# Clinical and Cross-Discipline Team Leader Review

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| **Review Completion Date** | March 13, 2017 |
| **From** | Virginia Sheikh, MD |
| **Subject** | Combined Clinical and Cross-Discipline Team Leader Review |
| **NDA #** | 205834 |
| **Supplement#** | S-017 |
| **Applicant** | Gilead Sciences, Inc. |
| **Date of Submission** | October 7, 2016 |
| **Priority or Standard** | Priority |
| **PDUFA Goal Date** | April 7, 2017 |
| **Proprietary Name** | Harvoni® |
| **Non-Proprietary Name** | Ledipasvir (LDV)/Sofosbuvir (SOF) |
| **Dosage form(s) / Strength(s)** | LDV 90 mg/SOF 400 mg fixed dose combination tablets |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of Genotype 1 Hepatitis C Infection in Children ages ≤12 -17 with or without compensated cirrhosis |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of pediatric patients 12 years of age and older or weighing at least 35 kilograms with HCV Genotype 1, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis |

# 1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of once daily Ledipasvir/Sofosbuvir (LDV/SOF) use in pediatric patients 12 years of age and older or weighing at least 35 kilograms (kg) with Hepatitis C virus (HCV) genotype (GT) 1, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis.

Up to forty-six thousand children are chronically-infected with HCV in the United States. Most of these children were infected in infancy via mother-to-child transmission. Left untreated over decades, HCV-infected patients are at high risk for cirrhosis, hepatocellular carcinoma, liver failure, and HCV-related death. The primary goal of treating HCV in children is to prevent HCV-related complications from occurring during childhood or later in adulthood. Although progression to cirrhosis typically takes place over a period of 10-30 years, four to five percent of HCV-infected children develop advanced liver fibrosis or cirrhosis during childhood, some of whom develop advanced liver disease requiring liver transplantation (Mack 2012). In addition, chronic HCV is associated with extrahepatic disorders in children including glomerulonephritis

and central nervous system HCV infection, which has been associated with developmental delay, learning disorders and cognitive deficits (Mack 2012).

The only HCV therapy currently approved for use in pediatric patients in the U.S. is the combination of pegylated interferon (IFN) and ribavirin (RBV). In the last several years, the approval of directly acting antivirals (DAAs) such as LDV/SOF have allowed adult patients to achieve sustained virologic response (SVR) rates greater than 95 percent with significantly fewer side-effects as compared to the RBV and IFN-based treatment. In pediatric patients with HCV GT 1 infection, 48 weeks of IFN /RBV therapy resulted SVR rates of less than 47 percent (Schwarz 2011). In the same pediatric study, this regimen was frequently associated with influenza-like illness, headache, gastrointestinal symptoms, neutropenia, and anemia (Schwarz 2011).

This review summarizes the efficacy, pharmacokinetic, and safety concerns relevant to NDA 205834 supplement 17 (S-17). The data discussed are derived from Group 1 of protocol GS-US-337-1116: A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of LDV/SOF Fixed Dose Combination in Adolescents and Children with Chronic HCV-Infection. Specifically, this submission includes the SVR 12 results from Group 1 (pediatric participants ages ≥12 to <18 years) with HCV GT1 infection.

Supplemental NDA application S-17 requests approval of LDV/SOF for treatment of chronic HCV GT 1 without cirrhosis or with compensated cirrhosis in pediatric patients 12 years of age and older. The submitted data demonstrate that administration of LDV/SOF 90mg/400mg in pediatric participants ages ≥12 to <18 years with HCV GT 1 infection had similar pharmacokinetics, safety and efficacy profile to those seen in adults without cirrhosis or with compensated cirrhosis. HCV GT does not affect LDV/SOF pharmacokinetics and previous trials in adults have demonstrated that equivalent LDV/SOF exposure is efficacious in adults with chronic HCV GT 4, 5, and 6. In addition, analysis of the submitted data supports the safety, efficacy, and pharmacokinetics of LDV/SOF in pediatric patients weighing at least 35 kilograms (kg). Therefore, approval is recommended for the indication to include the pediatric participants ages ≥12 to <18 years LDV/SOF or weighing at least 35kg with HCV Genotype 1, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis

# 2. Regulatory Background

Harvoni is a fixed dose combination product containing two HCV DAAs: LDV and SOF. LDV is an inhibitor of the HCV NS5A protein and SOF is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase. 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. LDV/SOF for use in adult patients with chronic HCV GT 1 infection was approved on October 10, 2014 and subsequent approvals included LDV/SOF for use in adult patients with chronic HCV GT 4, 5, and 6 on November 12, 2015.

At the time of initial approval, the following Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) was issued: *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C* (Reference ID: 3643151). This submission partially fulfills PREA PMRs 2780-1, 2983-1, and 2985-1. Gilead plans to fulfill the remaining PMRs by submitting data for the pediatric subjects ages 3-11 enrolled in protocol GS-US-337-1116 when available. In May 2016, FDA's Office of Orphan Products Development granted LDV/SOF orphan-drug designation for the treatment of chronic HCV infection in pediatric patients.

With this submission, Gilead requested priority review designation. The only HCV treatments currently FDA-approved for this age group require a combination of IFN, administered by subcutaneous injection, and RBV for 24 or 48 weeks depending on HCV GT. The RBV/IFN regimen was poorly tolerated and SVR rates in subjects with HCV GT 1, 4, 5, and 6 were only 54% (Manns, 2001). If approved, LDV/SOF will be the first IFN and RBV-free regimen approved for pediatric patients with HCV GT 1, 4, 5, and 6 HCV infections. LDV/SOF provides the potential for HCV cure with a once daily pill given for 12 weeks for most patients. In summary, the Division granted Gilead priority review designation because LDV/SOF offers a major advancement in the treatment of chronic HCV infection in the adolescent patient population with regard to safety, efficacy, and tolerability

# 3. CMC/Device

For a description of the product quality concerns of SOF and LDV, please refer to the original SOF NDA 204671 and LDV/SOF NDA reviews, respectively. No new biopharmaceutics information (e.g., formulation or dissolution data) is included with S-17. No quality inspections of manufacturing and testing sites were required as these sites were inspected during review of the original LDV/SOF NDA.

# 4. Nonclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology for SOF and LDV was extensively reviewed in the original SOF NDA and LDV/SOF NDA reviews. No new nonclinical pharmacology/toxicology information is included with S-17.

# 5. Clinical Pharmacology/Biopharmaceutics

This section provides summary results of the clinical pharmacokinetics of LDV/SOF in pediatric participants ages ≥12 to <18 years as reported by Gilead. Please see Dr. Jenny Zheng's review for an independent review of the clinical pharmacology data.

The first ten participants enrolled in GS-US-337-1116, all of whom were treatment naïve and weighed ≥45 kg, participated in the pharmacokinetic lead-in (PK-Lead-in) phase designed to

evaluate or confirm age appropriate LDV/SOF FDC doses. The primary PK endpoint was $AUC_{tau}$ of SOF metabolite GS-331007 and LDV. LDV, SOF, and GS-331007 $AUC_{tau}$ and $C_{max}$ were within the predefined PK equivalence boundaries (50-200%, **Table 1**). The upper 90 percent Confidence Interval for LDV $C_{tau}$ was slightly over the PK equivalence boundaries boundary at 202 percent. This slight increase is not significant based on prior exposure-safety analysis; therefore, analysis of the submitted safety data demonstrates an acceptable safety profile of LDV/SOF in these participants (see Section 8).

**Table 1. Mean SOF, GS-331007, and LDV Exposures in Adolescents with Adult Phase 2/3 PK Results for Comparison**

| PK Parameter Mean (%CV) | | Adolescents (12 to < 18 Years Old) (N = 100) | Adults LDV/SOF Phase 2/3 Population (N = 2113) | Adolescents vs Adults % GMR (90% CI) |
|---|---|---|---|---|
| **SOF** | AUCtau (ng•h/ml) | 1494 (45.2) | 1376 (34.0) | 102.3 (96.5, 108.5) |
| | Cmax (ng/ml) | 772 (51.1) | 659 (34.0) | 106.8 (98.7, 115.6) |
| **GS-331007** | AUCtau (ng•h/ml) | 13888 (18.9) | 12454 (29.2) | 114.1 (108.8, 119.7) |
| | Cmax (ng/ml) | 936 (17.8) | 736 (28.2) | 130.2 (124.2, 136.5) |
| **LDV** | AUCtau (ng•h/ml) | 12414 (45.7) | 8534 (60.8) | 153.3 (139.6, 168.4) |
| | Cmax (ng/ml) | 608 (44.2) | 364 (51.4) | 170.2 (156.8, 184.7) |
| | Ctau (ng/ml) | 439 (48.8) | 247 (59.2) | 184.4 (167.6, 202.8) |

Table generated by Gilead (Interim SCR Table 10.1), modified by Reviewer.

