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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review

Date	January 26, 2016
From	Wendy Carter, DO
Subject	Clinical Review
NDA/BLA # **Supplement#**	206843 S001, S002 and S003
Applicant	Bristol Myers Squibb
Date of Submission	August 5, 2015
PDUFA Goal Date	February 5, 2016
Proprietary Name / Established (USAN) names	Daklinza
Dosage forms / Strength	30 mg, 60 mg tablets
Proposed Indication(s)	1. HCV Genotype 1 including HIV-1 co-infection and HCV decompensated cirrhotic and post-transplant population.
Recommended:	*Approval*

1. Introduction

These supplemental New Drug Applications (sNDA) include the final Clinical Study Reports for clinical trials AI444215 (hereafter referred to as ALLY-1) and AI444216 (hereafter referred to as ALLY-2). These trials support submission of data for 3 supplements S001, S002, and S003 to expand the current HCV genotype 3 indication for daclatasvir (DCV) in combination with sofosbuvir to include treatment of HCV genotype 1 subjects, with and without HCV/ HIV-1 co-infection and HCV genotype 1 subjects with decompensated cirrhosis or recurrence of HCV genotype 1 post-liver transplantation.

Daclatasvir (Daklinza™) is an inhibitor of HCV nonstructural protein 5A (NS5A) approved for treatment of chronic hepatitis C genotype 3 as a component of an antiviral treatment regimen. Daclatasvir is marketed by Bristol Myers Squibb and was approved on July 24, 2015.

2. Background

HCV is a small positive-strand ribonucleic acid (RNA) virus in the Flaviviridae family. At least seven viral HCV genotypes (GTs) have been identified, numbered 1 to 7, and most GTs have been divided into multiple subtypes (e.g., GT 1 subtypes 1a and 1b). Globally it is estimated that approximately 170 million people are infected with chronic HCV infection, including approximately 3 to 5 million people in the US)[1]. The most

[1] http://www.epidemic.org/theFacts/theEpidemic/worldPrevalence/

common HCV GT in the US is GT 1 (70-75%), followed by GT 2 and GT 3. HCV GT 4 accounts for approximately 1% of chronic HCV infections in the US, and less than 1% of chronic HCV infections involve GT 5 or 6 (Messina 2015; Germer 2011; Blatt 2000).

The selection of treatment for chronic HCV infection depends upon factors such as HCV GT, prior HCV treatment history and cirrhosis status. The currently US approved drugs for the treatment of HCV infection are listed in Table 1. Most of the listed drugs are approved for use in combination with other HCV antiviral agents: refer to the specific approved product labels for complete dosage and administration recommendations.

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

Drug Class	Generic Name	Trade Name	HCV Genotype with Approved Indication
Pegylated interferons	Peginterferon alfa-2a	Pegasys®	1, 2, 3, 4, 5, 6
	Peginterferon alfa-2b	PegIntron®	1, 2, 3, 4, 5, 6
Interferons	Interferon alfa-2b	Intron-A®	All
Nucleoside Analogue	Ribavirin	Rebetol®, Copegus®	1, 2, 3, 4, 5, 6
Protease Inhibitors	Boceprevir	Victrelis®	1
	Telaprevir	Incivek®*	1
	Simeprevir	Olysio®	1, 4
	Paritaprevir (co-formulated with ombitasvir, ritonavir and copackaged with dasabuvir)	Viekira Pak®	1
	Paritaprevir (co-formulated with ombitasvir, ritonavir)	Technivie®	4
NS5B Inhibitors	Sofosbuvir	Sovaldi®	1, 2, 3, 4
	Dasabuvir (copackaged with ombitasvir, paritaprevir, ritonavir)	Viekira Pak®	1
NS5A Inhibitors	Ledipasvir (in combination with sofosbuvir as LDV/SOF)	Harvoni®	1, 4, 5 , 6
	Ombitasvir (co-formulated with paritaprevir, ritonavir and copackaged with dasabuvir)	Viekira Pak®	1
	Daclatasvir	Daklinza™	3

The natural history of chronic HCV infection involves progression to cirrhosis, hepatocellular carcinoma (HCC), liver failure, and death. In the US, chronic HCV

infection leading to decompensated cirrhosis and/or HCC 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 HCC, hepatic events, fibrosis, and all-cause mortality (van der Meer 2012; Backus 2011; Singal 2010; Veldt 2007).

Hepatitis C virus co-infection is found in about 30% of HIV-positive patients in the US. HCV/HIV-1 co-infection may result in multi-systemic disorders. The presence of HIV has been shown to accelerate the natural history of HCV infection, even in patients with well controlled HIV infection under highly active antiretroviral (ARV) therapy (HAART) treatment, and can result in increased frequency and speed of progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma, and a higher incidence of liver enzyme elevation during ARV treatment. Eradication of HCV in co-infected patients is associated with a reduction in mortality and liver-related events.

Several of the recently FDA approved DAAs include information related to HCV/HIV-1 co-infected patients in their prescribing information. For example, efficacy was assessed in HCV/HIV-1 co-infected subjects in the Viekira Pak (Dasabuvir Sodium; Ombitasavir; Paritaprevir; Ritonavir, approved on 12/19/2014) clinical trials submitted for approval. The SVR12 rates were 91% (51/56) for subjects with HCV GT1a infection and 100% (7/7) for those with HCV GT1b infection. SOF + PegIFN/RBV and SMV + PegIFN/RBV were also approved for the treatment of HCV/HIV-1 co-infected patients with either HCV GT1 or GT4 infection; SOF + RBV is approved for the treatment of HIV-infected patients with either GT2 or GT3 infection.

Current approaches to the management of chronic HCV infection in patients undergoing orthotopic liver transplant are treatment with antiviral therapy prior to transplant to prevent re-infection of the graft or post-transplant antiviral therapy administered for virologic cure and prevention of graft loss.

Recurrence of HCV infection post-liver transplant can lead to accelerated allograft injury and fibrosis which can significantly impact graft and overall patient survival (Gane, 1996). The rate of fibrosis progression of HCV in post-transplant patients is greatly accelerated compared to those without liver transplant, with 10-30% developing cirrhosis within 5 years of transplant (Gane, 1996; Berenguer 2000). This accelerated course is attributed, in part, to the need for potent immunosuppressants, treatment of acute rejection and other donor recipient factors. As a result, liver transplant patients with chronic HCV infection have a significantly lower 5-year survival rate compared to those without chronic HCV, primarily due to a higher rate of graft failure from recurrent disease (Forman, 2002; Lai 2011). Data supports that liver transplant recipients who achieve SVR have significantly improved survival when

compared with partial responders or those who are untreated (Veldt, 2008; Carrion, 2007; Picciotto, 2007).

Currently, there are no approved treatment options for HCV infected patients who have decompensated cirrhosis (Child-Pugh class B or C cirrhosis) and limited treatment options for those who have recurrence of HCV post-liver transplant. SOF/RBV is approved for patients awaiting liver transplantation; SOF/RBV can be given up to 48 weeks or until liver transplantation, whichever comes first. Viekira Pak for 24 weeks is approved only in HCV GT-1 patients who are post-liver transplant and have normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2). Therefore, this regimen is not indicated for patients with advanced fibrosis or cirrhosis (and is contraindicated for those with advanced cirrhosis equivalent to Child-Pugh class B or C). Additionally, significant drug-drug interactions (DDIs) with paritaprevir/RTV component of Viekira Pak and calcineurin inhibitors, such as cyclosporine and tacrolimus, limit the utility of this regimen in the post-transplant population (Kwo, 2014).

The current supplemental NDAs 001, 002 and 003 seek approval of DCV in combination with SOF with or without RBV, for the treatment of HCV GT1, including patients with HCV/HIV-1 co-infection, compensated cirrhosis, decompensated cirrhosis (Child-Pugh B or C) or for those with recurrence of HCV GT1 infection after liver transplantation.

Safety Considerations with Related and Combined Drugs

HCV NS5A Inhibitors

In addition to DCV, currently US approved HCV NS5A inhibitors include ombitasvir (as a component of the FDC copackaged Viekira Pak and FDC Technivie) and ledipasvir (as a component of the FDC LDV/SOF, Harvoni). The most common adverse reactions observed with treatment of Viekira Pak alone were nausea, pruritus and insomnia and with treatment of Technivie alone were asthenia, fatigue, nausea, insomnia, pruritus and skin reactions. The presence of multiple HCV DAAs in Viekira Pak and Technivie regimens, particularly the HCV PI, confounds causality assessment to the HCV NS5A component alone. The most common adverse reactions in subjects receiving a LDV/SOF-containing treatment compared with placebo were asthenia, headache, fatigue, cough, myalgia, dyspnea, irritability and dizziness.

HCV NS5B Nucleotide Polymerase Inhibitors

SOF is the only approved NS5B nucleotide polymerase inhibitor. SOF is used in combination with DCV with and without ribavirin (RBV) in the ALLY-1 and -2 trials supporting these supplemental NDAs. The most common adverse reactions observed with treatment of DCV plus SOF were headache, fatigue, nausea and diarrhea, events which are included in the current label.

Postmarketing cases of serious symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention were reported when amiodarone was coadministered with SOF in combination with another HCV DAA including LDV, DCV and simeprevir. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is currently unknown. Please see the current SOF and/or DCV product label for the details provided in the Warnings and Precautions section.

Guanosine Analogue

DCV/SOF was coadministered with RBV in the ALLY-1 trial. RBV is a guanosine analogue that enhances the efficacy of anti-HCV treatment by mechanism(s) that are not fully understood. 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, 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. CMC

Daclatasvir tablets are currently approved for use in the United States, and no new biopharmaceutics information (e.g., formulation or dissolution data) is included within sNDA S-001 through S-003. For a description of the clinical properties of DCV, please refer to the original NDA reviews. No quality inspections of manufacturing and testing sites were required as these sites were inspected during review of the original DCV NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology and toxicology programs were extensively reviewed in the original DCV NDA. Please refer to the original NDA review by Dr. Peyton Myers for details. No additional nonclinical data were submitted with sNDA S001-S003.

5. Clinical Pharmacology/Biopharmaceutics

Four clinical trials with drug-drug interaction information evaluating concomitant use of daclatasvir with buprenorphine/naloxone, darunavir/ritonavir, dolutegravir, or lopinavir/ritonavir and various in vitro reports, including evaluating daclatasvir as an

OCT1 substrate, were submitted as part of the daclatasvir sNDA S001-S003. The clinical pharmacology review findings are summarized below. Please see the review by Dr. Stanley Au for complete details.

In vitro reports

BMS submitted data evaluating DCV as an OCT1 substrate. Review by the clinical pharmacology team concludes that the data does not support (b) (4) that DCV is an OCT1 substrate.

Drug-drug interaction information

- Daclatasvir's effects on darunavir or lopinavir: the clinical pharmacology team reviewed the DDI data and concludes that there are no clinically relevant changes in darunavir or lopinavir exposure.
- Effect of darunavir or lopinavir on daclatasvir: The results support a daclatasvir 60 mg once daily dosage regimen with concomitant use (no dosage adjustment needed). Please see the clinical pharmacology review for related information regarding proposed FDA recommended changes for section 7 in the daclatasvir US prescribing information (USPI).
- Daclatasvir's effects on buprenorphine or buprenorphine/naloxone: the applicant proposed (b) (4)

  However, FDA proposes to include a clinical comment in section 7. Please see the clinical pharmacology review for additional information.
- Daclatasvir's effects on dolutegravir and vice versa: the applicant's statements in the daclatasvir USPI that no clinically relevant changes in daclatasvir or dolutegravir exposure were observed are considered reasonable by the Clinical Pharmacology team.

6. Clinical Microbiology

The clinical virology for DCV was extensively reviewed in the original DCV NDA. Please also see the clinical virology reviews by Dr. Lalji Mishra for a detailed review of DCV nonclinical virology.

For a detailed discussion of the antiviral activity, the impact of baseline polymorphisms and the development of resistance polymorphisms please see the review by Dr. Patrick Harrington. A clinical discussion of impact of key baseline polymorphisms on efficacy, the development of resistance associated polymorphisms at the time of virologic failure and the consequences of virologic failure is included below with the discussion of efficacy.

7. Clinical/Statistical- Efficacy

Sources of Clinical Data

To support these applications, BMS has submitted safety and efficacy data from two open-label phase 3 trials AI444215 (ALLY-1) and AI444216 (ALLY-2). Data are provided from ALLY-2 in 203 HCV/HIV-1 coinfected subjects treated with DCV/SOF (153 subjects with 12 weeks and 50 subjects with 8 weeks duration). Data are included from ALLY-1 in 60 subjects with cirrhosis (Child-Pugh A, B and C) and 53 post-liver transplant subjects all treated with DCV/SOF/RBV for 12 weeks from ALLY-1.

To support the safety profile of the DCV/SOF with or without RBV regimen, data from ALLY-3 and AI444040 were submitted. Both ALLY-3 and AI444040 were reviewed as part of the resubmission NDA application for the original approval of DCV. In total, safety and efficacy data are available from 679 subjects exposed to DCV/SOF± RBV in the above 4 trials (ALLY-1, -2 and -3 and AI444040; note that only safety data were reviewed from AI444040 because of the lack of a right of reference for the investigational formulation of SOF).

Additionally, the safety of DCV is supported by FDA review of the original safety data base of over 1900 clinical trials subjects who were exposed to the marketed dose and duration of DCV 60 mg once daily for 12 weeks or longer. The clinical investigation of DCV has been ongoing since 2007 and includes over 8000 subjects exposed to DCV.

Description of Clinical Trials

ALLY-2

ALLY-2 is an open-label, phase 3 study of 8 or 12 weeks of DCV/SOF in 151 HCV treatment-naive and 52 HCV treatment-experienced subjects coinfected with HCV/HIV. A total of 101 HCV treatment-naive subjects received 12 weeks of treatment, 52 HCV treatment-experienced subjects received 12 weeks of treatment, and 50 HCV treatment-naïve subjects received 8 weeks of treatment. Treated subjects had HCV GT-1, -2, -3, or -4 and this included 29 (14%) subjects with compensated cirrhosis at baseline. The study was open to subjects infected with any HCV GT, but no subjects with GT-5 or -6 infection were accrued.

While this trial was open to all genotypes, insufficient numbers of subjects with GT-2 through 6 enrolled to extend the indication to genotypes beyond 1 and genotype 3, which was approved with the resubmission NDA. The efficacy in the coinfected population supports those with mono-infection with chronic HCV. DAVP has used this rationale for other approvals, as data supports that subjects with HIV/HCV coinfection respond similarly to those with monoinfection with HCV. Therefore, specific indications are not given for HCV/HIV-1 coinfection, and labeling guidance is provided in Section 2 Dosage and Administration.

Subjects received once daily (QD) dosing of DCV 60 mg (dose-adjusted for concomitant cART) plus SOF 400 mg. Per protocol, subjects receiving ritonavir (RTV) boosted protease inhibitor (PI)-based cART were to receive DCV 30 mg QD and subjects on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART (except for rilpivirine) were to receive DCV 90 mg QD. Subjects on other permissible cART regimens, or not receiving concomitant ART were to receive the standard dose of DCV of 60 mg QD.

Dosing of DCV for subjects receiving any permissible RTV-boosted PI (atazanavir [ATV]/RTV, darunavir [DRV]/RTV, or lopinavir [LPV]/RTV) was based on DDI results demonstrating that DCV 30 mg QD was optimal for coadministration with ATV/RTV. Results from a subsequent DDI study in healthy volunteers (AI444093) demonstrated that, unlike with ATV/RTV, the optimal DCV dose for subjects receiving concomitant DRV/RTV or LPV/RTV is 60 mg QD. These DDI data only became available as last patient last treatment for ALLY-2 approached and, therefore, no changes to study conduct were made.

Subjects receiving cART had to have an HIV RNA < 50 copies/mL at screening and an HIV viral load < 200 copies/mL for 8 weeks prior. The CD4 count for subjects on cART had to be > 100 cells/μL at screening. For subjects not on cART, inclusion criteria mandated that the CD4 count be ≥ 350 cells/μL at screening.

The primary endpoint was the proportion of subjects achieving SVR12. SVR12 is defined as HCV RNA < lower limit of quantification (LLOQ), target detected (TD) or target not detected (TND) at follow-up week 12. Missing HCV RNA data were imputed using a next value carried backward approach (NVCB); subjects missing HCV RNA data at follow-up Week 12 could be counted as SVR12 responders if that had HCV RNA < LLOQ at the next available HCV RNA measurement.

The primary objective of the trial was to compare the SVR12 rate in treatment-naïve HCV GT1 subjects coinfected with HCV/HIV-1 who were treated with 12 weeks of DCV/SOF compared to a historical threshold (the SVR rate of pegIFN/RBV which was the standard therapy at the time of the study design). The historical threshold was based on the APRICOT trial and was estimated at 29% (51/176) for HCV/HIV GT1 coinfected subjects after 48 weeks of pegIFN/RBV.

ALLY-1

ALLY-1 is an open-label, Phase 3 study of DCV/SOF/RBV for 12 weeks in HCV infected subjects: 60 cirrhotic subjects with Child-Pugh class A, B, or C cirrhosis who were being monitored in a liver transplant center and may require future liver transplantation and 53 subjects who were post-liver transplant. Treated subjects had HCV GT-1, -2, -3, -4, or -6. The study was open to subjects infected with any HCV genotype, but no subjects with GT-5 infection were accrued.

