) at Week 12 to stop initial treatment or continue therapy to Week 24. N=2 re-randomized to continue the initial treatment through Week 24 were included in the 12-week subgroup because they discontinued treatment at Week 12. Therefore, N=33 and N=31 analyzed in Group 2 12-week and 24-week subgroups, respectively. Randomization and re-randomization stratified by GT 1a/1b and baseline HCV RNA (800,000 IU/mL) Group 1: SVR24=47.8%, Breakthrough 19.6% (9/46) Group 2: SVR24=58.5%, Breakthrough 10.6% (10/94) *Subgroup with vRVR maintained through Week 10 (N=64): --12 weeks therapy (N=33): SVR24=78.8% --24 weeks therapy (N=31): SVR24=93.5% LDV 90 mg dose selected for further clinical development due to higher overall SVR and lower breakthrough rates in Group 2. Location in submission: Module 5.3.5.4	X			Dose-ranging trials were conducted for each product separately.

	Content Parameter	Yes	No	NA	Comment
	Ledipasvir + Sofosbuvir: **Study Number**: **P7977-0523 (ELECTRON)** **Study Title:** *A Multi-center, Open-Labeled Exploratory Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 400 mg and Ribavirin for 12 Weeks With and Without Pegylated Interferon in Treatment-Naive Patients with Chronic HCV Infection Genotype 2 or Genotype 3* Phase 2 open-label, multi-arm trial including 6 and12 weeks of SOF 400 mg +RBV +/- LDV 90 mg in treatment-naive and null-responder subjects with genotype 1 HCV infection. Treatment-naïve: --12 weeks SOF+RBV (N=25): SVR12=84% --12 weeks LDV+SOF+RBV (N=25): SVR12=100% --6 weeks LDV/SOF+RBV (N=25): SVR12=68% Null responders: --12 weeks SOF+RBV (N=10): SVR12=10% --12 weeks LDV/SOF+RBV (N=9): SVR12=100% Null responders +cirrhosis: --12 weeks LDV/SOF (N=10): SVR12=70% --12 weeks LDV/SOF+RBV (N=9): SVR12=100% **Study Number**: **GS-US-337-0118 (LONESTAR)** **Study Title:** *A Phase 2, Randomized, Open-Label Study of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin in Subjects with Chronic Genotype 1 HCV Infection* Phase 2 trial of 8 or 12 weeks of SOF/LDV±RBV in treatment-naive and treatment-experienced subjects (including approximately 50% with compensated cirrhosis, and including prior HCV protease inhibitor failure) with genotype 1 HCV infection. Treatment-naïve: --8 weeks LDV/SOF + RBV (N=21): SVR12=100% --8 or 12 weeks LDV/SOF (N=39): SVR12=95% Treatment-experienced: --12 weeks LDV/SOF + RBV (N=21): SVR12=100% --12 weeks LDV/SOF (N=19): SVR12=95% Location in submission: Module 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? The application includes data from three pivotal Phase 3 trials: GS-US-337-0102 (ION-1), GS-US-337-0108 (ION-3), GS-US-337-0109 (ION-2). Pivotal Study #1 GS-US-337-0102 (ION-1): Phase 3 randomized, open-label, multicenter study that evaluated the antiviral	X			

	Content Parameter	Yes	No	NA	Comment
	efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF ± RBV treatment in treatment-naive subjects with genotype 1 HCV infection. After approximately 200 subjects were enrolled (Part A), an interim analysis was conducted to assess futility of the LDV/SOF ± RBV 12-week treatment groups using a conditional power approach under the observed trend. Stopping for futility would have been triggered if the conditional power had been ≥ 5% (equivalent to an observed response rate of 60% or less), but it was not. Subsequently, approximately 600 additional subjects were randomized across the 4 groups (Part B). This submission includes complete data through the SVR12 time point from the 12-week treatment groups. DAVP agreed that if 12 weeks of LDV/SOF ± RBV had SVR12 ≥ 90.0% in subjects with and without cirrhosis separately, efficacy data from the 24-week treatment groups would not be necessary for the initial LDV/SOF filing. Therefore, for this submission, results from the primary efficacy analysis for Groups 3 and 4 (12-week treatment groups) and all subjects in Part A are included. Pivotal Study #2 GS-US-337-0108 (ION-3): Phase 3 randomized, open-label, multicenter study that evaluated the antiviral efficacy, safety, and tolerability of LDV/SOF+RBV for 8 weeks and LDV/SOF (without RBV) for 8 and 12 weeks in treatment-naive subjects with genotype 1 HCV infection. Pivotal Study #3 GS-US-337-0109 (ION-2): Phase 3, randomized, open-label, multicenter study that evaluated the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF ± RBV treatment in treatment-experienced subjects with genotype 1 HCV infection. Approximately 50% of subjects had received prior PI+PEG+RBV regimen. Proposed Indication [TRADENAME] is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the	X			Clinical Overview

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data to U.S. population/practice of medicine in the submission?				(Module 2.5), Section 4.1
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Information is submitted for the separate products: (1) Sofosbuvir – previously reviewed under IND 106739 and NDA 204671 (2) Ledipasvir - Module 5.3.4.1, Protocol GS-US-344-0109, also submitted under IND (b) (4). The IRT is currently reviewing these data.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Ledipasvir is first-in-class (NS5A inhibitor). Sofosbuvir is approved, and was first-in-class as well. Currently there are no other approved HCV NS5B nucleotide inhibitors.
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives and CRFs are provided under each clinical study in m5 for deaths,

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					serious adverse events, pregnancies, and discontinuations due to adverse events.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Clinical Overview (Module 2.5), Section 4.1
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Narratives and CRFs are provided under each clinical study in m5 for deaths, serious adverse events, pregnancies, and discontinuations due to adverse events.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			See above.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no clinical comments for the 74-day letter.

Sarah Connelly, MD	3/11/14
Reviewing Medical Officer	Date
Kimberly Struble PharmD	3/11/14
Clinical Team Leader	Date

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

/s/

SARAH M CONNELLY
03/11/2014

KIMBERLY A STRUBLE
03/11/2014