The treatment phase of GS-US-337-1116 had no weight restrictions and sixteen participants who weighed less than 45 kg were enrolled including three participants who weighed ≤ 35 kg. Sparse PK data from the 15 participants with body weight >35 kg to ≤ 45 kg demonstrated that exposures were similar to those observed in pediatric participants >45 kg and in adults. These data support either age (ages ≥12 to <18 years LDV/SOF or weight at least 35 kilograms) based dosing.

# 6. Clinical Microbiology

This section provides a brief summary of the clinical virology relevant to S-17. Please refer to the Clinical Virology Review by Dr. Lisa Naeger for detailed assessment of the S-17 data and to the original SOF NDA and LDV/SOF NDA reviews for the extensive SOF and LDV review.

Of the 100 participants included in this submission, 98 achieved SVR 12 and two were lost-to-follow-up. Both of the participants who were lost-to-follow-up had HCV RNA levels below the limit of detection at their last visits. No participants experienced viral breakthrough or viral relapse. NS5A or NS5B polymorphisms and HCV GT subtype (1A/1B) did not affect efficacy. Gilead found no treatment emergent resistance mutations in this trial population.

# 7. Clinical/Statistical- Efficacy

The submitted data demonstrate that administration of LDV/SOF 90mg/400mg in adolescents was efficacious and led to exposures similar to those seen in adults. Ninety-eight percent of participants enrolled in GS-US-337-1116 achieved SVR 12. No participants experienced virologic breakthrough or viral relapse.

**7.1 Indication**

S-17 requests approval of LDV/SOF for treatment of chronic HCV GT 1 without cirrhosis or with compensated cirrhosis in pediatric patients 12 years of age and older.

**7.2 Methods.**

Trial GS-US-337-1116 is an ongoing phase 2, open-label, multicenter, multi-cohort trial designed to evaluate the pharmacokinetics, safety and efficacy of LDV/SOF fixed dose combination in adolescents and children with chronic HCV. Although the trial was amended to include participants with GTs 4,5, and 6 after LDV/SOF was approved for these GT in adults, this submission includes the SVR 12 results from Group 1 (children ages ≥12 to <18 years) with GT 1 HCV infection. Dose selection for pediatric participants targeted systemic exposures similar to those observed in adults at the marketed dose. All participants in this submission were treated with the dose and duration marketed for adults (90mg/400 LDV/SOF daily for 12 weeks). A total of 100 participants were included in the Intent to Treat (ITT) population, all of whom received LDV/SOF.

Unless otherwise specified, all analyses included in this review were performed by the clinical reviewer using JReview, JMP, or JMP Clinical.

**7.3 Demographics and Clinical Characteristics**

Participants were enrolled at 24 sites in the U.S. (21 sites, 91 percent of participants), Australia (two sites, eight percent of participants) and the United Kingdom (one site, one percent of participants). Most of the trial participants were white (90 percent) and non-Hispanic/Latino (85 percent) however minority populations were included in the trial, predominantly as treatment-naïve participants. Seven percent of participants were black/African American, two percent were Asian, and 13 percent were Hispanic/Latino. Sixty-three percent of participants were female. The median age was 15 (IQR 13-17). Select demographic of the trial population are summarized in **Table 2**.

| Table 2. Demographics | | | |
|---|---|---|---|
| **Characteristic** | **Treatment Experienced n=20** | **Treatment Naïve n=80** | **Total Participants n=100** |
| **Gender** | | | |
| Male | 7 (35%) | 30(37.5%) | 37 (37%) |
| Female | 13 (65%) | 50 (62.5%) | 63 (63%) |
| **Race** | | | |
| White | 19 (95%) | 71 (88.8%) | 90 (90%) |
| Black/African-American | 0 (0%) | 7 (87.5%) | 7 (7%) |
| Asian | 0 (0%) | 2 (2.5%) | 2 (2%) |
| Not disclosed | 1 (5%) | 0 (0%) | 1 (1%) |
| **Ethnicity** | | | |
| Hispanic or Latino | 3(15%) | 10 (12.5%) | 13 (13%) |
| Not Hispanic or Latino | 17 | 68 | 85 (85%) |
| Not disclosed | 0 | 2 | 2 (2%) |
| **Age** | | | |
| Median in years (IQR) | 14.5 (13-16) | 15 (13-16) | 15 (13-16) |
| **Country** | | | |
| United States | 18 (90%) | 73 (91.25%) | 91 (91%) |
| Australia | 1 (5%) | 7 (8.75%) | 8 (8%) |
| Great Britain | 1 (5%) | 0 | 1 (1%) |

Table produced by Clinical Reviewer using data provided by the Gilead.

The majority (84 percent) of enrolled participants weighed ≥45 kg at baseline and all but one of the 16 participants who weighed < 45 kg was treatment-naïve (**Table 3**). Only three participants weighed ≤ 35 kg.

All of the participants enrolled in this trial were infected with HCV GT1. Most were infected with HCV GT 1a (82 percent) and were infected through mother-to-child transmission. Of the 20 (20 percent) participants who were treatment-experienced, 15 had been previously treated with IFN and RBV. Only one participant had been previously treated with a DAA. The only participant with compensated cirrhosis was treatment naïve. Patients with decompensated cirrhosis were excluded from the trial. Select baseline clinical characteristics of the trial population are summarized in **Table 3**.

| Table 3. Baseline Clinical Characteristics | | | |
|---|---|---|---|
| **Characteristic** | **Treatment Experienced n=20** | **Treatment Naïve n=80** | **Total Participants n=100** |
| **Weight** | | | |
| Weight in kg (median/IQR) | 62.0 (50.3-66.6) | 57.3 (47.5-72.2) | 57.9 (48.0-71.7) |
| Weight ≥45 kg | 19 (95%) | 65 (82 | 84 (84%) |
| Weight <45 kg | 1 (5%) | 15 (19%) | 16 (16%) |
| Weight <35 kg | 0 | 2 (3%) | 2 (2%) |
| **Body Mass Index** | | | |
| BMI kg/m$^2$ (median/IQR) | 22.2 (19.8-25.0) | 20.9 (18.6-26.1) | 21.0 (18.9-26.0) |
| BMI < 30 kg/m$^2$ | 17 (85%) | 66 (83%) | 83 (83%) |
| BMI ≥ 30 kg/m$^2$ | 3 (15%) | 14 (18%) | 17 (17%) |
| **Hepatitis C RNA level** | | | |
| RNA IU/mL (median/IQR) | 5.9 (5.6-6.3) | 6.0 (5.6-6.4) | 6.0 (5.6-6.4) |
| RNA ≥ 800,000 IU/mL | 11 (55%) | 44 (55%) | 55 (55%) |
| RNA < 800,000 IU/mL | 9 (45%) | 36 (45%) | 45 (45%) |
| **Hepatitis C GT** | | | |
| GT 1a | 15 (80%) | 66 (82.5%) | 81 (81%) |
| GT 1b | 4 (20%) | 14 (18%) | 18 (18% |
| **IL28B GT** | | | |
| CC | 4 (20%) | 20 (25%) | 24 (24%) |
| CT | 11 (55%) | 42 (53%) | 53 (53%) |
| TT | 5 (25%) | 18 (23%) | 23 (23%) |
| **Mode of HCV transmission** | | | |
| Vertical Transmission | 19 (95%) | 65 (82%) | 84 (84%) |
| Contaminated Needle or IVDU | 0 (0%) | 5 (6%) | 5 (5%) |
| Blood Product Transfusion | 1 (5%) | 1 (1%) | 2 (2%) |
| Other or Unknown | 0 (0%) | 9(13%) | 9 (9%) |
| **Cirrhosis** | | | |
| No known cirrhosis | 20(100%) | 79(99%) | 99(99%) |
| Compensated cirrhosis | 0 (0%) | 1 (1%) | 1(1%) |
| Uncompensated cirrhosis | 0 (0%) | 0 (0%) | 0 (0%) |

### 7.3 Participant Disposition.

Trial retention was high with only two participants who left the trial prematurely. Ninety-nine participants (99 percent) completed study treatment and 98 (98 percent) achieved SVR12. Both participants who left the trial prematurely (GS-US-337-1116-01745-52006 and GS-US-337-1116-03903-52117) were lost-to-follow-up after completing treatment and had HCV RNA levels below the lower limit of quantitation (LLQ) at their last on-treatment study visit (week 12) The

one participant (GS-US-337-1116-09907-52140) who did not complete treatment achieved SVR12. The attrition of participants is expected for a study of this duration and in this patient population.

### 7.4 Analysis of Primary Endpoints

The primary efficacy endpoint of trial GS-US-337-1116 was SVR 12 weeks after stopping study treatment (SVR12) for all enrolled and treated participants. The COBAS AmpliPrep/COBAS Taqman HCV Quantitative Test was used to quantify HCV RNA and the LLQ of the assay was 15 International Units/milliliter. The protocol allowed for imputation of missing SVR12 values as successes if bracketed by values that were deemed successes. One participant did not have a Week 4 post treatment visit but did have a 24 week post treatment visit with an HCV RNA level <LLOQ and  is considered SVR12 success.