The eligible population for the cirrhotic cohort included subjects with a model for end-stage liver disease (MELD) score of ≥ 8 and ≤ 40. Subjects with HCC were eligible for enrollment if they met all Milan criteria for liver transplantation: a single tumor not more than 5 cm in greatest diameter, or up to 3 tumors ≤ 3 cm in greatest diameter, and no evidence of vascular invasion or extrahepatic metastasis.

The population for the post-liver transplant cohort included subjects who received a liver transplant ≥ 3 months prior to screening. Subjects in this cohort did not have clinical or pathologic evidence of moderate or severe liver rejection. The following immunosuppressants were allowed: cyclosporine, tacrolimus, sirolimus, everolimus, corticosteriods, mycophenolate mofetil (mycophenolic acid).

Subjects with cirrhosis (Child-Pugh class A, B or C), who received 12 weeks of treatment (and did not undergo a liver transplant during therapy), received 24 weeks of follow-up. Cirrhotic subjects, who underwent a liver transplant during treatment, could have their treatment extended for an additional 12 weeks after transplant, followed by 24 weeks of follow-up. Subjects with cirrhosis who had a liver transplant during follow-up, completed a total of 24 weeks of follow-up regardless of the time of transplant.

Post-transplant subjects received 12 weeks of therapy and 24 weeks of follow-up. Subjects who relapsed during follow-up were to be retreated with DCV/SOF/RBV for 24 weeks, followed by an additional 24 weeks of follow-up.

The primary endpoint was the proportion of subjects achieving SVR12. SVR12 is defined as HCV RNA < lower limit of quantification (LLOQ), target detected (TD) or target not detected (TND) at follow-up week 12. Missing HCV RNA data were imputed using a next value carried backward approach (NVCB); subjects missing HCV RNA data at follow-up Week 12 could be counted as SVR12 responders if that had HCV RNA < LLOQ at the next available HCV RNA measurement.

The primary objective of this study was to compare the SVR12 rate in GT-1 subjects who were treated with DCV/SOF + RBV therapy for 12 weeks to historical controls. The composite historical threshold for the cirrhotic group was estimated at 41.6%. The composite historical threshold was based on SVR rates from the Neutrino (sofosbuvir) and HPC 3007/C206 (simeprevir) trials, which were the available data at the time of the study design. Subjects enrolled in the cirrhotic cohort were expected to be transplant candidates with significantly more advanced liver disease and a correspondingly lower historical threshold in comparison to well compensated cirrhotic subjects treated in the Neutrino and HPC3007/C206 trials. Subjects who failed NS3 protease inhibitors were not included in those trials but it would be reasonable to consider them as non-responders to pegIFN/RBV with respect to historical SVR. Child-Pugh B and C cirrhotic subjects are not candidates for any interferon-based therapy so their historical threshold was set at 5%. Therefore the estimated historical threshold based on the enrolled population is provided below.

Table 2: Overall Historical Threshold

Patient Profile	Proportion	SVR - Point Estimate	SVR – Upper Bound 95% CI	New Threshold	Proportion * New Threshold
Child-Pugh A					
Naïve	10%	81%	90%	90%	9.0%
Relapser	10%	73%	82%	82%	8.2%
Non-responder	10%	54%	73%	73%	7.3%
PI Failure	20%	54%	73%	73%	14.6%
Child-Pugh B or C	50%	Not Available		5%	2.5%
Overall Historical Threshold SVR rate					41.6%

Source: Appendix 4 of Clinical Study Protocol No: 03 AI444215 ALLY-1

Based on the proposed weighing and the proportion of enrolled subjects, the historical threshold for SVR for the cirrhotic cohort was estimated at 41.6%.

At the time of the study design, pegIFN/RBV was the only approved regimen for treatment of post-transplant HCV recurrence. Because pegIFNα/RBV results in an SVR ≤ 30% of treated patients with histological HCV recurrence after liver transplantation, the historical threshold for pegIFNα/RBV was estimated at 30% per the analysis plan in the protocol.

Assays

The COBAS TaqMan HCV Test, v2.0 for use with the High Pure System was the assay used for quantitation of HCV RNA. The Abbott RealTime HCV Genotype II assay was used for all GT/subtype assessments in ALLY-2 and ALLY-1. For samples where HCV GT or subtype results were unavailable or inconclusive, the VERSANT HCV Genotype 2.0 Assay (LiPA) or viral sequence analysis could be used.

Demographics and Baseline Characteristics

ALLY-2

Among HCV/HIV-1 coinfected subjects, the baseline demographics and characteristics were comparable across the 3 cohorts in ALLY-2. The majority of subjects were white (62%) or black/African American (34%); and the majority were male (87%). A large proportion of subjects had a high HCV RNA baseline level ≥ 6 million IU/mL, and the majority of subjects (82%) had a baseline HCV RNA level ≥ 800,000 IU/mL. The overall median age was 52 years and 11 subjects (5%) were at or above 65 years of age. Thirty-six subjects (18%) self-identified as Hispanic or Latino. Additionally, most subjects were genotype 1 and the majority (73%; not shown in table) had IL28B rs12979860 non-CC genotypes.

Nearly all subjects (98%; 199/203) were on concomitant cART. Of the subjects on cART at baseline, 49% (99/203) were receiving PI-based regimens (most commonly DRV/RTV), 25% (50/203) were receiving NNRTI (most commonly efavirenz), and 25% (50/203) were receiving other cART regimens (most commonly integrase inhibitors plus nucleoside reverse transcriptase inhibitors [NRTIs]). Four subjects (2.0%) were not receiving concomitant cART.

The median CD4 count at baseline was 565 cells/μL.

Table 3: Baseline Demographics and Characteristics of Subjects in ALLY-2

	Treatment-Naïve DCV/SOF 12 W N=101(%)	**Treatment-Naïve DCV/SOF 8 W N=50 (%)**	**Treatment-Experienced DCV/SOF 12 W N=52 (%)**	**Total N=203 (%)**
Median Age	52	50.5	56.5	52
Age <65	96 (95)	47 (94)	49 (94)	192 (95)
Age ≥65	5 (5)	3 (6)	3 (6)	11 (5)
Gender				
Male	92 (91)	42 (84)	43 (83)	177 (87)
Female	9 (9)	8 (16)	9 (17)	26 (13)
Race				
White	66 (65)	28 (56)	31 (60)	125 (62)
Black/AA	30 (30)	19 (38)	20 (39)	69 (34)
Asian	2 (2)	2 (4)	0	4 (2)
Other*	4 (4)	2 (4)	1 (2)	7 (3)
Hispanic/Latino	18 (18)	8 (16)	10 (19)	36 (18)
Median HCV RNA (log10 IU/mL)	6.74	6.44	6.68	6.65
HCV RNA ≥ 800,000	79 (78)	44 (88)	44 (85)	167 (82)
HCV RNA ≥ 6,000,000 (IU/mL)	43 (43)	16 (32)	19 (37)	78 (38)
Genotype				
1a	71 (70)	35 (70)	33 (64)	139 (69)
1b	12 (12)	6 (12)	11 (21)	29 (14)
2	11 (11)	6 (12)	2 (4)	19 (9)
3	6 (6)	3 (6)	4 (8)	13 (6)
4	1 (1)	0	2 (4)	3 (2)
Cirrhosis				
Absent	90 (90)	44 (88)	34 (65)	168 (83)
Present	9 (9)	5 (10)	15 (29)	29 (14)
Not reported	2 (2)	1 (2)	3 (6)	6 (3)
Median CD4 Cell Count	520	575	636	565
CD4 (%)				
<200	4 (4)	1 (20	0	5 (3)
200-<500	42 (42)	21 (43)	12 (23)	75 (37)
≥500	55 (55)	28 (56)	39 (75)	122 (60)

Not reported	0	0	1 (2)	1 (1)
cART Regimen				
Protease Inhibitor	47 (47)	29 (58)	23 (44)	99 (49)
NNRTI	28 (28)	10 (20)	12 (23)	50 (25)
Other	25 (25)	9 (18)	16 (31)	50 (25)
None	1 (1)	2 (4)	1 (2)	4 (2)

*Other includes: American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and other
Source: Demographics for ALLY-2

A total of 29 subjects (14%) were determined to have cirrhosis at baseline. Cirrhosis status was determined based on results from liver biopsy, Fibroscan (>14.6 kPa) or FibroTest (≥0.75) and APRI (>2) laboratory testing. Results for baseline determination of cirrhosis status were used based on the ordered hierarchy of liver biopsy, fibroscan, and then laboratory testing (FibroTest/APRI). All subjects received fibrosis staging at baseline based on FibroTest/APRI laboratory results. It is important to note that in this trial of HCV/HIV-1 coinfected subjects, some results of the laboratory testing for fibrosis staging may be influenced by concomitant medications. The concomitant medications can influence the values of the individual analytes within the test. In particular for this population use of atazanavir, which may impact the bilirubin levels, may influence the fibrosis score determination.

The following table summarizes which method was used for determining liver staging (liver biopsy, fibroscan or FibroTest and/or APRI) and provides the results for discordant findings between the different modalities. There were 27 cases where the FibroTest result of F4 was higher than the liver biopsy result. Several factors likely influence this discordance; these may include influence of atazanavir on the FibroTest result or potentially progression of disease from the time of prior liver biopsy to Baseline assessment. In ALLY-2, 19 subjects had FibroTest results of F4 and were also on concomitant atazanavir. Liver biopsy could have been completed up to 3 years prior to enrollment, so some subjects may have had progression of their liver disease prior to enrollment. However, per protocol, the liver biopsy result would be used over the laboratory testing for determination of cirrhosis, even if the laboratory testing from baseline showed more advanced disease when compared to the liver biopsy.

Table 4: Modalities Used for Assessment of Cirrhosis and Discordance Between the Modalities

	Treatment Naïve 12W N=101	**Treatment Experienced 12W N=52**	**Treatment Naïve 8W N=50**	**Total N=203**
Liver Biopsy	42 (42%)	28 (54%)	24 (48%)	94 (46%)
Fibroscan	25 (25%)	8 (15%)	9 (18%)	42 (21%)
FibroTest and/or APRI	101 (100%)	52 (100%)	50 (100%)	203

				(100%)
Discordant results for cirrhosis (F4) vs non-cirrhosis (F0-3)				
FibroTest F4 > Biopsy[a] (F0-3)	10	6	11	27
Biopsy F4 > FibroTest (F0-3)	0	2[b]	2[c]	4
FibroTest (F4) > Fibroscan (F0-3)	3	0	2	5
Fibroscan (F4) > FibroTest (F0-3)	1	0	1	2

[a] Number of subjects by arm where biopsy was completed within 1 month: Treatment Naïve 12W n=6; Treatment-Experienced 12W n=2 ; Treatment-Naïve 8W n=1.
[b] One subject had liver biopsy on Day -579 the other subject had liver biopsy on Day -7
[c] Both subjects had liver biopsies within 1 month of enrollment
Source: adapted from Appendix 3.3 CSR ALLY2

This analysis highlights some of the issues surrounding the ability to accurately diagnose liver staging, particularly within the rapid paradigm shift towards use of less invasive testing such as a Fibroscan and the laboratory based testing such as FibroSure or FibroTest. This issue has become important when different treatment regimens (with or without RBV or by duration) are recommended for subjects who have cirrhosis compared to those without cirrhosis. While potentially cirrhosis was underdiagnosed in ALLY-2 based on the available FibroTest and APRI results, multiple factors may influence the diagnosis of cirrhosis including accuracy of the original liver biopsy due to variability in reading of the biopsy specimen, use of concomitant medications and body habitus potentially limiting the accuracy of Fibroscan results.

ALLY-1

The baseline demographic characteristics were comparable in subjects with cirrhosis and those who were post-liver transplant. More than half of subjects were male (67%), with a median age of 59 years and with 21 subjects (19%) above age 65 years. Almost all subjects were white, with 34% reporting Hispanic or Latino heritage.

African Americans, Asians and other minorities (American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and those self-identified as other) were under represented in this trial. Females were 33% of the trial population and were fairly well represented in this trial in comparison to some other HCV trials.

The baseline disease characteristics of the cirrhotic and post-transplant cohorts are consistent with their advanced stage of HCV disease. The median HCV RNA overall was 6.29 log10 IU/mL. Most subjects were GT-1 (n=86; 75%), with smaller proportions of GT-2, -3, -4 and -6. No GT-5 subjects enrolled. The majority of subjects (77%) were ILB28 non-CC genotype. In the cirrhotic cohort, the median MELD score at baseline was 13.3 and 35% of subjects had a MELD at or above 15,

while 8% had a MELD at or above 20. The mean Child-Pugh score was 8.3 and Child-Pugh Scores indicated that 20% of subjects were A, 53% were B and 27% were C.

More than half of the post-liver transplant subjects (n=29; 55%) in ALLY-1 had fibrosis stage F3 (n=13) or F4 (n=16) by screening FibroTest (note that cirrhosis status by liver biopsy, Fibroscan or FibroTest with APRI was not collected for this cohort).

Table 5: Baseline Demographics and Characteristics in ALLY-1

	Post-Transplant DCV/SOF/RBV 12 W N=53 (%)	**Cirrhosis DCV/SOF/RBV 12W N=60 (%)**	**Total N=113 (%)**
Median Age	59	58	59
Age <65	42 (79)	50 (83)	92 (81)
Age ≥65	11 (21)	10 (17)	21 (19)
Gender			
Male	38 (72)	38 (63)	76 (67)
Female	15 (28)	22 (37)	37 (33)
Race			
White	51 (96)	57 (95)	108 (96)
Black/AA	1 (2)	3 (5)	4 (4)
Asian	1 (2)	0	1 (1)
Hispanic/Latino	13 (25)	25 (42)	38 (34)
Median HCV RNA (log10 IU/mL)	6.61	6.01	6.29
HCV RNA ≥ 800,000	47 (89)	33 (55)	80 (71)
Genotype			
1a	31 (59)	34 (57)	65 (58)
1b	10 (19)	11 (18)	21 (19)
2	0	5 (8)	5 (4)
3	11 (21)	6 (10)	17 (15)
4	0	4 (7)	4 (4)
6	1 (2)	0	1 (1)
IL28 B rs1297860 genotype			
CC	13 (25)	13 (22)	26 (23)
Non-CC	40 (75)	47 (78)	87 (77)
Cirrhosis			
Present	-	59 (98)	-
Not reported	-	1 (2)	-
Prior HCV Therapy			
Naïve	22 (42)	24 (40)	46 (41)
Experienced	31 (59)	36 (60)	67 (59)
Fibrosis Stage (by FibroTest®)			
F0-F2	23 (43)	4 (7)	27 (24)
F3	13 (24)	8 (13)	21 (19)
F4	16 (30)	48 (80)	64 (57)

Not Reported	1 (2)	0	1 (1)
MELD Score **Mean (SD)** **MELD ≥ 15** **MELD ≥ 20**	-	13.3 (4.34) 21 (35) 5 (8)	-
Child-Pugh Score **Mean (SD)** **A** **B** **C**	-	8.3 (2.07) 12 (20) 32 (53) 16 (27)	-

Source: Demographics ALLY-1

Disposition

Both ALLY-1 and -2 had 98% of subjects complete the treatment period. Of the subjects who entered follow-up, 99.5% of HCV/HIV coinfected subjects from ALLY-2 and 94% of subjects in ALLY-1 completed the follow-up week 12 visit.

ALLY-2

A total of 203 HCV/HIV coinfected subjects were treated with 12 weeks of DCV/SOF. Of these 203 subjects, 199 (98%) subjects completed the treatment period. Two subjects discontinued due to poor/non-compliance and 2 due to 'other' reasons (incarceration). A total of 200/201(99.5%) subjects who entered follow-up completed the follow-up Week 12 visit at the time of the database lock.

ALLY-1

A total of 113 subjects were treated; 60 subjects with cirrhosis and 53 post-liver transplant subjects.

Four subjects with cirrhosis and HCC underwent liver transplantation while on treatment; 3 subjects (ID# 1-50, 3-104 and 3-17) received 12 weeks of treatment extension after transplant (per protocol) and the remaining subject (3-100), who was treated for 23 days prior to transplant, did not receive treatment extension after transplant. All 4 subjects achieved SVR12.

Of the 110 subjects who did not undergo liver transplant, 108 subjects (98%) completed the 12 week treatment period. Subject 3-100, mentioned above, discontinued early to receive a liver transplant at a remote site and Subject 3-116 discontinued at Week 4 due to an adverse event of headache; both achieved SVR12.

All 110 subjects without a treatment extension entered the follow-up period and 103 (93.6%) completed the follow-up Week 12 visit. The 7 subjects who did not complete the follow-up Week 12 visit included 6 relapsers (who relapsed before follow-up Week 12; at the time of database lock for the CSR, these 6 subjects were being retreated with 24 weeks of DCV/SOF/RBV [per protocol]) and 1 subject who was lost to follow-up.

The retention rate and compliance with study visits and medications in both trials was high and there were few discontinuations or subjects lost to follow–up. This led to little missing data for the enrolled subjects.