Ninety-eight percent of enrolled participants achieved SVR12 and no participants experienced on-treatment virologic failure or relapse (**Table 4**). The only participants who failed to achieve SVR12 were the two participants who were lost-to-follow-up described in section 7.3.

**Table 4. Sustained Virologic Response  after 12 Weeks of Treatment (SVR12)**

| | Treatment Experienced n=20 | Treatment Naive n=80 | Total n=100 |
|---|---|---|---|
| **Achieved SVR 12** | 20 (100%) | 78 (97.5%) | 98 (97%) |
| **Outcome for Participants without SVR** | | | |
| On-Treatment Virologic Failure | 0 | 0 | 0 |
| Relapse | 0 | 0 | 0 |
| Lost-To-Follow-up | 0 | 2 (2.5%) | 2 (2%) |

Table produced by Clinical Reviewer using data provided by Gilead.

### 7.5 Analysis of Secondary Endpoints

The secondary efficacy endpoints for the treatment phase of GS-US-337-1116 were virologic breakthrough, viral relapse, SVR 4, and SVR 24. No participants experienced virologic breakthrough or viral relapse.  The same 98(98%) participants who achieved SVR 12 also achieved SVR4. Complete data for the SVR24 data point were not available at the time of this submission and therefore will not be analyzed in this review.

### 7.6 Race, Ethnicity, and Sex

Because there were no participants who experienced viral relapse or viral breakthrough, formal subpopulation analyses were not conducted to assess for differences in efficacy based on race, ethnicity, or sex. The two participants who did not achieve SVR due to lost-to-follow-up were white and non-Hispanic/Latino. One of those participants was female. Race, ethnicity, and sex did not appear to influence efficacy with regard to the primary outcome of SVR12.

### 7.7. Weight

Although participation in the intensive phase of trial GS-US-337-1116 was limited to participants weighing ≥45 kg, the treatment phase of the trial was open to participants of any weight. Sixteen (16 percent) of participants weighed < 45 kg at baseline and only two participants weighed less than 35 kg (**Table 3**). All 16 participants who weighed <45 kg at baseline achieved SVR12. These data are adequate to support the efficacy of Harvoni in children weighing at least 35 kg.

## 8. Safety

Results from GS-US-337-1116 demonstrate that LDV/SOF was safe and well-tolerated in adolescents.

### 8.1. Methods

All of the 100 enrolled participants in trial GS-US-337-1116 were included in the safety analysis of LDV/SOF in pediatric participants ages ≥12 to <18 years and were treated with the dose and duration marketed for adults (900mg/400 LDV/SOF daily for 12 weeks). Ninety-nine participants completed treatment. The remaining participant was lost-to-follow-up after 4 weeks of treatment but ultimately returned to study at week 36 (SVR24).

Adverse events (AEs) are defined as any unfavorable and/or unintended sign, symptom, or disease temporally associated with LDV/SOF regardless of causality. Adverse drug reactions ADRs are defined as AEs deemed to be at least possibly related to LDV/SOF.

AEs are coded by MedDRA 18.1. The sNDA S-017 submission includes the AE dictionary files that consist of all verbatim and the preferred/dictionary-derived terms were mapped as SAS transport files for the relevant trials. Gilead's categorization of closely related events and coding of AE verbatim terms to preferred terms is appropriate.

Unless otherwise specified, all the analyses used to support this review were conducted with JReview, JMP, or JMP Clinical.

### 8.2 Adequacy of Safety Assessments

The safety monitoring plan implemented in trial GS-US-337-1116 was adequate.

Study visits for the PK-Lead in Phase occurred on Days 1, 2, and 10. Follow-up visits included a focused physical examination with vital signs, an assessment of AEs, medication adherence, and concomitant medications, and safety laboratory studies.

Study visits in the Treatment Phase occurred on Day 1 and at the end of weeks 1, 2, 4, 8, and 12. Participants returned for follow-up visits 4, 12, and 24 weeks after completing study drug. Each follow-up visit included a focused physical examination with vital signs, an assessment of AEs, medication adherence, and concomitant medications, and safety and virology laboratory studies.

**8.3 Routine Clinical Testing**

The routine clinical testing performed during the trial was adequate.

**8.4 Major Safety Results**

No major AEs or ADRs were reported. No deaths occurred during the study. No AEs led to premature discontinuation or to treatment interruption. No Grade 3 or higher ARs occurred in the trial. Three Serious AEs (SAEs) were reported but determined to be unrelated to LDV/SOF by investigators: pain, substance-induced psychotic disorder, and appendicitis. Each of these events occurred more than 30 days after completing LDV/SOF treatment. Because of the nature of these SAEs and the lack of temporal association with the LDV/SOF treatment, the investigators' assessments of causality are reasonable.

**8.5 Dropouts and Discontinuations.**

No participants discontinued study drug or interrupted treatment with study drug due to an AE. The one participant who discontinued study treatment after week 4 (GS-US-337-1116-09907-52140) reported no AEs and experienced only one laboratory abnormality graded higher than baseline (Grade 1 PT/INR). Two participants were lost-to-follow-up after completing treatment; one of those participants reported no AEs. The second participant, who is female, experienced two AEs; Grade 2 urinary tract infection which resolved with antibiotic treatment and Grade 1 iron deficiency which was ongoing at the time of her last visit. She also experienced concomitant Grade 3 hemoglobin and Grade 1 occult blood in the urine. Iron-deficiency anemia is unlikely to be related to LDV/SOF. In summary, none of the dropouts or discontinuations appears related to LDV/SOF toxicity.

**8.6 Common Adverse Events and Adverse Drug Reactions**

This section summarizes the AEs and ADRs that occurred in trial GS-US-337-1116.

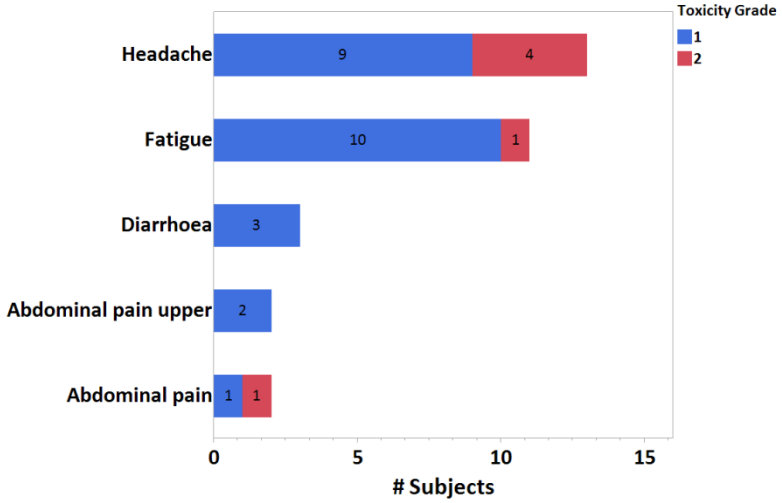
Overall, 287 AEs occurred in 71 of 100 participants. Forty-six percent of participants experienced AEs with maximum Grade 1 toxicity and 25 percent of participants experienced AEs with maximum Grade 2 toxicity. None of the AEs were Grade 3 or higher. The most common AEs fell under the following System Organ Classes; gastrointestinal, nervous system, respiratory, infectious and infestations, reproductive, and general disorders (**Table 5**).

| Table 5. AEs (Without Regard to Causality) ≥5% By System Organ Class | | |
|---|---|---|
| **Body System or Organ Class** | **Dictionary Derived Term** | **Number of Participants (%) n=100** |
| **Gastrointestinal disorders** | Diarrhea | 14 (14%) |
| | Vomiting | 11 (11%) |
| | Nausea | 11 (11%) |
| | Abdominal pain | 7 (7%) |
| | Abdominal pain upper | 7 (7%) |
| **Nervous system disorders** | Headache | 27 (27%) |
| **Respiratory, thoracic and mediastinal disorders** | Cough | 10 (10%) |
| | Oropharyngeal pain | 10 (10%) |
| | Nasal congestion | 6 (6%) |
| **General disorders and administration site conditions** | Fatigue | 13 (13%) |
| **Infections and infestations** | Nasopharyngitis | 7 (7%) |
| | Upper respiratory tract infection | 6 (6%) |
| **Reproductive system and breast disorders** | Dysmenorrhoea | 5 (5%) |

Table made by Clinical Review using data provided by the Gilead.

Fifty-two ADRs occurred in 25 participants. The majority (16 percent) of participants with ADRs experienced Grade 1 events and only 9 participants experienced Grade 2 ADRs. There were no Grade 3 or higher ADRs. As shown in **Figure 2**, the most common ADRs were headache (13 percent), fatigue (11 percent), abdominal pain (4 percent), and diarrhea (3 percent).

**Figure 2. Adverse Reactions (ARs) Occurring in >1 Participant**




Graph produced by Clinical Reviewer using data provided by the Gilead.

The frequency of ADRs reported in GS-US-337-1116 are consistent with those observed in clinical trials of LDV/SOF in adults (**Table 6**).

**Table 6. Adverse Drug Reactions occurring in ≥5% of Adults (Harvoni label) and/or Children (GS-US-337-1116) receiving 12 weeks of LDV/SOF.**

| Adverse Event | Adults 12 weeks LDV/SOF (N=539) | Children 12 weeks LDV/SOF (N=100) |
|---|---|---|
| Fatigue | 13% | 11% |
| Headache | 14% | 13% |
| Nausea | 7% | 1% |
| Diarrhea | 3% | 3% |
| Insomnia | 5% | 1% |

### 8.8 Laboratory Findings

Laboratory evaluations were assigned grades according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Version 1 April 2015 (Grade 0, 1, 2, 3, 4) as specified in the trial protocol. Seventy-three percent of participants experienced at least one Grade 1-4 laboratory abnormality that increased in grade from baseline (**Table 7**). Forty-seven percent of trial participants experienced laboratory abnormalities with maximum Grade 1 toxicity and 26 percent of participants experienced Grade 2-4 laboratory abnormalities. Twelve Grade 3 or 4 laboratory abnormalities occurred in ten participants. Notable laboratory events including changes in serum liver biochemistries, pancreatic enzymes, creatine kinase, and coagulation tests are discussed below. Grade 1 non-fasting hyperglycemia and Grade 1 hypoglycemia were common occurring in 17 percent and 12 percent of participants, respectively, however the clinical reviewer determined that these values are not clinically significant. In general, the frequency and severity of laboratories abnormalities seen over the course of the trial are similar to those seen in adults.

**Table 7. Grade 1-4 Laboratory Abnormalities (Increased in grade from baseline)**

| Parameter | Toxicity Grade | Result Range | Number (%) of Participants n=100 |
|---|---|---|---|
| **Alanine Aminotransferase, U/L (ALT/SGPT)** | 1 | 1.25 to 2.50 x ULN | 4 (4%) |
| | 2 | >2.50 to 5.0 x ULN | 1 (1%) |
| | 3 | >5.00 to 10.00 x ULN | 0 |
| | 4 | >10.00 x ULN | 0 |
| **Aspartate Aminotransferase, U/L (AST/SGOT)** | 1 | 1.25 to 2.50 x ULN | 2 (2%) |
| | 2 | >2.50 to 5.00 >ULN | 0 |
| | 3 | <5.00 to 10.00 x ULN | 0 |
| | 4 | >10.00 x ULN | 1 |
| **Bilirubin, mg/dL** | 1 | >1.0 to 1.5 x ULN | 2 (2%) |
| | 2 | >2.50 to 5.00 x ULN | 2 (2%) |
| | 3 | >2.5 to 5.0 x ULN | 1 (1%) |
| | 4 | >5.0x ULN | 0 |
| **Alkaline Phosphatase, U/L** | 1 | 1.25 to 2.50 x ULN | 3 (3%) |
| | 2 | >2.50 to 5.00 ULN | 0 |
| | 3 | <5.00 to 10.00 x ULN | 0 |
| | 4 | >10.00 x ULN | 0 |
| **Amylase, U/L** | 1 | 1.0 to 1.5 x ULN | 18 (18%) |
| | 2 | >1.5 to 2.0 x ULN | 7 (7%) |
| | 3 | >2.0 to 5.0 x ULN | 4 (4%) |
| | 4 | > 5.0 x ULN | 0 |
| **Lipase, U/L** | 1 | 1.0 to 1.5 x ULN | 0 |
| | 2 | >1.5 to 3.0 x ULN | 4 (4%) |
| | 3 | >3.0 to 5.0 x ULN | 0 |
| | 4 | > 5.0 x ULN | 1 |
| **Creatine Kinase, U/L (CK)** | 1 | 3.0 to 6.0 x ULN | 5 (5%) |
| | 2 | 6.0 to 10.0 x > ULN | 1 (1%) |
| | 3 | 10.0 to 20.0 x > ULN | 1 (1%) |
| | 4 | >20.0 x ULN | 0 |

**Table 7. Grade 1-4 Laboratory Abnormalities (Increased in grade from baseline)**

| Parameter | Toxicity Grade | Result Range | Number (%) of Participants n=100 |
|---|---|---|---|
| **International Normalized Ratio of Prothrombin (PT/INR)** | 1 | 1.00 to 1.5 x ULN | 10 (10%) |
| | 2 | >1.5 to 2.0 x ULN | 2 (2%) |
| | 3 | >2.0. to 3.00 x ULN | 1 (1%) |
| | 4 | >3.00 x ULN | 0 |
| **Activated Partial Thromboplastin Time, min** | 1 | >1.00 to 1.66 x ULN | 3 (3%) |
| | 2 | >1.66 to 2.33 x ULN | 0 |
| | 3 | >2.33 to 3.00 x ULN | 0 |
| | 4 | >3.00 x ULN | 0 |
| **Hemoglobin, g/dL (Anemia)** | 1 | 10.0 to 10.9 g/dL | 2 (2%) |
| | 2 | 9.0 to < 10.0 g/dL | 0 |
| | 3 | 7.0 to < 9.0 g/dL | 1 (1%) |
| | 4 | < 7.0 g/dL | 0 |
| **Platelets, $10^3$/µL (Thrombocytopenia)** | 1 | 100,000 to < 125,000/$mm^3$ | 2 (2%) |
| | 2 | 50,000 to < 100,000/$mm^3$ | 1 (1%) |
| | 3 | 25,000 to < 50,000/$mm^3$ | 0 |
| | 4 | <25,000/$mm^3$ | 0 |
| **Lymphocytes, $10^3$/uL (Absolute Lymphopenia)** | 1 | 600 to 650/ $mm^3$ | 0 |
| | 2 | 500 to < 600/ $mm^3$ | 0 |
| | 3 | 350 to < 500/ $mm^3$ | 1 (1%) |
| | 4 | < 350/ $mm^3$ | 0 |
| **Neutrophils, $10^3$/uL (Absolute neutropenia)** | 1 | 1000 to 1300/ $mm^3$ | 0 |
| | 2 | 750 to < 1000/ $mm^3$ | 0 |
| | 3 | 500 to < 750/ $mm^3$ | 1 (1%) |
| | 4 | < 500/ $mm^3$ | 0 |

**Table 7. Grade 1-4 Laboratory Abnormalities (Increased in grade from baseline)**

| Parameter | Toxicity Grade | Result Range | Number (%) of Participants n=100 |
|---|---|---|---|
| **Glucose, Non-Fasting, mg/dL (Hyperglycemia),** | 1 | 116 to 160 mg/dL | 17 (17%) |
| | 2 | > 160 to 250 mg/dL | 1 (1%) |
| | 3 | > 250 to 500 mg/dL | 0 |
| | 4 | > 500 mg/dL | 0 |
| **Glucose, mg/dL (Hypoglycemia),** | 1 | 55 to 64 mg/dL | 12 (12%) |
| | 2 | 40 to < 55 mg/dL | 5(5%) |
| | 3 | 30 to < 40 mg/dL | 0 |
| | 4 | < 30 mg/dL | 0 |
| **Potassium, mEq/L (Hypokalemia)** | 1 | 3.0 to 3.4 mEq/L | 4 (4%) |
| | 2 | 2.5 to < 3.0 mEq/L | 0 |
| | 3 | 2.0 to < 2.5 mEq/L | 0 |
| | 4 | < 2.0 mEq/L | 0 |
| **Potassium, mEq/L (Hyperkalemia)** | 1 | 5.6 to 6.0 mEq/L | 0 |
| | 2 | >6.0 to 6.5 mEq/L | 0 |
| | 3 | >6.5 to 7.0 mEq/L | 1 (1%) |
| | 4 | >7.0 mEq/L | 0 |

Table made by Clinical Reviewer using data provided by Gilead .

### 8.8.1 Liver Toxicity

As occurs in adults with chronic HCV, serum liver biochemistry elevations were common at baseline in the pediatric participants in trial GS-US-337-1116. At baseline, 33 percent of participants had Grade 1-3 ALT values, 20 percent had Grade 1-3 AST values, three percent had Grade 1-2 bilirubin, and seven percent had Grade 1 Alk Phos elevations. After the initiation of LDV/SOF, 12 participants (12 percent) experienced graded changes in serum liver biochemistries including eight participants who had changes with a maximum Grade 1 toxicity. The four subjects who experienced graded changes with a maximum Grade 2 or higher toxicity are described below.