Primary Efficacy Endpoint

The regulatory primary efficacy endpoint for DAA HCV clinical trials has been established as the proportion of subjects with HCV RNA ≤ LLOQ at follow-up Week12. Subjects that attain this endpoint are considered to have achieved a sustained virologic response at follow-up Week 12, or SVR12; and thus, a virologic cure.

For both trials, GT-1 subjects were primarily enrolled. The numbers of subjects representing non-GT-1 were too small to support new indications in labeling. Therefore, the clinical efficacy review focuses on the genotype 1 results. For details and overall analyses of all genotypes please see the statistical review by Dr. Wen Zeng.

ALLY-2

ALLY-2 randomized treatment naïve subjects to an 8 week or 12 week regimen of DCV/SOF, whereas all treatment experienced subjects were assigned to a 12 week regimen of DCV/SOF. The overall SVR12 results from the treatment naïve 8-week regimen were low: SVR12 of 76% (38/50) (95% CI (61.8, 86.9)). Evaluating only genotype 1 subjects resulted in a 76% (31/41) SVR12 rate (95% CI (59.7, 87.6), with unacceptably high relapse rates. Therefore, BMS did not seek an 8 week dosage recommendation; therefore, this review focuses on the 12 week duration.

The following table provides the imputed SVR12 results for the HCV GT-1 subjects, overall and by GT-1 subtype.

Table 6: Outcome Results for HCV Genotype 1 Subjects Who Received 12 Week Duration in ALLY-2

	Treatment-Naïve DCV/SOF 12 W	Treatment-Experienced DCV/SOF 12 W	Total N=127 (%)
Overall GT-1 (n/N)	80*/83 (96%)	43/44 (98%)	123/127 (97%)
GT-1a	68/71 (96%)	32/33 (97%)	100/104 (96%)
GT-1b	12/12 (100%)	11/11 (100%)	23/23 (100%)
Without Cirrhosis	72/74 (97%)	31/31 (100%)	103/105 (98%)
With Cirrhosis	8/9 (89%)	12/13 (91%)	20/22 (91%)

*One subject (19-138) was lost to follow up and considered a failure (incarcerated) and 2 subjects had virologic relapse.
Source: Efficacy dataset ALLY-2

These data support an indication for treatment of chronic HCV GT-1. Overall, SVR12 was 97% with a 95% CI (92.1%, 99.1%). The SVR12 rates for the treatment naïve and treatment experienced cohorts were comparable at 96% with a 95% CI of (89.8%, 99.3%), and 98% with a 95% CI (88.0%, 100%), respectively. Subjects with compensated cirrhosis achieved an SVR12 rate of 91% with a 95% CI (71%, 99%). ALLY-2 included 13 subjects with prior DAA-based treatment-experience (10 subjects boceprevir or telaprevir+ pegIFN/RBV, 3 subjects SOF/RBV; no subjects could have prior NS5A exposure).

Table 7 summarizes SVR12 and relapse rates by cirrhosis status considering only the 12 week duration treatment arms. Among these groups, only 2 subjects experienced virologic relapse, both of whom had HCV GT1a and cirrhosis. Minimal numbers of subjects with HCV GT1b had cirrhosis. All 13 subjects with prior DAA-based (excluding prior NS5A exposure) treatment experience achieved SVR12.

Table 7: ALLY-2 SVR12 and Virologic Failure Results for HCV GT1a and GT1b Subjects By Cirrhosis Status (DCV/SOF 12 arms only)

	DCV/SOF 12-Weeks Treatment-Naïve		DCV/SOF 12-Weeks Treatment-Experienced		DCV/SOF 12-Weeks Total	
	SVR12	Relapse	SVR12	Relapse	SVR12	Relapse
GT1A Subjects						
No Cirrhosis	58/60 (97%)	0/60 (0%)	20/20 (100%)	0/20 (0%)	78/80 (98%)	0/80 (0%)
Cirrhosis	8/9 (89%)	1/9 (11%)	10/11 (91%)	1/11 (9%)	18/20 (90%)	2/20 (10%)
Cirrhosis Unknown	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)	4/4 (100%)	0/4 (0%)
GT1B Subjects						
No Cirrhosis	12/12 (100%)	0/12 (0%)	8/8 (100%)	0/8 (0%)	20/20 (100%)	0/20 (0%)
Cirrhosis	none	none	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)
Cirrhosis Unknown	none	none	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)

Source: Adapted from Analysis by Dr. Patrick Harrington

Three subjects who achieved SVR12 failed to achieved SVR24 for virologic reasons. Two of the three subjects had evidence of HCV reinfection. The late relapse for subject 27-151 has little impact on the assessment of HCV virologic response because the subject received the shorter 8-week treatment duration which is not being considered in labeling.

The protocol defined criteria for an efficacy claim was to compare the SVR rate to the historical threshold of the APRICOT trial (pegIFN/RBV in HCV/HIV coinfected subjects treated for 48 weeks), which was estimated at 29% (51/176). The overall SVR12 rate of 97%, with the lower bound of the 95% CI of 92.1%, clearly demonstrates a large treatment benefit over the 29% SVR rate of the APRICOT trial. Additionally, and more clinically significant, the SVR12 rate from ALLY-2 is consistent with current SVR12 rates from other DAA programs in both HCV/HIV coinfected and monoinfected subjects.

SVR12 rates in HCV/HIV coinfected GT-1 subjects treated for 12 weeks with DCV/SOF were high (≥91%) regardless of baseline characteristics including race,

baseline HCV RNA level, IL28B genotype status, BMI, or concomitant cART. Please see the statistical review by Dr. Zeng for details on the subgroup analyses. The SVR12 rates in the cirrhotic subgroup were lower in this trial (91%); however the cirrhotic subgroup was small (n=22). Discussion of the impact of cirrhosis and baseline NS5A resistance associated polymorphisms, in particular for patients with HCV genotype 1a and cirrhosis is below (see subsection; *The impact of baseline NS5A polymorphisms on SVR12 rates in HCV genotype 1a subjects with cirrhosis* for more details).

Across the HCV DAA programs, data supports that subjects coinfected with HCV/HIV-1 have comparable response to subjects who are monoinfected with HCV. Therefore, specific indications for HIV/HCV coinfection have not been given and labeling includes mention of use in HCV/HIV coinfected subjects in Section 2 Dosage and Administration with supportive data provided in Section 14. ALLY-2 enrolled 10 subjects with GT-3 HCV; all achieved SVR12 (10/10, 100% 95% CI (69%, 100%)). DCV in combination with SOF is currently approved with and indicated for treatment of HCV GT-3. Therefore, SVR12 data from ALLY-2 supports use of DCV/SOF for treatment of both HCV GT-1 and GT-3 HCV/HIV coinfected and HCV monoinfected populations.

A total of 95% (189/199) of subjects had HIV RNA < 50 copies/mL at end of treatment (EOT). Among subjects with HIV RNA > 50 copies/mL at EOT, 8/10 re-suppressed their HIV viral load on subsequent testing without adjustment to their cART, 1 subject was lost to follow-up, and 1 subject had a repeat HIV RNA of 59 copies/mL at follow-up Week 12. Overall, 2 subjects (1.0%) experienced HIV virologic failure (confirmed HIV RNA ≥ 400 copies/mL), both at EOT (1 unconfirmed in a subject lost to follow-up due to incarceration, and 1 confirmed in post-treatment follow-up in a subject that later re-suppressed his HIV RNA without adjustment to the cART regimen). This rate of HIV virologic failure is consistent with the experience with HCV/HIV coinfected subjects receiving SOF/ ledipasvir (LDV) along with concomitant antiretrovirals in the smaller ERADICATE trial (2.7%; 1/37) (Osinusi, 2015). There was no change in mean absolute CD4 or CD8 counts throughout the treatment phase of ALLY-2, and no HIV-related opportunistic infections were reported.

ALLY-1

The review team focused on several complicated efficacy issues related to the ALLY-1 trial in order to determine the benefit-risk of the 12 week DCV/SOF/RBV in the respective subpopulations of subjects enrolled in this trial. As part of the pre-NDA discussions, the review team had determined that the numbers of enrolled subjects with HCV genotypes 2, 4 and 6 were too few to provide an indication for these specific genotypes in labeling. Therefore, efficacy analyses for ALLY-1 were focused on HCV genotype 1 and 3 infected subjects. The following bullets outline the main review challenges and questions regarding the efficacy results from ALLY-1 (with data from ALLY-2, where appropriate) which are presented in this section:

- Genotype 1 efficacy data: Are the data sufficient to determine dosing for patients with HCV genotype 1 infection and Child-Pugh class C cirrhosis? Are there adequate data to support an indication for treatment of patients with HCV genotype 1 compensated cirrhosis (Child-Pugh class A) and decompensated cirrhosis (Child-Pugh class B)? Is ribavirin necessary in the DCV/SOF regimen for treatment of compensated Child-Pugh class A cirrhosis?
- Genotype 3 efficacy data: Are there data to support extension of the HCV genotype 3 indication to subjects with decompensated cirrhosis (Child-Pugh class B or C) or for those with recurrence post-transplant? What data supports the use of DCV/SOF/RBV for 12 weeks in HCV genotype 3 subjects?
- What is the impact of baseline NS5A polymorphisms on HCV genotype 1 subjects with and without cirrhosis and what are the consequences of virologic failure in these subjects (these analyses include data from ALLY-2)?
- Are there clinically meaningful changes in Child-Pugh categories/scores or MELD scores for subjects in the cirrhotic cohort while on treatment and at follow-up Week 12? Are these changes supportive to the SVR results for subjects in the cirrhotic cohort of ALLY-1?
- How did RBV dosing and tolerability of RBV due to anemia in the decompensated cirrhotic population impact the SVR rates in ALLY-1?

Of note, there was extensive collaborative work to address these review issues within the review team, in particular, with the biostatistician Dr. Wen Zeng and the clinical virology reviewer Dr. Patrick Harrington. Please also see their reviews for details of the respective analyses.

Efficacy - ALLY-1

The overall SVR12 rate for ALLY-1 was 89% (100/113; 95%CI (81.1%, 93.7%)). In total, 12 subjects (11%) experienced virologic relapse and 1% (1/113) experience on-treatment failure. In the cirrhotic cohort, the SVR12 rate was 83% (50/60; 95%CI (71.5%, 91.7%)) compared to 94% (50/53; 95% CI (84.3%, 98.8%)) in the post-transplant cohort.

Genotype 1 Efficacy in ALLY-1

As discussed above, the majority of subjects enrolled into ALLY-1 were genotype 1. The following table provides the SVR12 rates for the HCV genotype 1 subjects enrolled in ALLY-1. The overall SVR12 rate in ALLY-1 was 88% for HCV genotype1 subjects with a 95%CI (79.7%, 94.3%). Consistent with findings in other DAA programs, the pre-transplant cirrhotic subjects had a lower overall SVR12 rate of 82% (37/45; 95%CI (68.0%, 92.0%)) compared to the post-transplant cohort SVR12 rate of 95% (39/41; 95%CI (83.5%, 99.4%)). Additionally, subjects with HCV genotype 1a achieved a lower SVR12 rate of 77% (26/34), compared to the small group of HCV genotype 1b subjects who all achieved SVR12 (11/11; 100%). SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B status or

baseline HCV RNA level. Because of the small numbers of non-white subjects, the generalizability of the data to other minority races is limited.

Table 8: SVR12 rates for HCV Genotype 1 Subjects by Baseline Characteristics in ALLY-1

	Cirrhotic Cohort N=45 (%)	Post-Transplant Cohort N=41 (%)	Total N=86 (%)
Overall	37 (82)	39 (95)	76 (88)
Gender			
Female	18 (90)	13/13 (100)	31/33 (94)
Male	19/25 (76)	26/28 (93)	45/53 (85)
Age			
<65 years	29/37 (78)	30/31 (97)	59/68 (87)
≤65 years	8/8 (100)	9/10 (90)	17/18 (94)
HCV RNA			
<800K	16/19 (84)	4/4 (100)	20/23 (87)
≥800K	21/26 (81)	35/37 (95)	56/63 (89)
HCV Subtype			
GT 1a	26/34 (77)	30/31 (97)	56/65 (86)
GT 1b	11/11 (100)	9/10 (90)	20/21 (95)
IL28 B Genotype			
CC	7/7 (100)	9/9 (100)	16/16 (100)
CT	22/26/(85)	22/24 (92)	44/50 (88)
TT	8/12 (67)	8/8 (100)	16/20 (80)
Baseline MELD Score			
<15	27/31 (87)	--	--
≥15	10/14 (71)		
Child-Pugh Score			
A	10/11 (91)	--	--
B	22/24 (92)	--	--
C	5/10 (50)		

Source: efficacy and demographics datasets ALLY-1

A limitation of the ALLY-1 trial was the small overall numbers of enrolled subjects with baseline Child-Pugh class C cirrhosis. In total there were 16 subjects with Child-Pugh class C designation at enrollment; 10 of these subjects were HCV genotype 1 (9 were genotype 1a and 1 genotype 1b). The SVR12 rate for these 10 subjects was 50% (5/10) with 95% CI (18.7%, 81.3%). No Child-Pugh C subjects had baseline NS5A polymorphisms in ALLY-1; therefore, baseline resistance is not the reason for the lower SVR rates in this group.

Despite the lower SVR12 rate observed in subjects with Child-Pugh class C cirrhosis a dosage recommendation was included in labeling. The view of the review team is that decompensated cirrhosis should be considered as a single subpopulation, rather

than further subdivided into 2 sub-subpopulations of Child-Pugh class B and Child-Pugh class C. Data in the decompensated subpopulation may be displayed by Child-Pugh class in labeling, but a dosage recommendation indication would be considered based on data available in all subjects with decompensated cirrhosis, regardless if they are classified as Child-Pugh B or C at baseline; unless a specific exposure or safety issue was identified. Data has demonstrated that subjects may shift from Child-Pugh B or C, and vice versa, between screening and baseline evaluations. Clinically, there also may be some subjective variability of these assessments, and therefore, we believe that the label should include the broader definition of decompensated cirrhosis.

Based on the topline efficacy and safety data from ALLY-1, Breakthrough Designation was given to DCV for HCV genotype 1 patients with Child-Pugh class B or C cirrhosis and for those who develop HCV genotype 1 recurrence post-liver transplant. Currently, there is no approved treatment regimen for patients with decompensated Childs-Pugh class B or C cirrhosis. DCV/SOF/RBV will provide a meaningful treatment option for patients with decompensated cirrhosis. However, because of the reduced SVR12 rates and the limited available data in those with Child-Pugh C cirrhosis, the DCV label will state that the optimal duration for subjects with HCV genotype 1 and Child-Pugh C cirrhosis has not been established.

Virologic Failure rates for HCV GT1 subjects are summarized in Table 9. There were 9 subjects who experienced virologic relapse and 1 subject who had on-treatment virologic failure. Overall, SVR12 rates were lower and virologic failure rates were higher for subjects with HCV GT1a subjects compared to those with HCV GT1b, consistent with previous clinical trials of DCV-containing regimens. Eight of the 9 prior DAA treatment-experienced subjects (boceprevir or telaprevir) achieved SVR12; the single non-SVR subject had HCV GT1a infection and Child-Pugh C cirrhosis. Additionally, the presence of HCV NS5A resistance-associated polymorphisms was associated with reduced DCV/SOF ± RBV treatment efficacy for HCV GT1a infected subjects in the ALLY-1 and ALLY-2 trials, particularly among subjects with cirrhosis (see detailed discussion below *The impact of baseline NS5A polymorphisms on SVR12 rates in HCV genotype 1a subjects with cirrhosis*).

Table 9: SVR12 and Virologic Failure Results for HCV GT1 in ALLY-1

	Cirrhotic w/ treatment extension	Cirrhotic w/o treatment extension	Post-transplant	Total
GT 1a-SVR12	**2/2 (100%)**	**26/34 (77%)**	**30/31 (97%)**	**56/65 (86%)**
On-Tx Failure	0/2	1/32 (3%)	0/31 (0%)	1/65 (2%)
Relapse	0/2	7/32 (22%)	1/31 (3%)	8/65 (12%)
GT 1b-SVR12	**0**	**11/11 (100%)**	**9/10 (90%)**	**20/21 (95%)**
Relapse		0/11	1/10 (10%)	1/21 (5%)

Source: Adapted from Analysis by Dr. Patrick Harrington

The review issue of whether RBV is necessary to treat patients with HCV genotype 1 and compensated cirrhosis was evaluated with data from both the ALLY-1 and 2 trial

data. Both ALLY-1 and ALLY-2 enrolled HCV genotype 1 subjects with compensated Child-Pugh A cirrhosis; however, subjects in ALLY-2 received only DCV/SOF for 12 weeks without RBV with SVR12 rates >90%. Subjects in ALLY-1 were to be considered transplant eligible within 1 year of enrollment and had to have a baseline MELD score of 8 or above; and therefore, the ALLY-1 Child-Pugh class A subjects may represent a more advanced group of subjects with compensated cirrhosis compared to those enrolled in ALLY-2. However, both groups are considered to have compensated cirrhosis. Therefore, efficacy results from the compensated cirrhotic subjects from ALLY-2 where subjects received 12 weeks of DCV/SOF were compared to the results from the ALLY-1 subjects who received 12 weeks of DCV/SOF/RBV. Table 10 provides the SVR12 rates and the associated 95% CIs for HCV genotype 1 Child-Pugh class A subjects from ALLY-1 and ALLY-2. As demonstrated, both groups resulted in a SVR12 rate of 91% with overlapping 95% CI. There was no difference determined between the regimens based on the limited available data. Therefore, the product label will reflect the ALLY-2 data and recommend treatment of HCV GT1 with compensated cirrhosis or without cirrhosis with 12 weeks of DCV/SOF.

Table 10: SVR12 Rates for HCV GT1 Child-Pugh A Cirrhotic Subjects who Received DCV/SOF compared to DCV/SOF/RBV

Child-Pugh A Subjects Only		Treatment-Naive		Treatment-Experienced		Total	
	SVR12	ALLY-1 DCV/SOF/ RBV	ALLY-2 DCV/SOF	ALLY -1 DCV/SOF/ RBV	ALLY-2 DCV/SOF	ALLY-1 DCV/SOF/ RBV	ALLY-2 DCV/SOF
GT-1 Only	% (n/N)	100% (5/5)	89% (8/9)	83% (5/6)	92% (12/13)	91% (10/11)	91% (20/22)
	95% CI	(47.8%, 100%)	(51.8%, 99.7%)	(35.9%, 99.6%)	(64.0%, 99.8%)	(58.7%, 99.8%)	(70.8%, 98.9%)

Source: Dr. Wen Zeng Statistical analysis of ALLY-1 and ALLY-2 efficacy datasets

The ALLY-1 outcome table for Section 14 of the product label displaying the SVR data for HCV genotype 1 subjects with Child-Pugh class A, B or C cirrhosis and those with recurrence post-liver transplant is in Table 12 below. Fourteen subjects in the cirrhotic cohort had baseline MELD scores ≥15 and 71% (10/14) achieved SVR12. SVR12 was achieved in 87% (27/31) of the cirrhotic subjects with baseline MELD<15. Regimen and duration recommendations will be presented by Child-Pugh categories for compensated cirrhosis (Child-Pugh A) or decompensated cirrhosis (Child-Pugh B or C) in Section 2 of the product labeling; and therefore, SVR outcomes based on baseline Child-Pugh class A, B or C cirrhosis will be displayed in the outcome table in Section 14 of the label. However, because of MELD scores are generally not widely used clinically except for evaluating patients for liver transplantation and because of the small subset of subjects with MELD ≥15, the SVR data will not be displayed in the label by baseline MELD score.

Table 11: Outcome Table for ALLY-1 from Proposed Product Label

Table 15:	**ALLY-1: SVR12 in Genotype 1 Subjects with Child-Pugh A ,B or C Cirrhosis or with HCV Genotype 1 Recurrence after Liver Transplantation Treated with DAKLINZA in Combination with Sofosbuvir and Ribavirin for 12 weeks**	
Treatment Outcomes	**Child-Pugh A, B, or C Cirrhosis n=45**	**Post-Liver Transplant n=41**
SVR12		
Genotype 1	82% (37/45)	95% (39/41)
Child-Pugh A	91% (10/11)	-
Child-Pugh B	92% (22/24)	-
Child-Pugh C	50% (5/10)	
Genotype 1a	76% (26/34)	97% (30/31)
Genotype 1b	100% (11/11)	90% (9/10)
Outcomes for subjects without SVR12		
On-treatment virologic failure	2% (1/45)[a]	0
Relapse[b]	9% (3/35)	5% (2/41)

[a] One subject had detectable HCV RNA at end of treatment.

[b] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at end of treatment.
Source: Table 15 proposed DCV label

Genotype 3 Efficacy

Currently, DCV/SOF is indicated for treatment of HCV genotype 3, including those with compensated cirrhosis. A Limitations of Use statement in the label states that SVR rates were reduced in cirrhotic subjects who received 12 weeks of DCV/SOF.

Seventeen HCV genotype 3 (15%) subjects were enrolled in ALLY-1. The cirrhotic cohort enrolled a total of 6 subjects, 3 subjects each were Child-Pugh class B and class C, respectively. The overall SVR12 for the decompensated cirrhotic HCV GT3 subjects was 83% (5/6); one subject with Child-Pugh C cirrhosis had virologic relapse. In the post-transplant cohort 11 subjects with HCV genotype 3 were enrolled, of which 10 (91%) achieved SVR12; none of which were considered cirrhotic by baseline FibroTest (data on cirrhosis status was not collected other than baseline FibroTesting for the post-transplant cohort in ALLY-1). The data in both decompensated and post-transplant subjects in ALLY-1 provides support for the activity of DCV/SOF/RBV for treatment of HCV GT3. These data, in addition to the demonstrated efficacy of DCV/SOF in HCV GT3 in the original approval from ALLY-3, are sufficient to extend the current labeling indication to include these HCV GT3 subpopulations.

Because dosage recommendations for HCV GT1 and 3 subjects with Child-Pugh B and C include RBV, the review team re-evaluated dosage recommendations for HCV GT3 subjects with Child-Pugh A to determine if there were sufficient data to

recommend DCV/SOF/RBV for 12 weeks. As stated in product labeling, the optimal regimen and duration for HCV GT 3 subjects with cirrhosis has not been established. Therefore, we requested BMS provide all data from their ongoing early access programs (EAPs) and any clinical trials data that supports subjects with HCV GT3 receiving 12 weeks of DCV/SOF/RBV. Data supporting HCV GT3 compensated cirrhosis were submitted from one clinical trial, ALLY-3+, and from two EAPs: the French Temporary Authorization for Use (ATU) and the UK cohort. ALLY 3+ evaluated 12 weeks compared to 16 weeks of DCV/SOF/RBV in HCV GT3 subjects with and without cirrhosis. Patients were eligible for the ATU cohort if they had: 1) hepatic fibrosis F3/F4 or HCV extra-hepatic manifestations with no appropriate therapeutic alternatives; or 2) were on a waiting list for hepatic or renal transplantation; or 3) had undergone hepatic transplant with recurrence of HCV infection. The treatment duration was 24 weeks; however, clinicians could choose a shorter duration (12 weeks) with or without RBV. In the UK cohort, patients were included if they had decompensation, Child-Pugh score ≥ 7, non-hepatic manifestation of HCV likely to result in irreversible damage within 12 months and exception circumstances as determined by a review panel. The treatment regimen was chosen by the treating physician. The data for HCV GT3 subjects who received 12 weeks of DCV/SOF/RBV from ALLY-3+ and the EAPs are provided in Table 13.

Based on these data, 86% (37/43) of subjects with HCV GT-3 and compensated cirrhosis achieved SVR12 after treatment with DCV/SOF/RBV for 12 weeks (Table 12). These data are consistent with the clinical trial findings from ALLY-1, as discussed above.

Table 12: Available SVR12 Data from the ATU and Other Trial Sources for GT-3 Subjects who Received 12 Weeks of DCV/SOF/RBV

	ALLY 1 (N = 17)	ALLY 3+ (N = 24)	FRENCH ATU[1] (N = 5)	UK Cohort (N = 116)[2]	Total (N=169)
Overall	15/17 (88.2%)	21/24 (87.5%)	5/5 (100%)	83/116 (72%)	124/162 (77%)
Non-Cirrhotic	10/11 (90.9%)	6/6 (100%)	1/1 (100%)	0	17/18 (94%)
Cirrhotic	5/6 (83.3%)	15/18 (83%)	4/4 (100%)	77/108 (71%)	101/136 (74 %)
Compensated	0	15/18 (83%)	4/4 (100%)	18/21 (86%)	37/43 (86%)
Decompensated	5/6 (83%)	0	0	59/87 (68%)	64/93 (69%)

[1]For French ATU data, 12 week window is defined as duration <14 weeks.
[2]8 subjects had unknown cirrhosis status (6/8 achieved SVR)
Source: Response to IR SN 071, SDN 122

In summary, cirrhosis has been determined to be an independent baseline factor generally leading to lower SVR12 response rates for many DAA regimens; and, often

RBV has been determined as an important addition to a DAA regimen to improve SVR rates in the cirrhotic subgroup. The rationale for the addition of RBV for treatment of subjects with HCV genotype 3 and compensated cirrhosis comes from demonstrated efficacy of DCV/SOF/RBV in ALLY-1 with support from the EAPs and ALLY-3+ data. Therefore, based on the limited clinical trial data, the supportive data from the expanded access programs described above and the supportive general knowledge of improved SVR12 rates with the addition of RBV in subjects with baseline cirrhosis, the review team recommends DCV/SOF/RBV for 12 weeks for treatment of HCV genotype 3 in patients with compensated cirrhosis. The recommended treatment regimens and duration for DCV in patients with HCV genotype 1 or 3 infection is outlined in the following table.

Table 13: Recommended Treatment Regimen for DCV in Patients with HCV GT1 or GT3

	Patient Population	Treatment and Duration
Genotype 1	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated (Child-Pugh B or C) Cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post- transplant	
Genotype 3	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child- Pugh A) or decompensated (Child-Pugh B or C) cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	

Source: Table 1 proposed DCV product label

Additionally, in Section 14.4 of the DCV label, the following statement will be included: SVR12 rates were comparable between genotype 3 (5/6 with Child-Pugh B or C cirrhosis and 10/11 post-liver transplant) and genotype 1 subjects with or without decompensated cirrhosis. The rationale for extending the GT3 indication to include those with decompensated cirrhosis and those who are post-liver transplant with inclusion of this data in the label is based on the known efficacy of DCV/SOF for treatment of HCV GT3 from the ALLY-3 trial, and that subjects with HCV GT3 with decompensated cirrhosis or recurrence post-transplant in the ALLY-1 trial, albeit in limited numbers, also demonstrated efficacy. This allows use of DCV/SOF/RBV in the broader subpopulations of HCV genotype 3 infected patients, and provides another treatment option for those with limited to no currently approved therapies. Safety has

also been demonstrated in the decompensated cirrhosis and post-transplant population and there are no genotype-specific safety issues.

The impact of baseline NS5A polymorphisms on SVR12 rates in HCV genotype 1a subjects with cirrhosis

Extensive analyses of the available resistance data were completed by Dr. Harrington and are detailed in his review. This review provides a high level overview of the conclusions of these analyses. Please reference Dr. Harrington's review for the full analyses and discussion.

Based on a pooled analysis of the ALLY-1 and ALLY-2 trials, SVR12 rates were lower among HCV GT1a infected subjects with HCV NS5A resistance-associated polymorphisms. Considering the four most critical DCV resistance-associated positions in NS5A (M28, Q30, L31 or Y93), and excluding subjects who received the 8-week treatment duration in ALLY-2, SVR12 rates were 76% (13/17) and 95% (142/149) for those with or without a DCV NS5A resistance-associated polymorphisms, respectively.

Subgroup analyses of the ALLY-1 and ALLY-2 trials are limited by the different treatments used (i.e., with or without RBV), and the relatively small sizes of key subgroups, but the available data supports that the impact of NS5A polymorphisms was restricted to HCV GT1a subjects with cirrhosis. Among pre-transplant HCV GT1a subjects with Child-Pugh A or B cirrhosis, SVR12 rates were 2/6 (33%) and 38/39 (97%) for those with or without a key DCV resistance-associated polymorphism, respectively. In other words, of the 5 virologic failure subjects with Child-Pugh A or B cirrhosis who received DCV/SOF ± RBV for 12 weeks, 4 of the 5 failures had virus with a key DCV resistance-associated polymorphism prior to treatment. In contrast, 9/9 (100%) HCV GT1a non-cirrhotic subjects with a key NS5A polymorphism achieved SVR12. No HCV GT1a subjects with Child-Pugh C cirrhosis had any NS5A resistance associated baseline polymorphisms. Furthermore, data from the post-transplant cohort in ALLY-1 are insufficient to determine if resistance polymorphisms have an impact in this population, but we expect that, as in pre-transplant patients, NS5A polymorphisms would have a greater impact in those with more advanced liver disease post-transplant.

No subjects with NS5A Q30 polymorphisms experienced virologic failure, despite the fact that amino acid substitutions at this position were most common among subjects who experienced virologic failure. However, data are only available for a single subject with cirrhosis and a Q30 polymorphism, which may explain the lack of an association with treatment outcome. Given that this position appears to be a critical DCV resistance-associated position in GT1a, the review team believes that it should be included in the screening algorithm along with positions 28, 31 and 93.

There were resistance consequences of failure among subjects who had NS5A polymorphisms and experienced virologic failure in the ALLY-1 and ALLY-2 trials.

Two of the four virologic failure subjects with baseline NS5A resistance-associated polymorphisms had additional treatment-emergent, resistance-associated substitutions in NS5A at the time of virologic failure, raising concerns that these subjects may not respond optimally to re-treatment with another NS5A inhibitor-containing regimen. Also, three of the four subjects had a treatment-emergent NS5B substitution possibly associated with sofosbuvir drug exposure (L159F, E237G or Q355H). The precise clinical impact of these NS5B substitutions is unclear, but this observation raises concerns that these subjects may have a viral population that also is not optimally sensitive to sofosbuvir.

Based on the data, the review team determined that the screening recommendation should be included in a subsection of Section 2 (Dosage and Administration) termed "2.1. Testing Prior to Initiation of Therapy" (or similar), with the following draft language:

"Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, or Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin [see Microbiology (12.4]), Table X]."

The decision to consider NS5A resistance screening for HCV GT1a patients with cirrhosis is based on an observation from a relatively small number of subjects. However, this observation is not unexpected, as data from multiple other trials have demonstrated a clear impact of NS5A polymorphisms on treatment efficacy in the context of other DCV-containing regimens or HCV genotypes/subtypes (see also the original NDA clinical and virology reviews of DCV/ASV). Ultimately, the review team believes there is a strong signal of an impact of NS5A polymorphisms on treatment efficacy in this subgroup. The following factors contributed to the decision to add a consideration for pre-screening for GT1a patients with cirrhosis:

- HCV GT1a is the most common subtype in the US
- There are reasonable available alternative treatment options that seem to be less impacted by NS5A polymorphisms (e.g. Harvoni™)
- There are potential resistance consequences of virologic failure in those with NS5A polymorphisms which may impact subsequent retreatment: 2 of the 4 virologic failure subjects had additional treatment-emergent NS5A resistance associated substitutions and 3 subjects had treatment-emergent NS5B substitutions, possibly associated with SOF resistance.
- There are possible clinical consequences of treatment failure in this population with more advanced liver disease.
- At least two assays are commercially available to identify NS5A polymorphisms in HCV GT1a virus isolates.

The review team avoided recommending screening directly because there is currently no FDA-approved assay available and because we believe the treatment decision should not be restricted but should be made by the prescriber and patient, and based on all the available data and factors for each individual. However, we believe

screening for NS5A polymorphisms and excluding patients from treatment with DCV/SOF±RBV will improve the overall SVR rates for HCV GT1a patients with cirrhosis and will provide an improved chance of success for virologic cure for individual patients by having all the available data to guide the choice a treatment regimen.

NS5A Polymorphism Screening for HCV Genotype 3 Infected Patients

The NS5A Y93H polymorphism was a key factor associated with reduced efficacy of DCV+SOF in HCV GT3 infected subjects in ALLY-3, including in subjects with or without cirrhosis. Having a Y93H baseline polymorphism decreased SVR12 rates by 30% or more compared to those without it (see Table 15 in Dr. Harrington's review for full details). During the original review of the ALLY-3 trial, the review team considered adding a Limitations of Use to statement in Section 1 (Indications and Usage) to restrict the use of DCV in HCV GT3 infected patients with the NS5A Y93H polymorphism. However, the review team ultimately decided to describe the data in the Microbiology (12.4) section of the label and not include a Limitations of Use statement. There were several factors that influenced these conclusions. HCV GT3 represents approximately 10% of the chronic HCV infections in the US, and the subset of HCV GT3 patients with a baseline Y93H polymorphism would be an even smaller subset of the overall GT3 population. Additionally, at the time, an assay to identify the Y93H polymorphism in HCV GT3 infected patients was not commercially available and it was unclear when one might become available, and drug resistance-related risks for subjects with the Y93H polymorphism appeared to be small in that additional major DCV resistance-associated substitutions did not emerge in virologic failures with the Y93H polymorphism. Providing a less restrictive screening recommendation in Section 2.1 of the label was not considered at the time. Additionally, SOF/RBV was the only approved alternative treatment option and DCV/SOF provided the first non-RBV containing option for HCV GT3 infected patients.

(b) (4) There are alternative treatment options that do not include an NS5A inhibitor and are therefore not impacted by the NS5A Y93H polymorphism (e.g., SOF+RBV with or without Peg-IFNα). These alternate treatment regimens may be less clinically desirable than an all DAA regimen, however, these treatment options are available for those with a Y93H polymorphism. Based on all these considerations, the review team did not recommend including consideration for pre-screening for Y93H in HCV GT3 patients. This decision may be revisited in the future as more data are obtained to guide the optimal treatment of HCV GT3 infected patients with baseline Y93H polymorphisms. The team did not believe it was critical that a prominent screening recommendation is included in the label at this time until an ideal IFN-free alternative treatment regimen is approved for those with a Y93H polymorphism. However, the baseline NS5A Y93H polymorphism data will be displayed in Section 12.4 Microbiology of the product label. The Limitations of Use statement is retained in the labeling and Section 2.2 also

retains the statement that the optimal duration of DCV/SOF with or without RBV for patients with HCV GT3 cirrhosis has not been established.