Participant GS-US-337-1116-09348-52109, who had Grade 1 ALT and normal AST value at baseline, experienced a Grade 4 AST elevation along with Grade 2 ALT four weeks after completing treatment. The Grade 4 event was the only laboratory abnormality reported as an AE within the Hepatic and Hepatobiliary High Level Group Term in the trial. Both laboratory abnormalities resolved by the subsequent visit four weeks later.

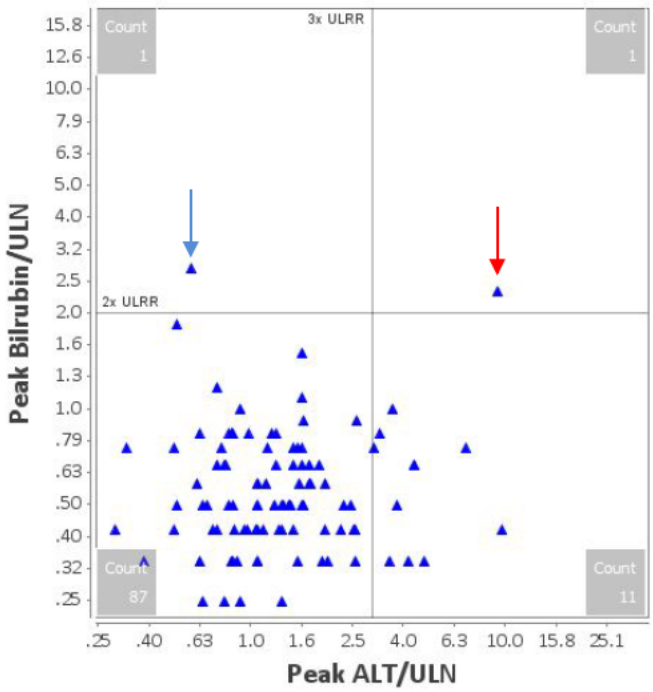
Participant GS-US-337-10074-52188 had Grade 2 bilirubin at baseline and experienced a Grade 3 bilirubin at week 1 (**Figure 3A,** Blue Arrow) without AST or ALT elevation. The participant's bilirubin level returned to Grade 2 by week 2 and remained Grade 2 or lower for the remainder of the trial.

Participant GS-US-337-1116-01733-52159 had a Grade 1 bilirubin at baseline and experienced a Grade 2 bilirubin at week 4 which normalized by week 12.

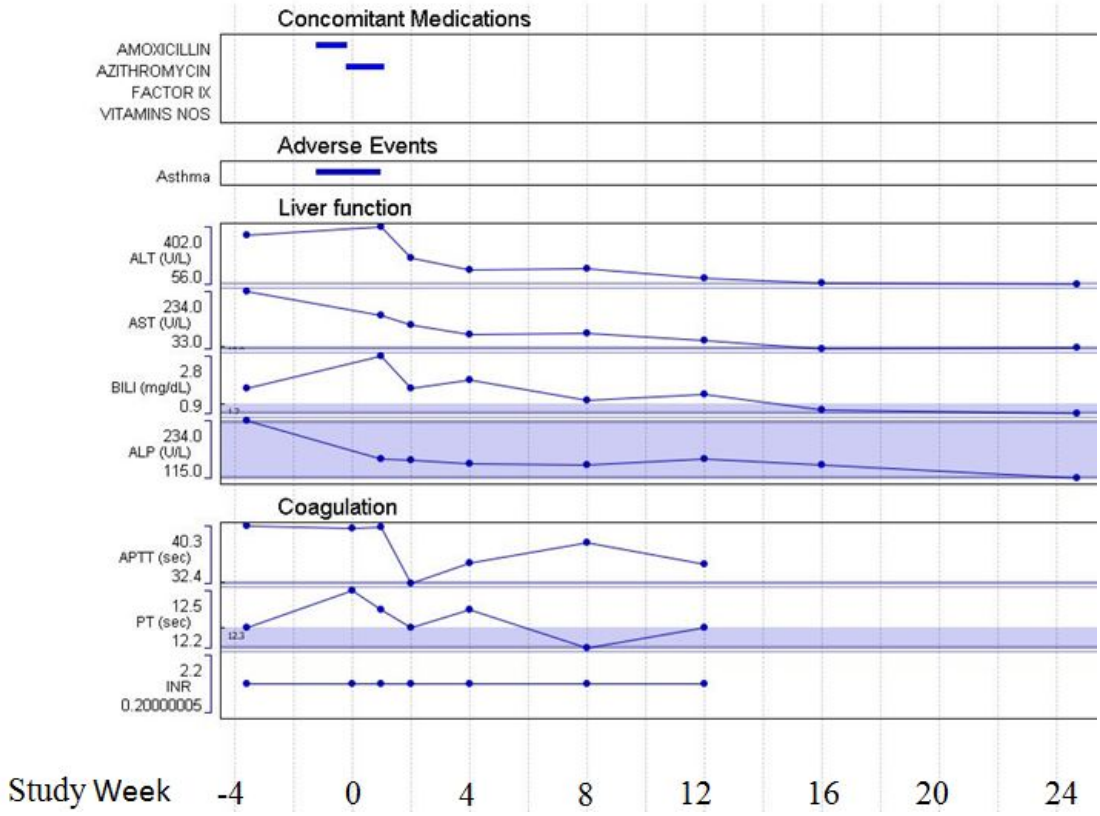
Participant GS-US-337-1116-01756-52153, who was the one participant with cirrhosis, had Grade 3 ALT and Grade 1 bilirubin elevations at baseline. His bilirubin increased to Grade 2 at week 2 at which time his ALT remained at his baseline (Grade 3), meeting laboratory criteria for Hy's Law (**Figure 3A, Red Arrow**). Between weeks -1 and 1, the participant was also taking concomitant medications amoxicillin and azithromycin, both of which are associated with elevations in serum liver biochemistries. The participant's ALT and bilirubin decreased over the 12 weeks of LDV/SOF therapy (**Figure 3B**.) Although the contribution of LDV/SOF cannot be excluded, the participant's underlying liver disease coupled with these two co-administered antibiotics is the more likely cause of this participant's laboratory abnormalities.

**Figure 3. Liver Toxicity in GS-US-337-1116**

**A. Peak Bilirubin and Peak Alanine Aminotransferase (ALT) in all Participants.**
The blue arrow indicates participant GS-US-337-10074-52188 who experienced the Grade 3 bilirubin elevation. The red arrow indicates participant GS-US-337-1116-01756-52153 whose laboratory abnormalities met the laboratory criteria for Hy's Law.



**B. Serum Liver Biochemistries, Coagulation tests, AEs, and Concomitant medications for participant GS-US-337-10074-52188 whose peak bilirubin and ALT met Laboratory Criteria for Hy's Law.**




In summary, no new safety concerns related to liver toxicity in the adolescent population were identified.

### 8.8.2 Pancreatitis Events and Elevations in Pancreatic Enzymes

No cases of clinical pancreatitis were reported in trial GS-US-337-1116. As shown in Table 8, elevations in amylase were common in participants who were treated with LDV/SOF: 19 (19%) participants had Grade 1, 8 (8%) had Grade 2, and 4 (4%) had Grade 3 amylase elevations. Six(6%) participants had elevated lipase including 4 participants (4%) who had Grade 2 elevation and 1 participant (1%) who had a Grade 4 elevation. Only one participant with elevated pancreatic enzymes reported gastrointestinal symptoms during the trial; participant GS-US-337-1116-09341-52143 experienced nausea, back pain, and abdominal pain however each of these symptoms either preceded the laboratory abnormality or persisted after normalization of the laboratory abnormality.

In conclusion, new safety concerns related to elevations in pancreatic enzymes or pancreatitis events in the adolescent population were not identified.

### 8.8.3 Elevations in Creatine Kinase and Rhabdomyolysis and Myopathy Events

No participants on GS-US-337-1116 developed rhabdomyolysis or myopathy during the trial. Seven participants experienced elevations in creatine kinase. One participant had a Grade 3 CK elevation at week 10, which was not associated with pain, myopathy, or arthralgia and normalized by week 12. Another participant had a Grade 2 CK elevation at week 16 (4 weeks after stopping LDV/SOF), which normalized at the next study visit 8 weeks later (week 24). Although this participant reported back pain, myalgia, and arthralgia over the course of the trial, the onset of these symptoms preceded the laboratory abnormality and persisted after its normalization. The other four participants experienced grade 1 CK elevations which were not associated with any AEs and normalized by the subsequent visit.

In summary, new safety concerns related to rhabdomyolysis, myopathy, or elevations in CK in the adolescent population were not identified.

### 8.8.4 Prolongation of the International Normalized Ratio of Prothrombin (PT/INR)

Thirteen participants experienced elevations in PT/INR above baseline including ten participants who experienced a maximum toxicity Grade 1 INR increase, two participants (two percent) who had Grade 2 increases, and one participant (one percent) who had a Grade 3 increase. One of the participants who had a Grade 1 INR increase experienced an AE potentially associated with coagulopathy (Grade 1 dysmenorrhea), however this event, which lasted one day, took place more than four weeks prior to the laboratory abnormality and was determined by the investigators to be unrelated to LDV/SOF. The clinical reviewer agrees with the investigators' assessment of causality. No other participants with INR abnormalities experienced AEs related to coagulopathy. As was described in the original LDV/SOF review written by Dr. Sarah Connelly, 0.4% adult trial subjects experienced Grade 3 or 4 INR elevations.

In summary, no new safety concerns related to coagulopathy were identified in the adolescent population.

### 8.9 Product-Specific Primary Safety Concerns

The Warnings and Precautions Section of the LDV/SOF label cautions prescribers and patients not to use LDV/SOF in patients taking Amiodarone because serious bradycardia has occurred in patients taking both drugs simultaneously. Because of this concern, Gilead sought to investigate this adverse event in the adolescent population enrolled in GS-US-337-1116. However, no participants reported cardiac AEs and no participants took Amiodarone while on the trial.

No changes to the label with respect to Warnings and Precautions are needed.

### 8.10 Growth and Development in Adolescents

Post-marketing commitment (PMR) 2780-2, which was issued at the time of LDV/SOF approval, stipulated that Gilead collect and analyze long-term pediatric safety data including assessments of growth and sexual maturation. Gilead plans on fulfilling this commitment with results from a separate long-term follow-up protocol (GS-US-334-1113) in which all participants in GS-US-337-1116 will enroll. This section will summarize the baseline and initial repeated assessments of growth and development which were included in S-17. Because trial GS-US-337-1116 was of short duration and not powered to detect meaningful differences in growth parameters and because growth parameters are expected to be highly variable in this age group, the analyses described here are exploratory.

Height and weight were assessed at baseline and at the end of treatment (week 12). Both male and female participants gained weight over that period with the mean overall weight increasing from 61.3 kg at baseline to 62.4 kg at week 12 (p=0.413). Similarly, both male and female participants gained height over that period with a mean overall height increasing from 162.5 cm at baseline to 163.3 cm at week 12 (p=0.594). Although the data are limited, this trial shows no evidence of significant effect of LDV/SOF on weight or height in the adolescent age group.

Bone Age Assessment consisting of a single x-ray of left wrist, hand, and fingers was performed for each participant at Day 1 and repeated at the 24 week post-treatment visit. Because the data submitted with S-17 did not include complete data for the week 24 visit, changes in bone age are not analyzed in this review but will be analyzed following submission of a supplement containing that data.

In conclusion, notable effects of LDV/SOF treatment on adolescent growth or development were not apparent in this small trial of short duration. Analysis of long-term data from GS-US-334-1113, when available, will be more meaningful.

### 8.11 Race, Ethnicity, Gender, and Weight <45 kg

Subpopulation analyses were performed by the clinical reviewer to assess differences in safety between key groups. Because protocol GS-US-337-1116 was not powered to detect differences between these individual populations, the analyses are exploratory. Race, ethnicity, and gender did not appear to influence the frequency or severity of adverse events or laboratory abnormalities (**Table 8).**

**Table 8. Adverse Drug Reactions by Race, Ethnicity, and Gender**

| Adverse Event | All | Race & Ethnicity | | | | Gender | |
|---|---|---|---|---|---|---|---|
| | n=100 | White*/ Not Hispanic n=77 | Hispanic /Latino n=13 | Black/ African American n=7 | Asian n=2 | Female n=63 | Male n=37 |
| All Events | 25 (25%) | 23 (29%) | 4 (31%) | 2 (29%) | 0 | 14 (22%) | 11 (30%) |
| Abdominal distension | 1 (1%) | 1 (1%) | 1 (8%) | 0 | 0 | 0 | 1 (3%) |
| Abdominal pain | 2 (2%) | 1 (1%) | 1 (8%) | 1 (14%) | 0 | 1 (2%) | 1 (5%) |
| Abdominal pain upper | 2 (2 %) | 2 (3%) | 1 (8%) | 0 | 0 | 0 | 2 (5%) |
| Acne | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Decreased appetite | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 | 1 (3%) |
| Dental caries | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Depression | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 | 1 (3%) |
| Diarrhea | 3 (3%) | 3 (4%) | 0 | 0 | 0 | 0 | 3 (8%) |
| Fatigue | 11 (11%) | 10 (13%) | 1 (8%) | 1 (14%) | 0 | 6 (10%) | 5 (14%) |
| Headache | 13 (13%) | 11 (14%) | 3 (23%) | 2 (29%) | 0 | 7 (11%) | 6 (16%) |
| Insomnia | 1 (1%) | 0 | 0 | 1 (14%) | 0 | 1 (2%) | 0 |
| Malaise | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Mood swings | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 | 1 (3%) |
| Nausea | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Night sweats | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Esophagitis | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 | 1 (3%) |
| Oral herpes | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Pain | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Pigmentation disorder | 1 (1%) | 1 (1.%) | 0 | 0 | 0 | 1 (2%) | 0 |
| Sinusitis | 1 (1%) | 1 (1%) | 1 (8%) | 0 | 0 | 0 | 1 (2.7%) |
| Vomiting | 1 (1%) | 1 (1%) | 1 (8%) | 0 | 0 | 1 (1.6%) | 0 |

Table made by Clinical Review using data provided by Gilead .
*One participant who reported being of the white race but did not disclose ethnicity is excluded from this analysis.

As was discussed in section 7.6, all of the participants who participated in the PK-Lead-in Phase of trial GS-US-337-1116 weighed ≥45 kg. Because Gilead did not collect intensive PK data in participants who weighed <45 kg, it is possible that participants who weighed <45 kg had higher exposures than adults and therefore may be more likely to experience LDV/SOF toxicity. Therefore, the clinical reviewer performed an analysis to assess differences in adverse event rates by baseline weight <45kg. Among participants who weighed <45kg at baseline (n=16), only five treatment-related AEs were reported (**Figure 3**). Similarly, among participants weighing less than 45kg at baseline, laboratory abnormalities were uncommon and were no higher than Grade 1 toxicity (**Figure 4**).

**Figure 3. Adverse Reactions by Weight**

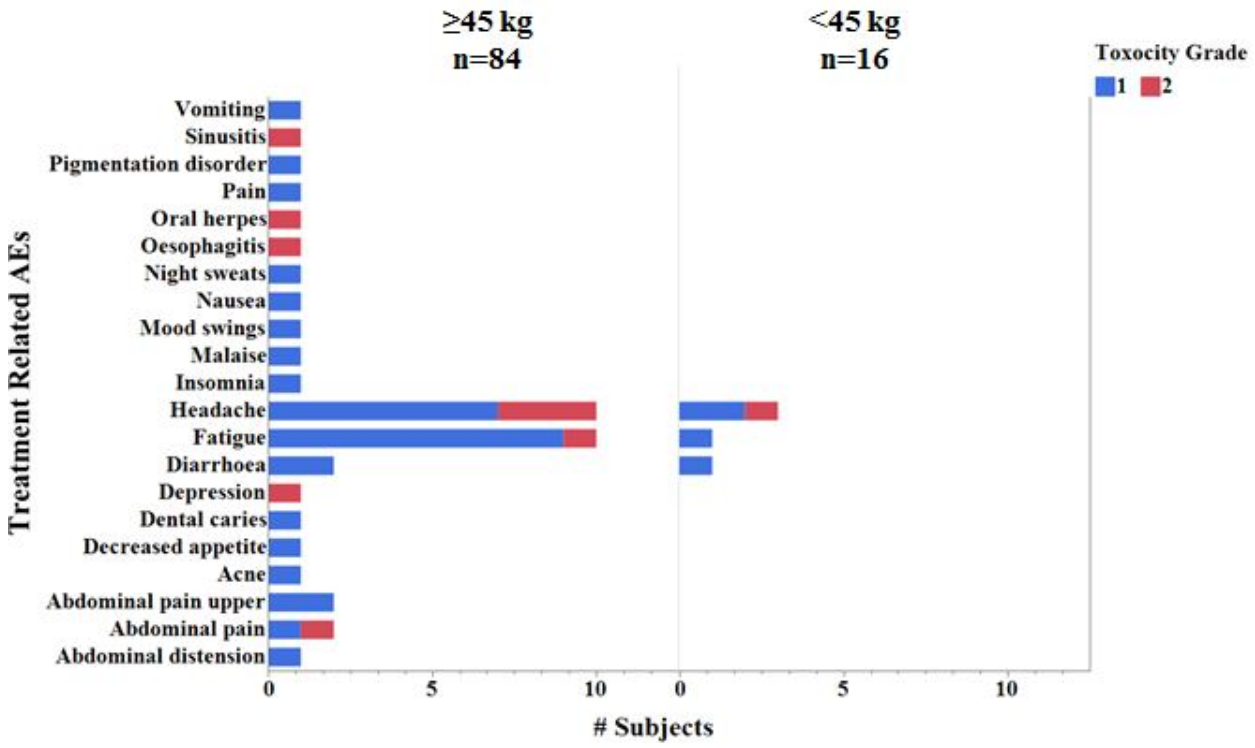
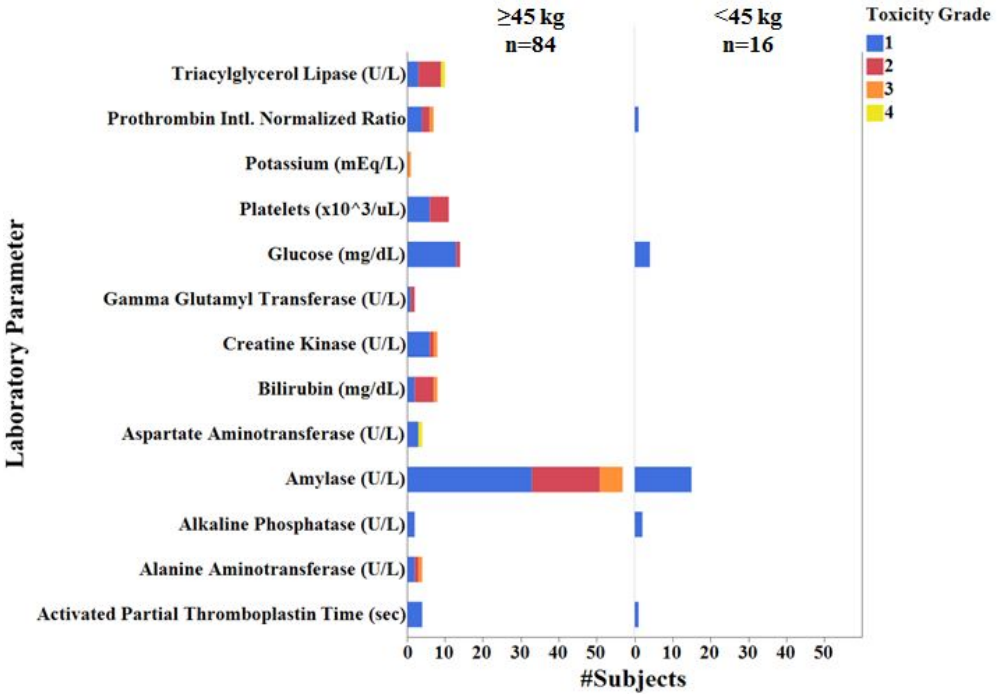