Impact of Changes in MELD Score and Child-Pugh Class

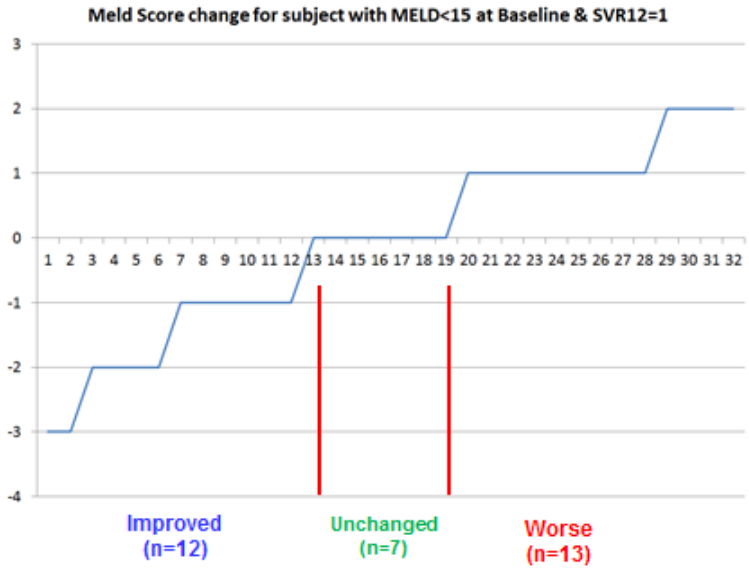
Achieving SVR and therefore, virologic cure from HCV, has demonstrated long term clinical benefit in patients with compensated cirrhosis and in those without cirrhosis. The long term benefit of SVR has yet to be fully determined for subjects with advanced, decompensated cirrhosis as there are limited data in this subpopulation. Subjects with decompensated cirrhosis were contraindicated for treatment with pegIFN based regimens; however with the era of improved tolerability and safety with the combination DAA therapies, treatment of patients with advanced decompensated cirrhosis is possible. Still, there are currently no approved DAA treatment regimens for patients with decompensated cirrhosis; and, currently approved protease-inhibitor containing HCV treatment regimens are either not recommended or are contraindicated for use in patients with decompensated cirrhosis.

Overall, in the cirrhotic cohort the mean Child-Pugh, MELD and FibroTest scores decreased from baseline to follow-up Week 12 by -0.9 [n=50], -0.8 [n=49] and -0.074 [n=50], respectively.

Analyses were completed to evaluate what the clinical impact of changes the MELD scores in the cirrhotic pre-transplant cohort of ALLY-1. Patterns of improvements in MELD scores may indicate positive treatment effects and worsening of MELD scores could potentially indicate a safety concern for the treatment regimen. In the cirrhotic cohort of ALLY-1, 54 subjects had available baseline MELD score and data at Follow-Up Week 12, which was the longest duration of full data available for the cohort. Change in MELD score was defined as a change of at least 1 point in either direction from the baseline to the Follow-Up Week 12 timepoint. Analyses were done by those who achieved and did not achieve SVR12 and by baseline MELD <15 and ≥15. The following graphs show the results by these variables (Figures 1-3).

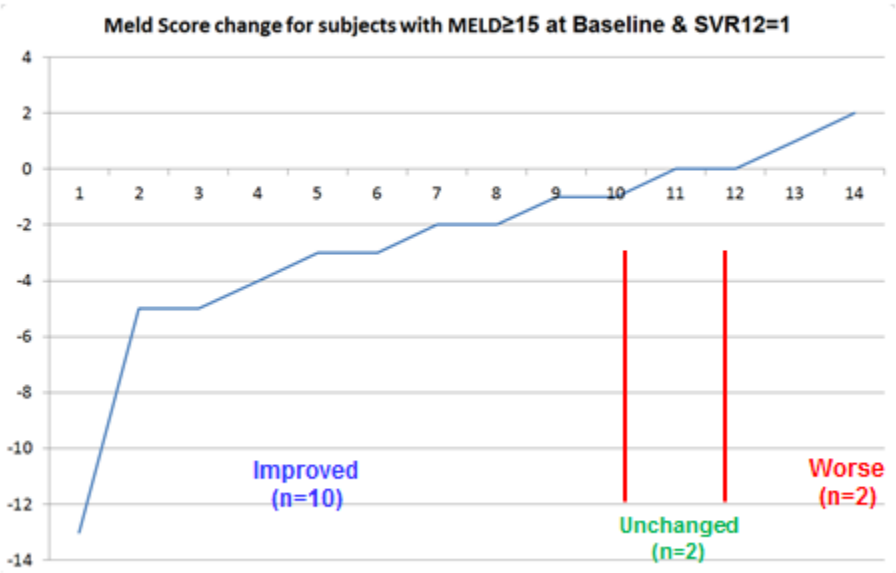
Examination of Figures 1 and 2, show that regardless of Baseline MELD for subjects who achieved SVR12, the majority of subjects improved or stayed unchanged. However, most subjects improved their MELD score by only 1 or 2 points and very few improved dramatically by Follow-Up Week 12. Similarly, for those that worsened the change was not dramatic, and the MELD score was generally worse by 1 or 2 points. Figure 3 shows the changes in MELD scores for those who did not achieve SVR12. There are 4 subjects with baseline MELD <15 and 4 subjects with baseline MELD ≥15. Regardless, there is no definitive pattern in this limited group, as half of the subjects improved or did not change and half worsened. Results were similar and consistent for analyses completed with only subjects with HCV genotype 1.

Figure 1: Change in MELD Score for Subjects who Achieved SVR12 and with Baseline MELD <15 (n=32)



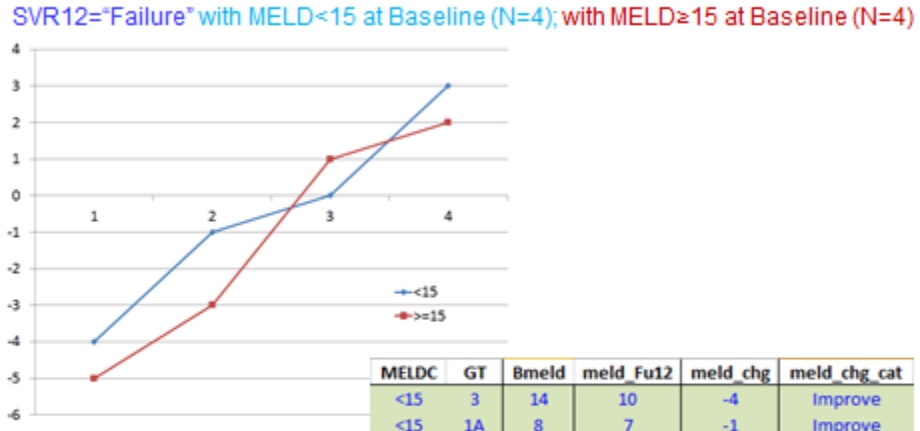
Source: Dr. Wen Zeng Statistical Review

Figure 2: Change in MELD Score for Subjects who Achieved SVR12 and with Baseline MELD ≥15 (n=14)



Source: Dr. Wen Zeng Statistical Review

Figure 3: Change in MELD Score for Subjects who Did Not Achieve SVR12 with Baseline MELD <15 (Blue) and ≥15 (Red)



MELDC	GT	Bmeld	meld_Fu12	meld_chg	meld_chg_cat
<15	3	14	10	-4	Improve
<15	1A	8	7	-1	Improve
<15	1A	14	14	0	NoChg
<15	1A	12	15	3	Wrose
>=15	1A	19	14	-5	Improve
>=15	1A	20	17	-3	Improve
>=15	1A	16	17	1	Wrose
>=15	1A	17	19	2	Wrose

Source: Dr. Wen Zeng Statistical Review

While on DCV/SOF/RBV treatment, most subjects remained in the same Child-Pugh class as they were at baseline. Of the 12 subjects with Child-Pugh A cirrhosis at baseline, 9 (75%) remained class A and 3 (25%) worsened to class B. Of the 32 subjects with Child-Pugh class C, 26 subjects (81%) remained class C, 3 (9%) improved to class A and 2 (6%) worsened to class C. All of the 16 subjects with Child-Pugh class C at baseline remained class C on treatment.

In summary, no definitive conclusions to support the overall efficacy of DCV/SOF/RBV could be determined based on analyses of the changes in MELD score or Child-Pugh class in the pre-transplant cirrhotic cohort of ALLY-1. The variability of the changes in MELD scores with, and despite, achieving SVR12 did not allow for meaningful clinical interpretation of the data. In general, clinically significant improvement in advanced fibrosis of the liver takes years after achieving SVR in patients with advance cirrhosis. It is likely that the current data are not interpretable, in part due to the short duration of follow-up data available. The review team determined that longer term data would be necessary to support any definitive conclusions for product labeling regarding improvement from baseline MELD scores or Child-Pugh class.

Impact of RBV dosing and tolerability due to anemia

Ribavirin dosing, dose reduction and time on therapy were evaluated to determine the impact on SVR rate for subjects in ALLY-1. Per protocol, subjects were initiated on 600 mg of RBV daily, increasing up to 1,000mg daily as tolerated. The starting dose

and on-treatment dose of RBV could be adjusted according to hemoglobin and creatinine values. The following table (Table 15) was provided for management of RBV dosing in ALLY-1. Table 14 is based on recommendations from the RBV package insert and was modified in accordance with AASLD guidelines for HCV treatment (based on version cited 20 February 2014) for ALLY-1. Investigators could modify RBV dosing based on clinical judgment. For subjects with baseline anemia and CrCl <50 mL/min, RBV dosing could be determined by the investigator. In ALLY-1 lower doses of RBV 400 mg, 200 mg daily or 200 mg every other day were prescribed by Investigators according to hemoglobin and creatinine clearance (CrCl) and Investigator discretion. When hemoglobin and CrCl lab values suggested contradictory dosing guidelines, the more conservative dosing regimen was applied. Additionally, the RBV dose could be increased as tolerated to a maximum of 1000 mg per day. However, only one cirrhotic subject had RBV dosing increased and maintained above 600 mg in ALLY-1 (800mg between Week 8-10 and then went on to liver transplant); and only 3 post-transplant subjects had RBV doses increased to 800mg or higher at Week 6 or later (displayed in Figure 4 below). There was no use of erythropoietin stimulating agents in ALLY-1 and only one subject had a blood transfusion because of RBV induced anemia.

Table 14: ALLY-1 Protocol RBV Dosing Guidelines

Table 4.3.1-1: Ribavirin Dosing Guidelines		
Laboratory Value/Clinical Criteria:	**RBV Dose:[a,b]**	**Additional Instructions:**
Hemoglobin:		
> 12 g/dL	600 mg daily	Take 3 tablets in the morning.
>10 to ≤ 12 g/dL	400 mg daily	Take 2 tablets in the morning
> 8.5 to ≤ 10 g/dL	200 mg daily	Take 1 tablet in the morning.
≤ 8.5 g/dL	Discontinue RBV	Continue dosing with DCV/SOF
Creatinine Clearance (CrCl):		
> 50 mL/min	RBV to be administered according to guidelines provided based on subject's hemoglobin results	
> 30 to ≤ 50 mL/min	200 mg every other day	
≤ 30 mL/min	Discontinue RBV	Continue dosing with DCV/SOF
Hemodialysis	Discontinue RBV	Continue dosing with DCV/SOF

[a] If tolerated, the RBV dose may be titrated up to 1000 mg/day at the discretion of the investigator.

[b] RBV dosing of ≥ 800 mg/day should be administered in divided doses. RBV dosing of < 800 mg/day should be administered once daily.

Source: Adapted from Ribasphere® package insert

Source: ALLY-1 protocol

Overall for all subjects in ALLY-1, the majority of subjects (58%; 65/113) had an average dosage of RBV >400 - ≤600 mg per time on RBV treatment; 23% (26/113) of subjects had an average dosage of RBV >200 mg - ≤400 mg and 16% (18/113) of subjects had an average dosage of ≤ 200 mg per time on RBV treatment. As stated

above, only 6 subjects (5%)had an average dosage of RBV above 600 mg per time on RBV treatment. Four subjects (4%) in ALLY-1 had sustained dosing of RBV above 600 mg daily.

The summary of average daily RBV dose (mg/day; calculated as total RBV dose received over actual duration on RBV) and time to RBV dose reduction or discontinuation (days) is provided in Table 15 by Child-Pugh category and MELD score for all genotypes and genotype 1 alone. Of the 60 subjects in the cirrhotic cohort, 4 subjects received a liver transplant during the treatment period and are excluded from the following analysis. For the cirrhotic cohort (Child-Pugh A, B or C), the median RBV dose was 446 mg daily (range, 101-607), the median time to reduction in RBV dose was 26 days (range, 3-55) and the median time to discontinuation of ribavirin was 43 days (range, 8-82). For the post-transplant cohort, the median RBV dose was 478 mg daily (range, 99-755), the median time to reduction in RBV dose was 29 days (range 11-57) and the median time to discontinuation of ribavirin was 20 days (range, 3-57). This analysis shows that, as expected, the more decompensated subjects and those with higher MELD scores, generally had lower mean and median RBV doses, and had shorter duration to RBV reduction or discontinuation. It is possible that the dose and duration of RBV affected the overall SVR rates in these more advanced patient populations; these data are limited by the small numbers and because there is no comparison or alternative RBV dosing strategy, the impact of RBV dose reduction or early discontinuation on SVR outcome is difficult to determine. However, these data also demonstrate that the subjects in ALLY-1 had advanced disease with comorbidities which inhibited their ability to tolerate RBV at doses of 600mg daily.

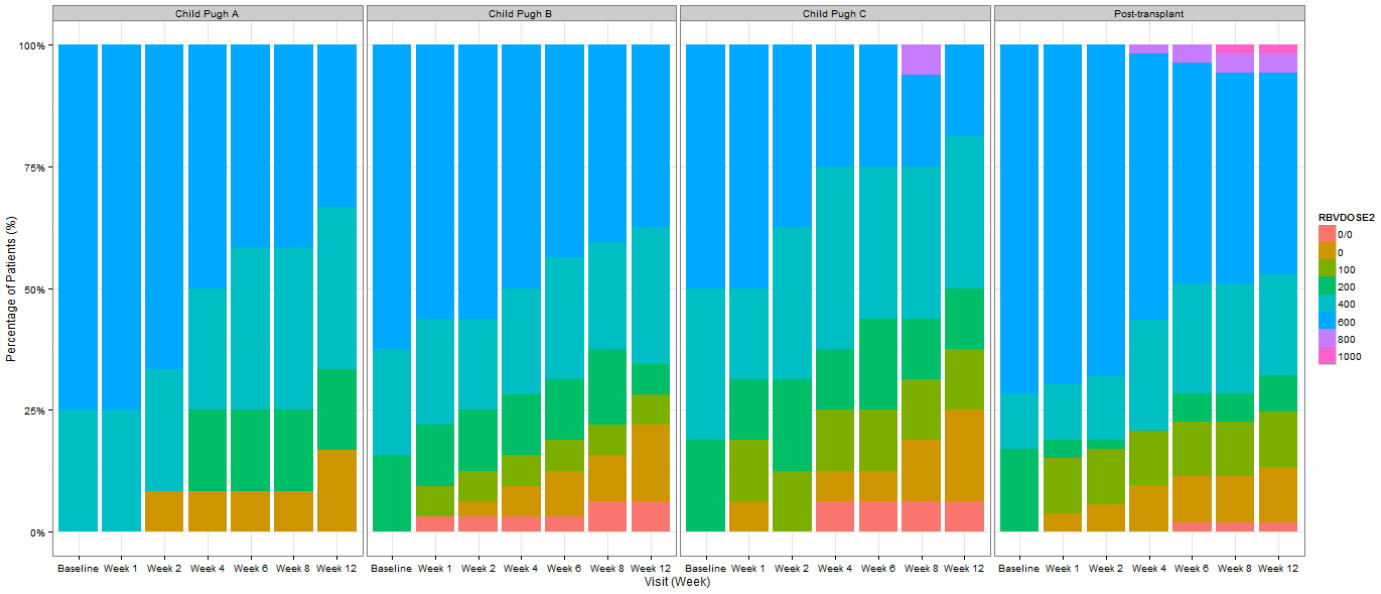
Table 15: Summary of Average Daily RBV dose (mg/day) and Time to RBV Dose Reduction or Discontinuation (days)

	Child A	Child B	Child A/B	Child C	MELD <15	MELD ≥15
All genotypes	N=12	N=30	N=42	N=14	N=37	N=19
Mean RBV dose	489.34	450.82	461.82	363.04	450.20	411.68
Median RBV dose	534.57	473.78	482.80	397.62	466.67	400.00
Median time to RBV Dose reduction	N=4 26	N=8 26.5	N=12 26.5	N=5 15	N=11 23	N=6 29
Median time to RBV Discontinuation	N=2 45	N=5 43	N=7 43	N=2 27	N=6 43	N=3 11
GT1 subjects	N=11	N=22	N=33	N=10	N=29	N=14
Mean RBV dose	490.54	436.06	454.22	345.20	439.29	407.28
Median RBV dose	592.94	436.31	466.67	374.12	432.94	400.00
Median time to RBV Dose reduction	N=3 23	N=5 27	N=8 25	N=4 12.5	N=8 16.5	N=4 29
Median time to RBV Discontinuation	N=2 45	N=4 49.5	N=6 49.5	N=1 11	N=5 43	N=2 34

Average daily RBV dose for each subject was calculated as total RBV received/actual duration on RBV.
Time to RBV dose reduction summary was based on subjects who had RBV dose reduction, where RBV dose reduction was defined as any non-zero RBV dose after Day 1 was lower than Day 1 RBV dose.
Time to RBV discontinuation summary was based on subjects who had RBV discontinuation, where RBV discontinuation was defined as last RBV date < last treatment date - 1.
Source: Response to IR SN 071, SDN 122

The following figure displays the RBV dosing by on-treatment week for all subjects in ALLY-1 (Figure 4). Subjects are displayed by Child-Pugh class for the cirrhotic cohort. Overall, by Week 6 approximately 50% of subjects were on 400 mg or less of RBV across the trial. RBV dosing was adjusted based on laboratory criteria and tolerability. The high proportion of reductions in RBV dosing reflects the advanced liver disease status of the pre-transplant cirrhotic patients and the post-transplant cohort. Additionally, presumably the advanced disease status of even the Child-Pugh A subjects in the cirrhotic cohort is the reason that Investigators did not increase RBV dosing to 1000mg as per protocol; however, no specific reasons were provided.