**Figure 4. Laboratory Abnormalities (Increase in Grade from Baseline) by Weight**




In summary, this analysis supports the safety of LDV/SOF in patients 12 years of age and old or weighing at least 35 kg.

# 9. Subpopulations

The adult LDV/SOF development program included dedicated clinical trials in several subpopulations of patients including those with cirrhosis, HIV-1/HCV coinfection, and HCV GT 4, 5, and 6. The FDA recommended studying these populations because it was not yet clear whether these clinical factors would affect the safety or efficacy of LDV/SOF. As is summarized in Dr. Sarah Connelly's Clinical Review of Supplements 2, 3, 4, 5, and 6, clinical trial results demonstrated a favorable risk/benefit assessment of LDV/SOF in these populations and provided the rationale for expanding the indication for use in adults. This section describes these subpopulations as they apply to pediatric patients and outlines the clinical review team's rationale for recommending inclusion of pediatric patients with compensated cirrhosis, HIV-1/HCV coinfection, and HCV GT 4, 5, and 6 in this pediatric approval.

**Cirrhosis**

Cirrhosis is uncommon among children with chronic HCV. Trial GS-US-337-1116 was open to both treatment-naïve and treatment experienced pediatric participants with compensated cirrhosis. The one cirrhotic participant 12 years of age or older who enrolled in GS-US-337-1116 was treatment-naïve and was therefore treated with 12 weeks of LDV/SOF. This participant achieved SVR12 and experienced no treatment-related AEs. At baseline, he had Grade 3

elevations in AST and ALT and Grade 2 elevation in GGT likely due to underlying liver disease. In the week prior to starting LDV/SOF, the participant was diagnosed with asthma for which he was prescribed potential hepatoxic drugs Amoxicillin and Azithromycin. As is discussed in Section 8.8.1 (Liver Toxicity), this participant had a mild increase in ALT and moderate increase in bilirubin at week 1 which met Hy's Law by laboratory criteria but did not change in grade from baseline. Liver-associated tests returned to baseline levels by week 2 and subsequently improved over the course of the trial. He also experienced Grade 2 thrombocytopenia which returned to baseline (Grade 1) by week 4. Adult LDV/SOF trial participants with cirrhosis experienced decreases in platelets at a similar rate as participants taking placebo. In summary, review of the safety data from this treatment-naïve participant with cirrhosis revealed no new safety concerns.

The current Harvoni label includes a recommendation for 24 weeks of LDV/SOF for treatment-experienced adult subjects with GT1 and compensated cirrhosis. The trial did not enroll any treatment-experienced participants with cirrhosis and, consequently, the submitted data did not include any data from participants age 12 to <18 years of age who received 24 weeks of LDV/SOF. Many pediatricians have been deferring HCV treatment pending the approval of DAAs, therefore this is not unexpected. However, Gilead was able to provide safety data from three pediatric subjects 6 to <12 years of age who received 24 weeks of LDV/SOF with (n=2) or without (n=1) RBV. All three participants completed treatment and none experienced any Grade 2-4 AEs, AEs leading to study drug discontinuation, serious AEs, or Grade 3-4 laboratory abnormalities.

HCV-infected children with cirrhosis are rare; however they are at the high risk of disease progression without treatment. Clinical trials in adults demonstrated the safety profile of LDV/SOF in adults is similar over 12-24 weeks and the presence of cirrhosis did not have a significant impact on safety. With this knowledge, the data from the three younger trial participants, who were 6 to < 12 years of age, along with the safety data demonstrated over 12 weeks in the 12 to <18 years of age cohort support the safety and efficacy of LDV/SOF treatment for this patient population. For pediatric patients 12 to <18 years of age or at least 35 kg with compensated cirrhosis, the clinical team recommends approval of 12 weeks of LDV/SOF for treatment–naïve patients and 24 weeks of LDV/SOF treatment for treatment-experienced patients. .

**HIV-1/HCV Co-infection**

Among pediatric patients in the United States, HIV-1/HCV co-infection is rare and trial GS-US-337-1116 did not include pediatric participants in this subgroup. Adult trials of LDV/SOF in adult participants with HIV-1/HCV co-infection, however, demonstrated high SVR12 rates (96 percent, ION-4) comparable to subjects with HCV mono-infection with a similar safety profile. In summary, adult data showing that HIV-1 co-infection does not impact LDV/SOF response rates obviate the need for a trial in this small subgroup of pediatric patients. Therefore, dosing recommendations were extended to pediatric patients 12 to <18 years of age or weighing at least 35 kilograms regardless of HIV co-infection.

**HCV GT 4, 5, and 6**

Infection with hepatitis C GT 4, 5, and 6 are rare in the United States and although the trial was amended to include pediatric participants with these GTs, none were enrolled during this phase of the trial. HCV GT does not affect LDV/SOF exposure and previous trials in adults have demonstrated that equivalent LDV/SOF exposure is efficacious in adults with chronic HCV GT 4, 5, and 6. Therefore, the submitted PK data are adequate to support the efficacy of HARVONI for treatment of HCV GTs 4, 5, or 6 in patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis.

# 10. Advisory Committee Meeting

Not applicable.

# 11. Pediatrics

Two PREA Postmarketing Requirements (PMRs) for pediatric patients were issued in the initial approval letter for the LDV/SOF NDA 205834 dated 10 October 2014 (Reference ID: 3643151).

*2780-1.* *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C.*

*2780-2* *Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy*

Supplemental NDAs S-03 and S-05 triggered PREA and therefore FDA issued two additional PMRs. These supplements pertained to adult patient subpopulations that FDA determined might not be feasible or reasonable to study in the pediatric population as is described in section 9 (Subpopulations). Therefore the wording in these PMRs is non-specific with regard to these subpopulations and identical to the wording in PMR 2780-1.

2983-1 *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 through 17 years of age with chronic hepatitis C*

2985-1 *Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 through 17 years of age with chronic hepatitis C*

The interim results of trial GS-US-337-1116, which include data for pediatric participants ages 12-17, partially address PMRs 2780-1, 2983-1, and 2985-1. Gilead plans to fulfill all of the above PMRs by submitting data for the pediatric participants ages 3-11 enrolled in protocol GS-US-337-1116 when available. The FDA waived the pediatric study requirement from birth to less than 3 years because necessary studies are highly impracticable due to the high rate of spontaneous HCV clearance in that age group.

Gilead plans to fulfill PMR 2780-2 with results from a separate long-term follow-up protocol (GS-US-334-1113) in which all participants in GS-US-337-1116 will enroll. Participants in GS-US-334-1113 will undergo assessments of growth, quality of life, and long-term viral suppression every 6 months for a five year period.

# 12. Recommendations/Risk Benefit Assessment

**Recommended Regulatory Action**

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of LDV/SOF 90mg/400mg for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV GT 1, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis.

**Risk Benefit Assessment**

The overall risk benefit assessment is favorable for LDV/SOF. Efficacy and safety data presented in this sNDA do not alter the risk-benefit assessments made during the original NDA and supplemental reviews of LDV/SOF. Ninety-eight percent of participants enrolled in GS-US-337-1116 achieved SVR 12 and no participants experienced virologic breakthrough or viral relapse. Although interpretation of safety data is limited by the single-arm, open-label trial design, no new safety concerns for adolescents emerged in the analysis of this clinical trial.

**Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The NDA contains no safety information necessitating a REMS.

**Recommendation for other Postmarketing Requirements and Commitments**

The FDA will not issue any new PMR or PMC as a result of this review.

# 13. Labeling

Although the labelling changes have not yet been finalized at the time of this review, Gilead and the FDA have agreed to the following modifications to the clinically-relevant sections of the label.

Section 1. Indications and Usage

- The adult indication was revised to align with recently approved HCV DAAs and to comply with regulation (§201.57(c)(2)(i)(A)) which says that, when a drug is indicated for use in combination with other therapy, this must be clearly stated in the Indications and Usage section. In this case, for adults, the revised label clearly describes when HARVONI is to be used in combination with Ribavarin.
- A separate statement providing indications for pediatric subjects was added. Based on the rationale described in Sections 7.6 and 8.10 of this review, the pediatric indication includes pediatric patients 12 years of age or older or weighing at least 35 kg regardless of age, pediatric patients with GT 1,4, 5 or 6 HCV infection, and without cirrhosis or with compensated cirrhosis.

Section 2. Dosage and Administration

- A new section titled "General Dosing Recommendations" was added to describe dosing instructions relevant to both adult and the pediatric patients included in this supplement. This includes the recommended dose (90 mg ledipasvir and 400 mg sofosbuvir) and a statement about relapse rates.
- A new section was added for dosage instructions pertinent to adults.
- A new section was added for dosage instructions pertinent to the pediatric patients included in this supplement. The section includes the new table included below.

*Table 2. Recommended Duration for Harvoni in Pediatric Patients 12 years of Age or Older or Weighing at Least 35 kg with Genotype 1, 4, 5, or 6 HCV without Cirrhosis or with Compensated Cirrhsosis*

| | *Patient Population* | *Treatment Regimen and Duration* |
|---|---|---|
| *Genotype 1* | *Treatment-naïve pediatric patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)* | *HARVONI 12 weeks* |
| | *Treatment-experienced pediatric patients without cirrhosis* | *HARVONI 12 weeks* |
| | *Treatment-experienced pediatric patients with compensated cirrhosis (Child-Pugh A)* | *HARVONI 24 weeks* |
| *Genotype 4, 5, or 6* | *Treatment-naïve and treatment-experienced pediatric patients without cirrhosis or with compensated cirrhosis* | *HARVONI 12 weeks* |

| | | |
|---|---|---|
| | *(Child-Pugh A)* | |

Section 6.1 Clinical Trials Experience

- This section is updated to include a summary of the safety data used to support the approval of HARVONI for the treatment of pediatric subjects 12 years of age and older or weighing at least 35 kg. See section 8.0 of this review for a detailed review of safety. The following paragraph was inserted:

*The safety assessment of HARVONI in pediatric subjects 12 years of age and older* (b) (4) *is based on data from a Phase 2, open-label clinical trial (Study 1116) that enrolled 100 subjects without cirrhosis or with compensated cirrhosis who were treated with HARVONI for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of HARVONI in adults. Limited safety data are available in pediatric subjects receiving HARVONI for 24 weeks. No Grade 3 or 4 reactions or discontinuations due to adverse reactions were observed in those pediatric subjects receiving HARVONI for 24 weeks*

Section 6.2 Postmarketing Experience

- The current label includes the following "Skin and Subcutaneous Tissue Disorders Skin rashes, sometimes with blisters or angioedema-like swelling" based on serious rash events seen in the Clinical Review of NDA 205834 s02-06. With this supplement, this section was updated to include "angioedema" as a postmarketing ADR based on one published case report (Hynicka LM and Khambaty, 2016), one FAERS report, and Gilead's analysis of 200 potential angioedema events, 11 of which can be plausibly linked to LDV/SOF. The majority of cases resolved without treatment after LDV/SOF discontinuation and did not require emergency intervention. In addition, please refer to the Pharmacovigilance Review prepared by Dr. Mihaela Jason on March 2, 2017. Dr. Jason's review summarizes the FAERS report and the literature report regarding angioedema with the use of LDV/SOF. Even though "angioedema-like swelling" is currently in section 6.2, the Division of Pharmacoviligence II states angioedema is not labeled. The events appear different in presentation from the "angioedema-like swelling" event. In summary, the clinical review team agrees with Gilead and Dr. Jason's assessment to include angioedema in section 6.2.

Section 8.4 Pediatric Use

- This section was updated to provide the rationale for and limitations of the pediatric indication. The following text is included:

(b) (4)

(b) (4)

*The safety and efficacy of HARVONI have not been established in patients less than 12 years of age or less than 35 kg, in pediatric patients with decompensated cirrhosis, or in pediatric liver transplant recipients.*

Section 12.3 Pharmacokinetics

- This section was updated to include a summary of the PK results of trial GS-US-337-1116. Please see Section 5 of this review or Dr. Jenny Zheng's Clinical Pharmacology Review for further details regarding PK results from this trial.

Section 12.4 Microbiology

- Based on the Division's review of microbiology data Gilead submitted in response to PMC-2985-2, information on antiviral activity against genotypes 4, 5 and 6 and their subtypes were added to the antiviral section. For further detail, please refer to Dr. Lisa Naeger's review.
- A new subsection titled pediatrics was added to state that in trial GS-US-337-1116 the presence of NS5A and NS5B resistance-associated polymorphisms did not impact treatment outcome. For further relevant details, please refer to section 7 of this review or Dr. Naeger's review.

Section 14.6. Clinical Trial in Pediatric Subjects

- This section has been added to describe trial GS-US-337-1116 and includes the following text.

*The efficacy of HARVONI was evaluated in an open-label trial (Study 1116) that evaluated 12 weeks of treatment with HARVONI once daily in genotype 1 HCV treatment-naïve (N=80) and treatment-experienced (N=20) pediatric subjects 12 years of age and older without cirrhosis or with compensated cirrhosis.*

(b) (4)

*The SVR12 rate was 98 overall (98% [78/80] in treatment-naïve subjects and 100% [20/20] in treatment-experienced subjects). No subject experienced on-treatment virologic failure or relapse. Two subjects were lost to follow-up*.

Patient Information

- This was updated to clarify that safety and efficacy have not yet been established in children less than 12 years of age and weighing less than 35 kg.

# 14. Other Relevant Regulatory Issues

Clinical Investigator Financial Disclosure Review Template.
Application Number: 205834 S-17

Submission Date(s):

Applicant: Gilead Sciences, Inc

Product: Harvoni (Ledipasvir [LDV]/Sofosbuvir [SOF])

Reviewer: Virginia Sheikh, MD

Date of Review: 03/01/2017

Covered Clinical Trial (Name and/or Number): GS-US-337-1116

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | **Yes** ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: **140** | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): **0** | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **2** | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0**<br>Significant payments of other sorts: **2**<br>Proprietary interest in the product tested held by investigator: **0**<br>Significant equity interest held by investigator in sponsor of covered study: **0** | | |
| Is an attachment provided with details of the disclosable financial | **Yes** ☒ | No ☐ (Request details from applicant) |

| | | |
|---|---|---|
| interests/arrangements: | | |
| 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) 0 | | |
| Is an attachment provided with the reason: N/A | **Yes** ☐ | No ☐ (Request explanation from applicant) |

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*. Two investigators, both sub-investigators, had disclosable financial interest >$25,000. Both of these investigators were associated with one site ( (b) (6) ) which enrolled (b) (6) participants.

*Medical Officer Comment: Only 2 of 140 investigators had disclosable financial interests. The primary and secondary efficacy endpoints are objective laboratory results from assays that are performed at sites external to the study sites. All safety data, including adverse events, were 100% source document verified by a Clinical Research Associate working on behalf of Gilead to evaluate for under- or over-reporting. Hence, the disclosed financial interests/arrangements do not affect the approvability of the application.*

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

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/s/

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VIRGINIA M SHEIKH
03/13/2017

KIMBERLY A STRUBLE
03/13/2017