Figure 4: Ribavirin Dosing by On-Treatment Week for ALLY-1



Source: Exposure datasets ALLY-1, analysis by Dr. Jeffery Florian

Excluding subjects who had a liver transplant during treatment, a total of 16 cirrhotic or post-transplant subjects (16/110; 15%) completed less than 12 weeks (defined as < 81 days) of RBV therapy. Of these 16 subjects, 12 (75%) achieved SVR12 and 4 (25%) did not. Similarly, 11 subjects (11/110; 10%) completed less than 6 weeks of RBV (defined as <42 days) of which 9 subjects (82%) achieved SVR12 and 2 subjects (18%) did not. Overall these numbers are small and clear conclusions regarding the impact of RBV dose and duration on SVR12 rates cannot be made.

Additional discussion of anemia and RBV dosing as a safety issue is discussed below in the laboratory analysis section of the Safety review.

8. Safety

This sNDA clinical review focuses the primary safety evaluation on data available from AI444216 (ALLY-2) and AI444215 (ALLY-1). Data are provided from ALLY-2 in 203 HCV/HIV-1 coinfected subjects treated with DCV/SOF (153 subjects with 12 weeks and 50 subjects with 8 weeks duration). Data are included from ALLY-1 in 60 subjects with cirrhosis (Child-Pugh A, B and C) and 53 post-liver transplant subjects all treated with DCV/SOF/RBV for 12 weeks from ALLY-1.

To support the safety profile of the DCV/SOF with or without RBV regimen, data from AI444218 (ALLY-3) and AI444040 were submitted. Both ALLY-3 and AI444040 were reviewed as part of the resubmission NDA application for the original approval of DCV. In total, safety and efficacy data are available from 679 subjects exposed to DCV/SOF± RBV in the above 4 trials (ALLY-1, -2 and -3 and AI444040; note that only safety data were reviewed from AI444040 because of the lack of a right of reference for the investigational formulation of SOF, see original NDA review for details).

Additional supportive safety data from six phase 2 trials of DCV in combination with pegylated interferon (pegIFN) and RBV in 505 subjects were reviewed in the original NDA clinical review. These data are considered supportive to the overall efficacy and safety profile of DCV, in particular, because these DCV/pegIFN/RBV trials were all randomized, double-blind, placebo-controlled trials. Lastly, data from AI444043 was submitted in support of overall DCV efficacy and safety. AI444043 evaluated DCV in combination with pegIFN/RBV in 301 HCV/HIV coinfected treatment-naïve GT-1 subjects. Review of safety data from this trial was driven by the labeled events associated with use of pegIFN and RBV and is consistent with prior findings from other clinical trials including DCV/pegIFN/RBV. Because there were no unique safety findings or trends and no indication with a DCV/pegIFN/RBV containing regimen is being sought, data from trial AI444043 is not detailed in the following clinical safety review.

Analysis Methods

Version 17.1 of MedDRA was used for coding AEs for the integrated safety analysis. There may be some small differenced in report of AEs between individual CSRs and the overall integrated safety analysis due to different version of MedDRA in ongoing trials.

An on-treatment AE was one with an onset date during the on-treatment period. On-treatment AEs were reported by SOC and preferred term. If a subject had an AE with different intensities during a study period, only the worst grade was reported. Frequencies of worst grade of on treatment AEs judged by investigators to be related to study therapy or leading to discontinuation were also reported. The causal

relationship to study drug was determined by the investigator and a determination of relatedness indicated that at least one of the drugs in the treatment regimen was considered related to the event. Investigators were not instructed to identify which of the drugs in a treatment regimen was associated with the AE related to study therapy.

Laboratory results were graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0. All laboratory data are reported using US conventional units. Certain laboratory abnormalities were reported as clinical AEs. These events reflect investigators' clinical judgment of the importance of the event in the context of patient care and are not a complete reporting of the measurement of laboratory abnormalities. Laboratory data were also provided in Système International (SI) units.

Deaths

There were no on treatment deaths in ALLY-1 or ALLY-2.

There were two deaths in ALLY-2, both of which occurred during the follow-up period:

Subject 30-90 (treatment-naïve, 8 week group) was a 52 year old HCV/HIV coinfected male without cirrhosis who received DCV/SOF for 8 weeks. The subject's history included angina, deep vein thrombosis, COPD, GERD, osteopenia, rheumatoid arthritis, stable benign brain neoplasm, ongoing tobacco use and depression. At post-treatment Week 4 (40 days post-last dose of study medication), the subject experienced a Grade 4 SAE of cardiac arrest which resulted in death. The investigator considered the event unrelated to study therapy.

Subject 28-187 (treatment-naïve, 12 week group) was a 53 year old HCV/HIV coinfected male without cirrhosis who received DCV/SOF for 12 weeks. The subjects history included disseminated Cryptococcus, right kidney calcified lesion, arthritis of the knees and seasonal allergies. At post-treatment Week 3, the subject underwent left total knee arthroplasty. At post-treatment Week 24, the subject underwent pre-operative cardiac evaluation for gallbladder surgery. He was found to have a Grade III/VI apical systolic murmur consistent with mitral valve insufficiency. He was considered low risk for surgery and 4 days later had a successful cholecystectomy. Following surgery, he developed shortness of breath and was admitted to the hospital. He reported multiple first-degree relatives dying at an early age from sudden cardiac death. An echocardiogram showed an ejection fraction of 10% with 3+ tricuspid valve insufficiency and 3+ mitral valve insufficiency. Approximately 27 weeks post-treatment, the subject worsened and was transferred to ICU care where he was started on hemodialysis. Progressive multiorgan failure developed and on Week 27 post-treatment (Day 277) the subject died due to congestive cardiac failure, cardiogenic shock and multiorgan failure. The events of congestive heart failure, and cardiogenic shock with multiorgan failure were considered not related to study drugs by the Investigator and BMS.

There were two deaths in ALLY-1, both of which occurred in subjects in the cirrhotic cohort during the follow-up period:

Subject 4-77 (Child-Pugh A cirrhosis, Baseline MELD 9) was a 68 year old female who completed 12 weeks of DCV/SOF/RBV and died from sepsis (post-treatment Week 18) with contributing factors of massive ascites, spontaneous bacterial peritonitis, B-cell lymphoma, deep venous thrombosis and pulmonary embolism. In addition, the subject had significant event of renal failure, small intestinal obstruction and chronic diarrhea prior to death.

Subject 3-8 (Child-Pugh C cirrhosis, Baseline MELD 17) was a 62 year old male with history of splenomegaly, portal hypertension, hepatitis A, hypertension, peripheral edema, obesity, thrombocytopenia, tobacco and marijuana use and past alcohol use, and hyperbilirubinemia who died due to progressive liver failure during the 12th week of relapse-retreatment with DCV/SOF/RBV. The subject had worsening hyponatremia which started as a Grade 2 event off treatment prior to starting re-lapse retreatment (subject relapsed at Week 16 post-treatment). The hyponatremia worsened to Grade 3 and the subject was hospitalized (Day 297) and he died 6 days later on Day 333.

No new clinical safety concerns for DCV are raised based on analysis of the deaths observed in the clinical database. The deaths reflect progression of advanced cirrhosis or are complicated by underlying comorbidities and pre-existing medical conditions.

Serious Adverse Events

ALLY-2

In ALLY-2 a total of 4 (2%) subjects reported on-treatment SAEs. None of the SAEs were considered to be related to study treatment and none resulted in discontinuation or required medical intervention. One subject developed priapism at Day 23; one subject developed grade 3 chest pain on Day 1 and grade 3 pre-syncope on Day 42; one subject had grade 3 drug abuse on Day 51 and grade 3 pulmonary embolism on Day 80 and one subject had grade 3 hypertensive crisis on Day 51 with grade 3 syncope on Day 54.

Additionally, 4 subjects had SAEs during follow-up. One subject developed grade 3 cholangiocarcinoma considered related by the investigator and not related by BMS; one subject reported SAE of pneumonia; one SAE of osteoarthritis leading to hospitalization for total knee arthroplasty (Subject 28-187 who subsequently died as discussed above); and one SAE of cardiac arrest (Subject 30-90 as discussed above).

No HIV opportunistic infections or HIV-related SAEs were reported.

ALLY-1

In ALLY-1 a total of 15 (13%) subjects reported on-treatment SAEs; including 10 (17%) subjects in the cirrhotic cohort and 7 (9%) subjects from the post-transplant cohort. None of the SAEs were considered treatment related. All SAEs (by preferred term) were reported by single subjects, except for hepatocellular carcinoma (HCC) which was report by 3 (3%) subjects (all cirrhotic) and hepatic encephalopathy which was reported by 2 (2%) subjects (1 subject each from cirrhotic and post-transplant cohort). In addition to the 2 subjects who developed hepatic encephalopathy on treatment (Subjects 2-68 and 5-62), 2 additional subjects (Subjects 3-9 and 3-97) developed grade 3 hepatic encephalopathy during follow up. Both subjects were Child-Pugh Class C at baseline and were hospitalized with worsening of baseline hepatic encephalopathy.

Based on analyses of SAEs, there was no pattern or new safety signal attributable to DCV and based on review of the narratives and data I agree with the assessment of the investigators with the exception of the relatedness of the cholangiocarcinoma which developed after completion of treatment. The temporal relationship and exposure to DCV/SOF/RBV is likely too short to have been the direct cause of this event of cancer in this subject with underlying HCV/HIV coinfection.

However, an area of ongoing safety concern across the DAA programs is the potential for worsening of liver function, or the progression of liver-related complications such as hepatic encephalopathy and ascites, particularly in advanced cirrhotic patients. The ALLY-1 safety database is limited by a small sample size; however, the compassionate use and broader post-marketing database for DCV is extensive and has also been evaluated for trends or safety signals related to use of DCV/SOF with and without RBV. BMS has submitted a post-marketing assessment of hepatic safety which focuses on safety evaluation of worsening from baseline liver disease in both compensated and decompensated patients with cirrhosis who are treated with a DCV/SOF containing regimen. At this time, there is no definitive related safety signal for DCV and progression of liver disease; however, a full safety assessment and safety monitoring of post-marketing data are ongoing.

Adverse Events leading to Discontinuations

There were no AEs leading to treatment discontinuation in ALLY-2. In addition, there were no changes in cART therapy due to concerns about compromise in the efficacy of the anti- HIV regimen. In total, 3 (1%) subjects changed their ARV regimen due to underlying chronic medical conditions related to use of tenofovir; 2 subjects had chronic renal insufficiency with low baseline creatinine clearance values and 1 had osteoporosis.

In ALLY-1, 15 subjects had an AE leading to discontinuation of at least 1 of the study drugs. All but 2 subjects who had an AE leading to discontinuation (13/15; 87%) discontinued RBV only. The most common reason for RBV discontinuation was

anemia/decreased hemoglobin (7 subjects), followed by rash (2 subjects); all other AEs leading to RBV discontinuation were reported by 1 subject each (other reasons included fever, fatigue, decreased creatinine clearance, joint pain and transplant). The 3 subjects who discontinued RBV only completed 12 weeks of DCV/SOF; 10 of 13 achieved SVR12.

Two subjects in ALLY-1 discontinued DCV/SOF/RBV due to AE. One subject developed a persistent grade 2 AE of headache from Day 1. The subject discontinued all 3 study drugs at Week 4. The subject achieved SVR12. The other subject discontinued all HCV treatment at the time of a liver transplant on Day 23. The transplant was received at a remote transplant center. This subject did not enter treatment extension and this subject did not achieve SVR12.

Significant Adverse Events

In ALLY-2, 4% (8/203) of subjects reported on-treatment grade 3 or 4 AEs. All of the grade 3 or 4 AEs were reported by a single subject each. One treatment-related grade 3 AEs was reported (grade 3 decreased appetite); and there were no grade 4 treatment-related AEs.

In ALLY-1, 13% (15/113) of subjects reported on-treatment grade 3 or 4 AEs. All of the grade 3 or 4 AEs were reported by single subjects with the exception of HCC (3 subjects) and arthralgia (2 subjects). Two subjects (of the 3 with HCC) reported grade 4 AEs of HCC, both considered not related to study treatments by the investigator (Subjects 3-100 and 3-17). One subject (Subject 4-1) reported grade 3 treatment emergent arthralgia that was considered related to study therapy and led to treatment discontinuation. The other subject with reported grade 3 arthralgia had a specific complaint of left hip pain, that was considered not related to study treatment and no action was taken with study drugs. The left hip pain was ongoing in this subject at study completion.

There are no new safety trends for DCV/SOF with or without RBV based on review of the AEs leading to discontinuation and the grade 3 or 4 AEs.
Based on review of narratives and the datasets I agree with the assessment of causality by the investigators. The reasons for discontinuation of RBV in ALLY-1 are consistent with the common AEs leading to RBV discontinuation (rash and anemia) and are included in the product labeling.

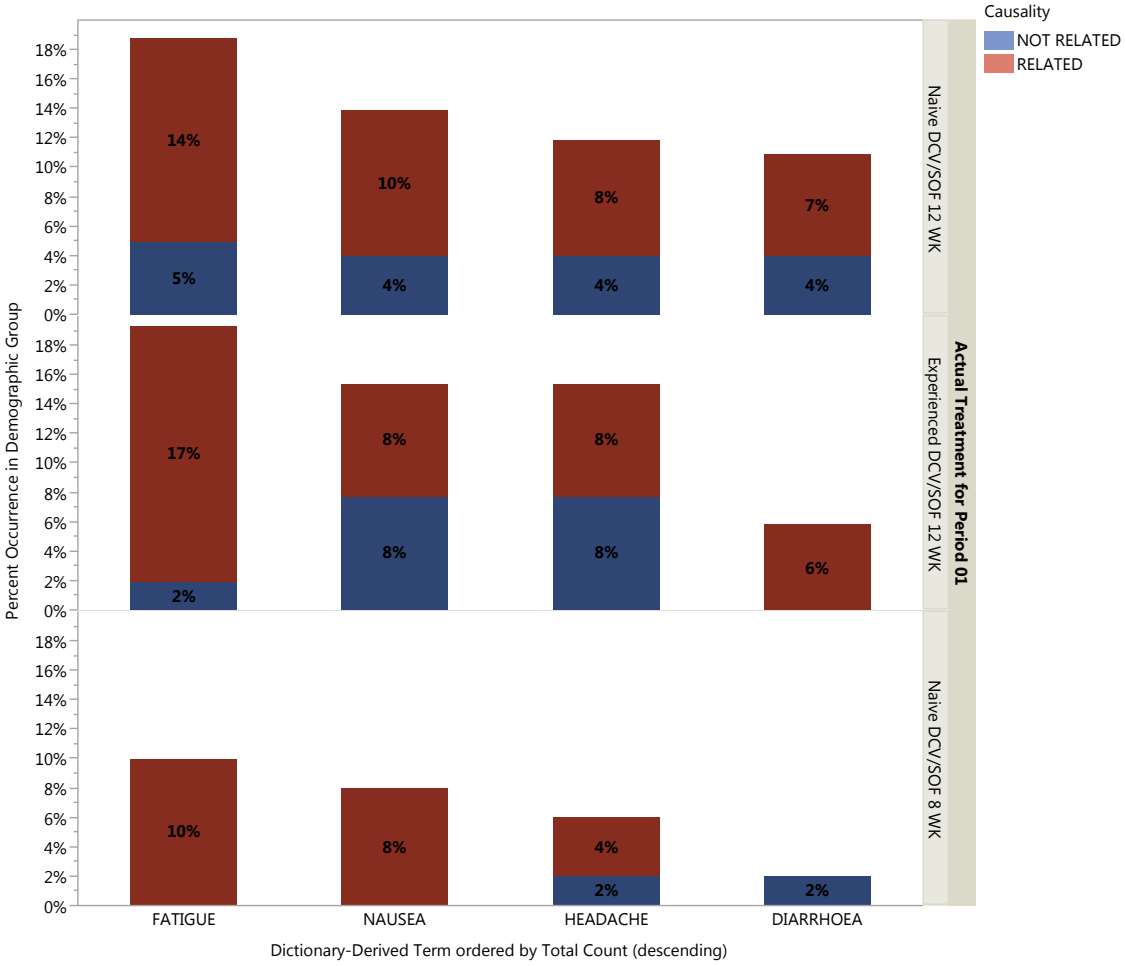
Common Adverse Events

ALLY-2

In ALLY-2, 69% of subjects reported an on-treatment AEs of any grade. Most AEs were mild or moderate in severity and none led to treatment discontinuation.

The most common AEs (≥5%) were fatigue (17%; 34/203), nausea (13%; 26/203), headache (11%; 23/203) and diarrhea (7%; 15/203). More AEs were reported in the 12 week arms compared to the 8 week treatment arm. Additionally, most (71%) of the common AEs were considered related to study treatment (see Figure 5 below); although all AEs were mild to moderate and none led to treatment discontinuation. The majority of events also occurred within the first 2 weeks of treatment. There were no clinically significant differences in trends by sex, age, and race, cART regimen or by cirrhosis status for the common AEs.

Figure 5. Most Common On Treatment AEs ≥5% by Causality in ALLY-2



Source: AE datasets ALLY-2

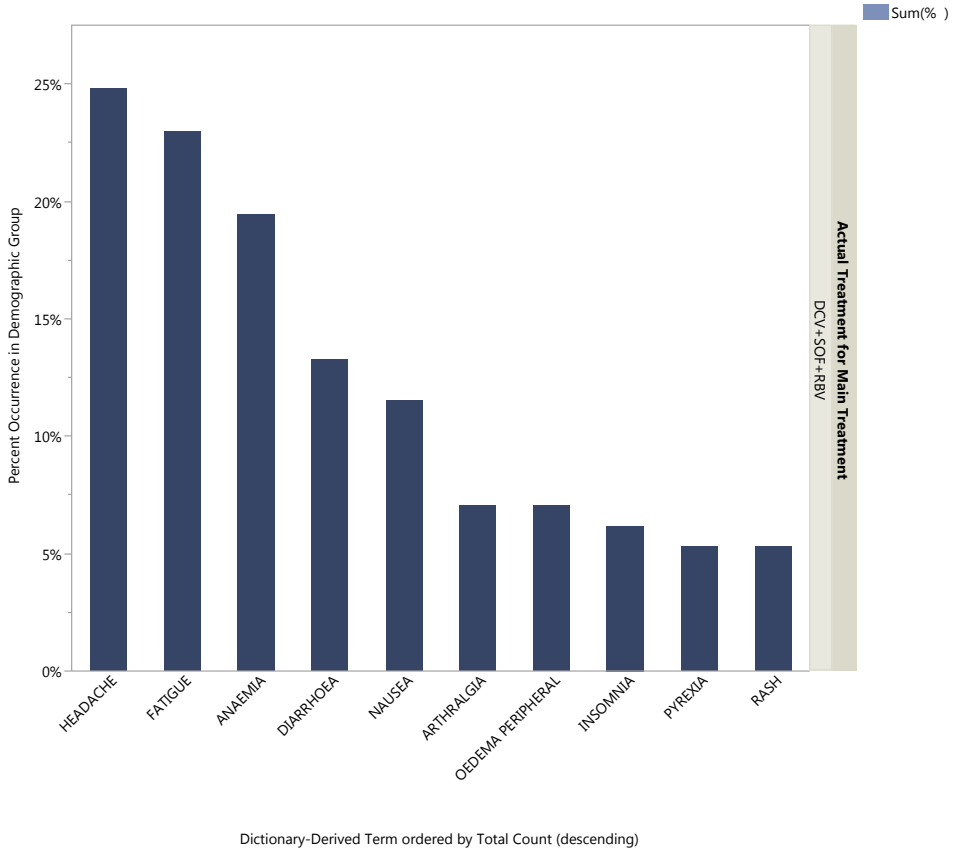
In addition, 9 subjects (4%) reported rash while on-treatment; of which, 4 subjects (2%) were considered to have treatment-related rash. Eight of the 9 subjects had mild rash and 1 subject had moderate rash. None of the rash AEs led to interruption or discontinuation of therapy.

ALLY-1

In ALLY-1 common AEs were evaluated for labeling (and shown below) includes all subjects while on-treatment and does not include events for those subjects who had extended therapy post-transplant or those events that occurred during relapse retreatment. However, multiple analyses were completed looking at all phases of treatment, including evaluation of the post-transplant extension phases and the relapse retreatment phase. There were no meaningful clinical differences in these safety analyses.

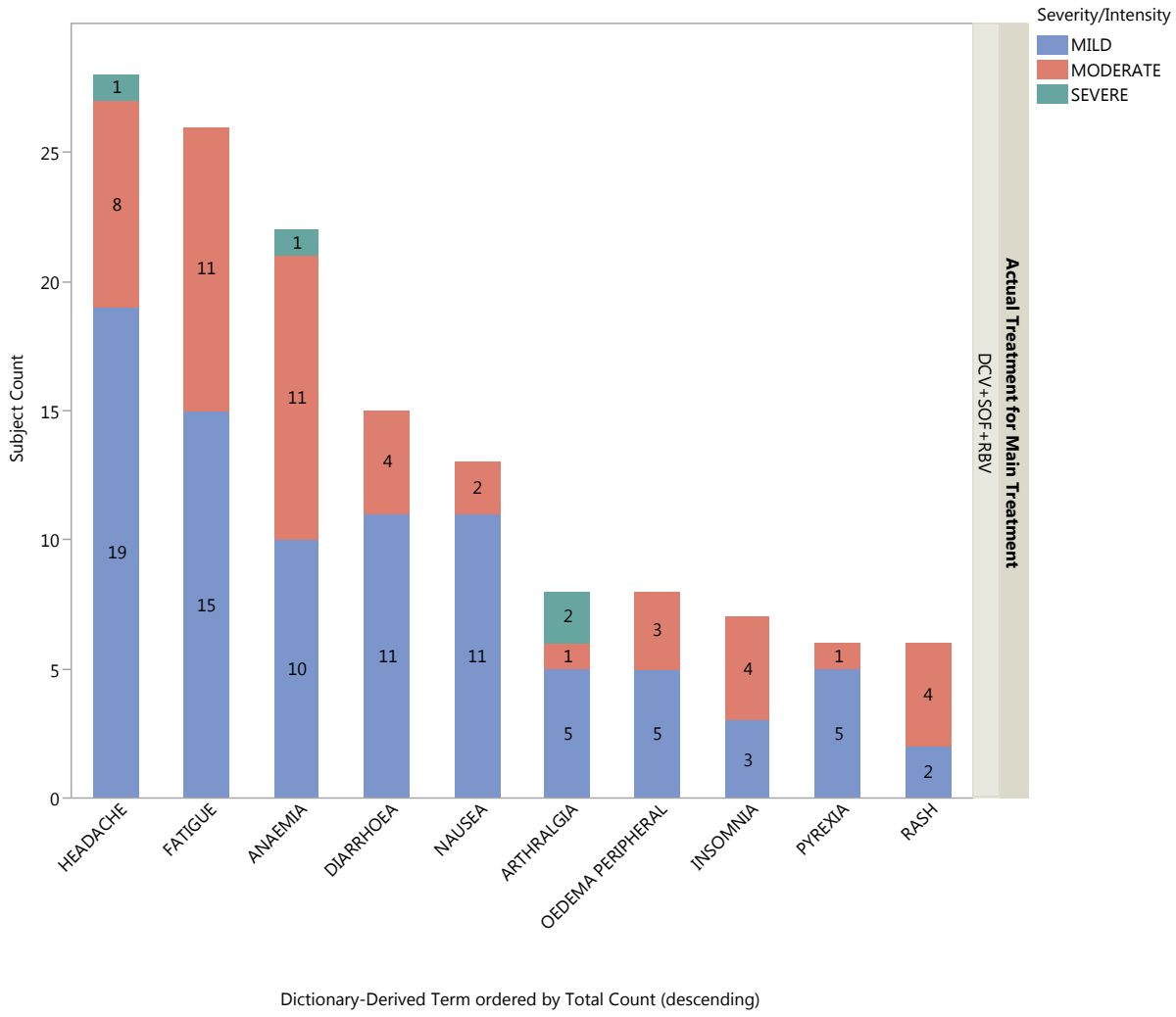
Overall in ALLY-1, 95 (84%) subjects reported at least 1 grade 1-4 AE; including 50 (83%) subjects in the cirrhotic cohort and 45 (85%) subjects in the post-transplant cohort. The most common AEs overall in both cohorts (≥5%) were headache (25%; 28/113), fatigue (23%; 26/113), anemia (20%; 22/113), diarrhea (13%; 15/113), nausea (12%; 13/113), peripheral edema (7%; 8/113), arthralgia (7%; 8/113) insomnia (6%; 7/113), pyrexia (5%; 6/113) and rash (5%; 6/113) (see Figure 6 below). Most events were mild to moderate in severity (only 4 AEs were considered SAEs and are discussed above; see Figure 7).

Figure 6: Most Common On-Treatment AEs ≥5% in ALLY-1



Source: AE dataset ALLY-1

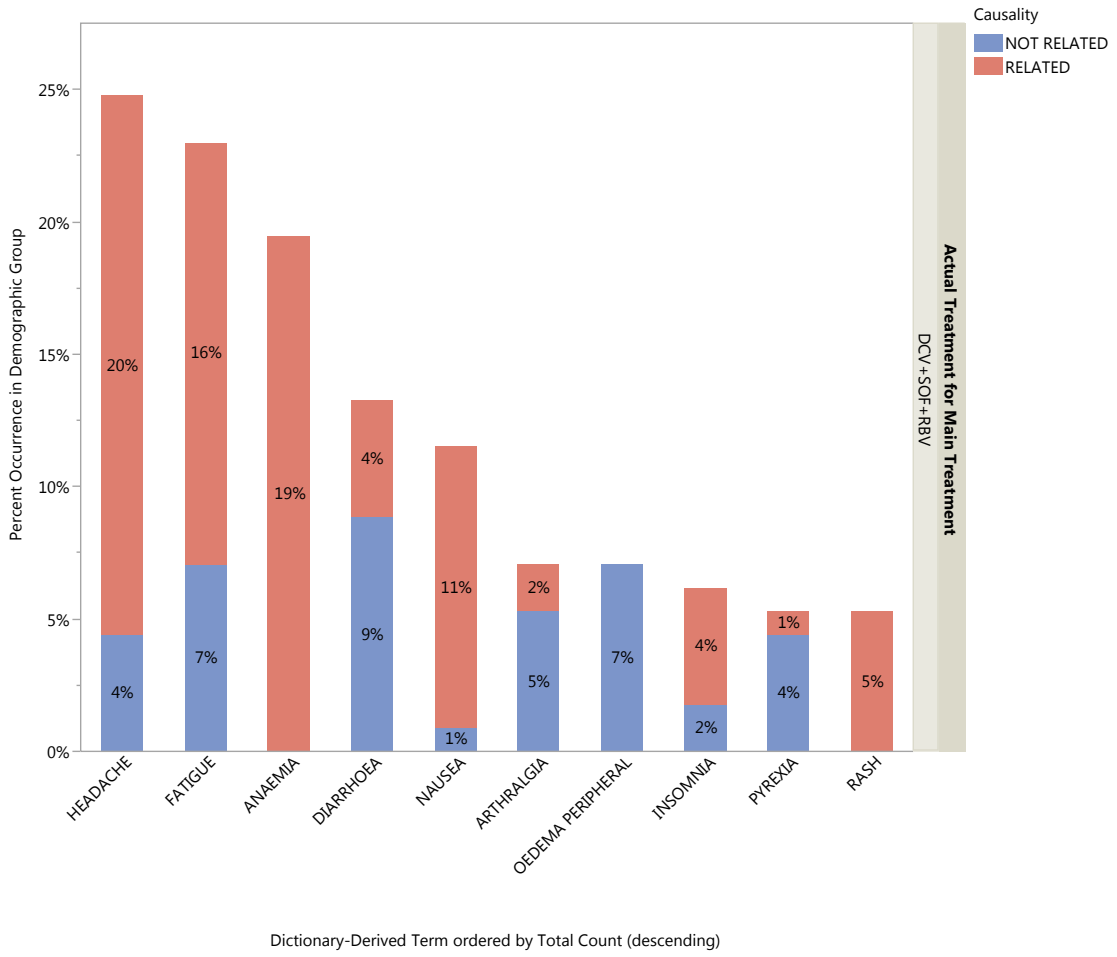
Figure 7: Most Common On-Treatment AEs ≥5% by Subject Count and Severity in ALLY-1



Source: AE dataset ALLY-1

Treatment-related AEs were reported in 63% (71/112) of subjects. The most common treatment related AEs (≥5%) were headache (20%), anemia (20%), fatigue (16%) nausea (11%) and rash (5%) (see Figure 8). No treatment related AEs was considered serious; a treatment related AE of grade 2 headache led to discontinuation of DCV/SOF/RBV. All other treatment-related AEs that led to discontinuation were specific to RBV only and are discussed above.

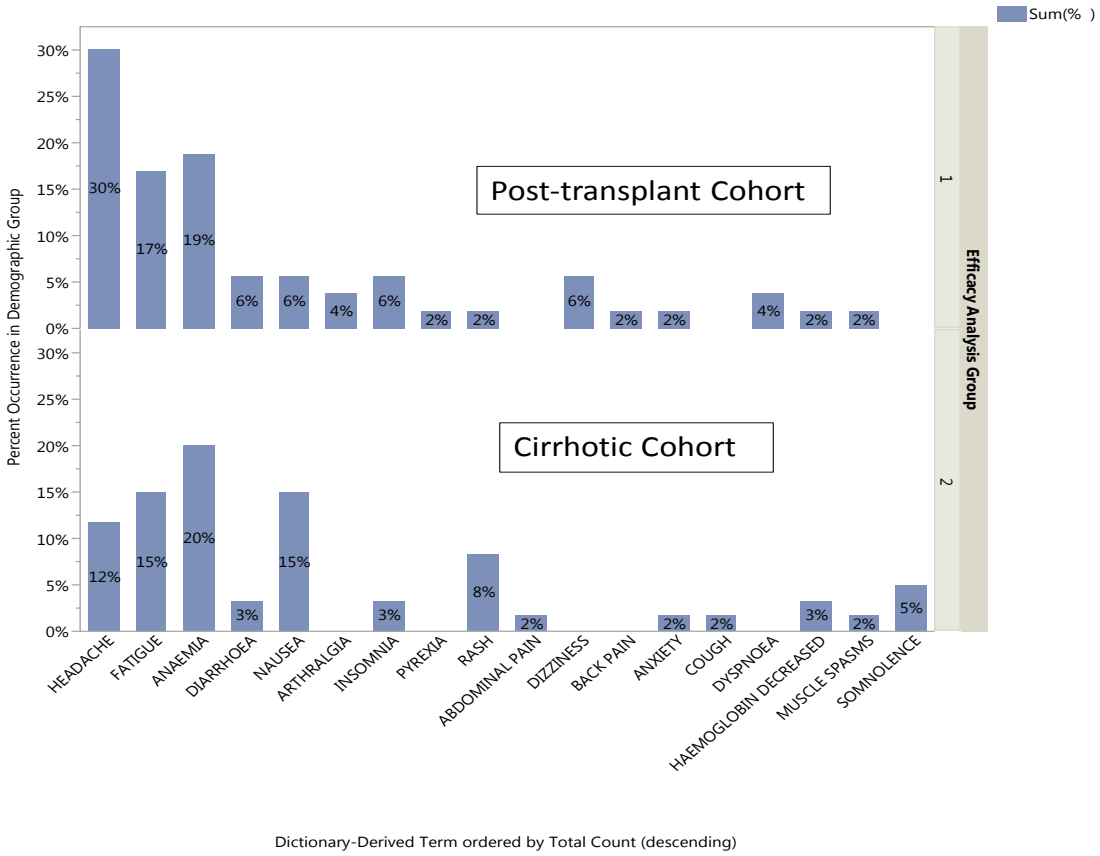
Figure 8: Most Common On-Treatment AEs ≥5% by Percent Occurrence and Causality in ALLY-1



Source: AE dataset ALLY-1

The most common adverse drug reactions (ADRs) ≥2% were also evaluated by study cohort in ALLY-1. Figure 9 provides the analysis of ADRs (AEs considered at least possibly related to study treatment) by study cohort and at least ≥ 2%. As shown, this analysis includes many of the same common AEs as the overall analysis (headache, anemia, fatigue, nausea, diarrhea, rash, and insomnia). However, for the purposes of product labeling the cut point of 5% was considered more clinically relevant. With the cut point of any ADR above 5% for either treatment cohort, the preferred terms of dizziness and somnolence are also included as dizziness was reported in 6% (3/53) of subjects in the post-transplant cohort and somnolence was reported in 5% (3/60) of subjects in the cirrhotic cohort. Additionally, arthralgia and pyrexia are no longer included as their proportions are both below the 5% cut point. The ADRs with proportions ≥5% as displayed in Figure 9 will be included in product labeling.

Figure 9: ADRs by Study Cohort and At Least ≥ 2%- ALLY-1



1=post-transplant cohort; 2= cirrhotic cohort
Source: AE datasets ALLY-1

Laboratory Findings

Analyses of treatment-emergent worst toxicity grade laboratory abnormalities were completed for ALLY-1 and ALLY-2 (Table 16). The clinically significant laboratory test abnormalities are presented in the following table for both trials. ALLY-2 data are presented pooled for the treatment-naïve and treatment-experienced 12 week arms only because rates of events were similar or fewer in the 8 week arm and the 8 week arm will not be included in product labeling as discussed in the efficacy section. The ALLY-1 trial is provided by the post-transplant and cirrhotic cohorts and the overall totals are given.

Generally in ALLY-1, the post–transplant and cirrhotic cohorts had similar proportions of lab abnormalities except for platelets, INR, total bilirubin and albumin where there were higher proportions of subjects in the advanced cirrhotic cohort with treatment-emergent abnormalities compared to the post-transplant cohort. These findings are not unexpected and are consistent with the more advanced liver disease status of the pre-transplant cirrhotic cohort compared to the post-transplant cohort. Overall, the

majority treatment-emergent lab worst grade abnormalities were grade 1 or 2 in severity.

Table 16: Treatment-Emergent Worst Grade Toxicity Laboratory Abnormalities for Subjects in ALLY-1 and ALLY-2 who received a 12 week regimen of DCV/SOF±RBV

	ALLY-2 DCV/SOF x 12 W	ALLY-1 DCV/SOF/RBV x 12 W		
Lab Test	**N=153 (%)**	**Post-Transplant N=53 (%)**	**Cirrhotic N=60 (%)**	**Total N=113 (%)**
Hemoglobin				
Grade 1	0	6 (11)	10 (17)	16 (14)
Grade 2	0	5 (9)	5 (8)	10 (9)
Grade 3	0	2 (4)	5 (8)	7 (6)
Grade 4	0	0	0	0
Platelets				
Grade 1	13 (9)	3 (6)	3 (5)	6 (5)
Grade 2	4 (3)	2 (4)	6 (10)	8 (7)
Grade 3	0	0	4 (7)	4 (4)
Grade 4	0	0	0	0
INR				
Grade 1	8 (5)	2 (4)	13 (22)	15 (13)
Grade 2	0	1 (2)	10 (17)	11 (10)
Grade 3	2 (1)	0	1 (2)	1 (1)
Grade 4	0	0	0	0
ALT				
Grade 1	2 (1)	1 (2)	0	1 (1)
Grade 2	0	2 (4)	1 (2)	3 (3)
Grade 3	0	0	0	0
Grade 4	0	0	2 (3)	1 (2)
AST				
Grade 1	6 (4)	0	1 (2)	1 (1)
Grade 2	3 (2)	3 (6)	0	3 (3)
Grade 3	0	0	1 (2)	1 (1)
Grade 4	0	0	2 (3)	2 (2)
ALP				
Grade 1	0	2 (4)	2 (3)	4 (4)
Grade 2	0	0	0	0
Grade 3	0	1 (2)	0	1 (1)
Grade 4	0	0	0	0
Total Bilirubin				
Grade 1	5 (3)	3 (6)	7 (12)	10 (9)
Grade 2	9 (6)	3 (6)	9 (15)	12 (11)
Grade 3	7 (5)	2 (4)	6 (10)	8 (7)
Grade 4	1 (1)	0	1 (2)	1 (1)
Albumin				
Grade 1	0	2 (4)	4 (7)	6 (5)
Grade 2	0	2 (4)	7 (12)	9 (8)
Grade 3	0	0	1 (2)	1 (1)
Grade 4	0	0	0	0
Lipase				
Grade 1	18 (12)	8 (15)	6 (10)	14 (12)

Grade 2	11 (7)	7 (13)	16 (27)	23 (20)
Grade 3	3 (2)	1 (2)	2 (3)	3 (3)
Grade 4	3 (2)	1 (2)	1 (2)	1 (1)
Creatinine				
Grade 1	22 (14)	10 (19)	3 (5)	13 (12)
Grade 2	12 (8)	9 (17)	6 (10)	15 (13)
Grade 3	0	0	2 (3)	2 (2)
Grade 4	0	1 (2)	0	1 (1)

Source: Laboratory Datasets ALLY-1 and ALLY-2

Hematologic Parameters and Anemia

In ALLY-2 there were no grade 4 on-treatment hematology abnormalities. There were 2 grade 3 treatment emergent abnormalities both for elevations of INR. One subject was on anticoagulation therapy for an aortic valve replacement and had a baseline INR considered therapeutic at grade 2, he developed a grade 3 elevation at Week 8. All liver-related lab values remained within normal limits while on study. The other subject had an isolated grade 3 INR of 3.1 at Week 6 which normalized on repeat testing at Week 8. This subject's liver-related labs also remained within normal limits while on study.

In ALLY-1, more hematologic abnormalities were observed which is expected because of the use of RBV in the treatment regimen. However, the majority were grade 1 and 2 in severity. There were no treatment-emergent grade 4 hematologic lab abnormalities. Grade 3 treatment-emergent abnormalities of hemoglobin, platelets and INR occurred in 6%, 4% and 1% of subjects in ALLY-1, respectively.

Of the 7 subjects (6%) with treatment emergent grade 3 decreases in hemoglobin in ALLY-1, 5 subjects discontinued RBV therapy due to an AE of anemia (Subjects 3-16, 3-85, 3-97, 3-22 and 3-27), 1 subject discontinued RBV due to hepatic cirrhosis (Subject 1-50) and 1 subject continued therapy with RBV (Subject 3-108).

Four subjects (4%) overall in ALLY-1 had treatment emergent decreases in platelet levels. All 4 subjects had Child-Pugh class C cirrhosis. The treatment emergent decreases in platelets were consistent with the advanced stage of their underlying liver disease (Subjects 3-9, 3-100, 5-83 and 3-85).

One subject with Child-Pugh class B cirrhosis had a single treatment emergent grade 3 increase of INR at Week 8, which decreased to grade 2 at Week 12 and grade 1 at follow-up Week 4.

Anemia in ALLY-1

As discussed above, there were no treatment emergent decreases in hemoglobin in subjects who received DCV/SOF for 12 weeks in ALLY-2; however, consistent with the hemolysis caused by RBV, treatment emergent anemia was observed for subjects who received DCV/SOF/RBV in ALLY-1. In ALLY-1, 16 subjects (14%) had treatment

emergent grade 1 (10-10.9 g/dL) decreases in hemoglobin and 10 subjects (9%) had grade 2 (9-9.9 g/dL) decreases in hemoglobin. The proportions of subjects with grade 1 or 2 decreases in hemoglobin were similar between the post-transplant and cirrhotic cohorts.

Overall, 7 subjects (6%) had treatment emergent grade 3 (7- 8.9 g/dL) decreases in hemoglobin. As expected, more subjects had treatment- emergent grade 3 hemoglobin decreases in the cirrhotic cohort (n=5; 8%) compared to the post-transplant cohort (n=2; 4%). No subjects had treatment-emergent grade 4 (< 7 g/dL) decreases in hemoglobin while on DCV/SOF/RBV.

Table 17 provides a summary of subjects who had a grade 2 or 3 worst grade on treatment decrease in hemoglobin in all subjects from ALLY-1 (19 subjects are included here as this is worst grade on treatment and not a treatment-emergent analysis). The table provides the baseline Hb, the Hb nadir and Week, the RBV dose and adjusted dose, duration on RBV and SVR12 outcome. Of the 19 subjects, 9 (47%) subjects completed 12 weeks of RBV and 10 subjects (52%) had early discontinuation of RBV. Two subjects that did complete 12 weeks did not achieve SVR12 (both had relapse) and 2 subjects that did not complete 12 weeks also did not achieve SVR12 (relapse and transplant). Therefore, as discussed above in the efficacy section, it is inconclusive based on the limited data whether early discontinuation of RBV due to anemia affected SVR rates. From a safety standpoint, 7 subjects (6%) had grade 3 anemia events, none had grade 4 anemia events, 1 subject (1%) subject required transfusion and there was no use of erythropoietin stimulating agents. Generally, RBV at doses of 600 mg and lower were well tolerated by the advanced cirrhotic and post-transplant populations in ALLY-1; few subjects (n=4; 3.5%) had RBV dosing increased and maintained above 600 mg in ALLY-1.

Table 17: Subjects with Worst Grade 2 or 3 On Treatment Decreases In Hemoglobin Summarized by Child-Pugh Class, Baseline and Nadir Hemoglobin, Ribavirin Dose/Duration and SVR outcome

Patient ID	Baseline Child-Pugh Class/ Post-transplant (PT)	Baseline Hb	Hb nadir/Week	RBV Dose	Duration on RBV	SVR12 outcome
2-26	PT	11.4	9.9/W4	200 mg QOD D1-84	12W	Yes
2-55	PT	14.4	9.9/W4	600 mg D1-28 200 mg D31-84	12W	Yes
3-105	C	10.4	9.1/W8	400 mg D1-9 200mg D10-84	12W	No-Relapse
3-17	B	14.1	9.3/W6	600 mg D1-39 600 mg D42-51	7.3W	Yes
3-25	PT	13.1	9.9/W4	600 mg D1-28 400 mg D29-33 200 mg D34-84	12W	Yes
4-101	PT	11.2	9.8/W8	400 mg D1-84	12W	Yes
4-39	C	10.3	9.3/W2	200 mg D1-84	12W	Yes
4-74	A	11.4	9.9/W4	400 mg D1-17 200 mg D18-83	12W	Yes
4-80	A	13.0	9.9/W6	600 mg D1-26 400 mg D27-47 200 mg D48-57	8W	Yes
5-73	PT	12.6	9.8/W4	600 mg D1-30 200 mg D31-84	12W	Yes
5-84	C	10.6, 9.3	9.2/W2	400 mg D1-2 200 mg D3-35 200 mg QOD D36-84	12W	No- Relapse
1-50	C	12.6	7.8/W10	600 mg D1-43; 800mg D44-78	11.1 W	No-transplant at W10

3-108	B	10.2	8.9/W6	400 mg D1-11; 200mg D12-56	8W	Yes
3-16	B	9.7	7.8/W6	200 mg D1-42	6W	Yes
3-22	PT	12.3	7.4/W4	400 mg D1-27	3.8W	Yes
3-27	PT	12.8	7.8/W4	600 mg D1-21	3W/ transfusion 2U at W4	Yes
3-85	C	9.8	7.2/W2	200 mg D1-11	1.6 W	Yes
3-97	C	9.4	8.0/W12	200 mg D1-43	6.1W	Relapse
5-62	B	9.7	7.8/W4	200 mg D1-8	1.1W	Yes

Source: Child-Pugh, laboratory, exposure and efficacy datasets ALLY-1

Hepatic parameters – Hy's Law and pDILI

In ALLY-2 there were no grade 3 or 4 treatment-emergent abnormalities of ALT, ALP or albumin. There was 1 subject (8-week arm) with a grade 3 increase in AST at Week 8 (Day 57) which improved to grade 1 on treatment by EOT (Day 63). This subject had no other abnormal liver tests and no associated AE was reported.

The most frequent grade 3 or 4 treatment emergent laboratory abnormality in ALLY-2 was increase in total bilirubin (n=8, 6%); however, all these subjects were on concomitant atazanavir which elevates total bilirubin (indirect hyperbilirubinemia). None of the 8 subjects had other reported signs or symptoms of hepatic dysfunction.

There were no cases which met laboratory criteria for Hy's Law or potential DILI in ALLY-2.

In ALLY-1, a total of 3 (3%) of subjects had a grade 3 or 4 treatment-emergent ALT/AST abnormalities. Subjects 1-50 and 3-17 experienced grade 3 or 4 ALT, AST and total bilirubin levels in the immediate post-liver transplant period. The elevated liver biochemistry levels in these 2 subjects were considered to be caused by transient ischemia and liver graft reperfusion, and liver graft reperfusion and anastomotic duct stenosis, respectively. These subjects met laboratory criteria for both Hy's Law and pDILI, but clinically these cases were consistent with post-transplant reperfusion of the liver and not drug induced injuries. The third subject (Subject 3-100) had a grade 3 AST level on Day 19 upon hospitalization for complications of cirrhosis and HCC. The subject received a liver transplant on Day 23 and did not receive treatment extension.

In ALLY-1, a total of 9 (8%) subjects had grade 3 or 4 treatment-emergent increased total bilirubin levels; this includes 2 subjects in the post-liver transplant cohort with FibroTest F4 fibrosis and 7 subjects in the cirrhotic cohort. All cirrhotic subjects with treatment-emergent grade 3 or 4 elevation of total bilirubin had Child-Pugh class B or C liver disease with abnormal total bilirubin at baseline. In most cases, the elevation of total bilirubin on-treatment was consistent with hemolysis induced by RBV. Only 1 of these subjects (Subject 1-37) had an increase in direct bilirubin greater than or equal to 1.0 mg/dL above baseline; this subject had multiple hospitalizations for abdominal pain, which the investigator attributed to cholelithiasis. The subject was subsequently treated with cholecystectomy.

In ALLY-1, one subject (Subject 3-109) in the post-liver transplant cohort with F3 fibrosis by FibroTest, had a treatment-emergent Grade 3 ALP level. This subject had a past history of liver transplant complicated by hepatic artery stenosis and a large fluid collection in the porta hepatis requiring percutaneous drainage. The ALP was elevated at baseline, but was not accompanied by bilirubin elevation at any time. The

elevated ALP did not resolve during treatment or follow up and was not attributed to HCV therapy by investigator assessment.

In ALLY-1, in which RBV was part of the regimen, a total of 6 (5.3%) subjects met Hy's Law with an ALT or AST level ≥ 3xULN and a total bilirubin level ≥ 2xULN during the study, all cases were considered related to underlying liver disease or liver transplant, and not drug-induced hepatotoxicity. Four of the 6 subjects met these criteria during screening or at baseline prior to initiating study therapy. The remaining 2 subjects (Subjects 1-50 and 3-17) met pDILI criteria immediately after liver transplant and are discussed above. Review of the narratives and data confirms that there is no causal association of DCV/SOF/RBV to the hepatic laboratory abnormalities in these subjects, but rather the severity of the underlying cirrhosis or immediate post-transplant reperfusion which were related to the laboratory findings. Additional discussion of hepatic safety is below under Submission Specific Primary Safety Concerns.

Lipase and Creatinine

In ALLY-2 there were no treatment-emergent grade 3 or 4 creatinine abnormalities. Thirty-four subjects (22%) had treatment-emergent grade 1 or 2 creatinine abnormalities without associated AEs. HIV-1 and some cART regimens, as well as underlying HCV, can have renal effects which may contribute to the number of grade 1 or 2 elevated creatinine events observed in ALLY-2.

While on treatment, 6 subjects (4%) had grade 3 or 4 treatment emergent elevations of lipase; all of these subjects were receiving concomitant nucleoside reverse transcriptase inhibitors as part of their cART and none of these subjects had clinical AEs of pancreatitis.

In ALLY-1 a total of 5 (9%) post-transplant subjects and 4 (7%) cirrhotic subjects had a decrease in creatinine clearance > 25% from baseline at any point on treatment. In all cases, these changes were mild and transient and complicated by the pre-existing comorbid conditions as well as advanced cirrhosis. A total of 3 (3%) subjects overall had a grade 3 or 4 treatment-emergent increased creatinine level.

Overall, 5 (4%) subjects had a grade 3 or 4 treatment-emergent lipase level; and none of these subjects had pancreatitis or discontinued drug due to elevated lipase levels.

In summary, the laboratory analyses of ALLY-1 and ALLY-2 did not reveal any novel safety signals. The label will include a table providing the treatment-emergent worst grade 3 and 4 laboratory abnormalities for the following selected lab tests: Hb, ALT, AST, Total Bilirubin, and Lipase as shown above in Table 16. These lab tests were selected based on both their proportions of events and their clinical relevance to the populations studied and indicated in the USPI.

Submission Specific Primary Safety Concerns

Additional analyses were completed to evaluate particular areas of concern related to DCV/SOF with and without RBV. The following subsections highlight significant findings.

Hepatic Safety

To date, DCV in combination with SOF has not been associated with a hepatic safety signal. The ALLY-1 trial was the first clinical trial of DCV/SOF/RBV in an advanced decompensated cirrhotic population. Because of this, there are additional hepatic safety concerns regarding tolerability of the treatment regimen in this population. While DCV or other NS5A inhibitors have not been associated with a hepatic safety signal to date, concerns have arisen for some protease inhibitors, including asunaprevir which was reviewed in detail for hepatic safety during the original DCV/ASV NDA submission. Hepatic safety was explored and a summary of the analyses are provided in the following section.

There were no clinically significant hepatic safety events or laboratory findings related to use of DCV/SOF in ALLY-2.

Evaluation for Worsening of Hepatic Status of Subjects in the Cirrhotic Cohort of ALLY-1

Analyses were completed to evaluate changes in Child-Pugh scores and categories, MELD scores and FibroTest scores for subjects receiving DCV/SOF/RBV in the cirrhotic cohort of ALLY-1. Overall, in the cirrhotic cohort the mean Child-Pugh, MELD and FibroTest scores decreased from baseline to follow-up Week 12 -0.9 [n=50], -0.8 [n=49] and -0.074 [n=50], respectively. However, 21 of the 60 subjects in the cirrhotic cohort also had worsening hepatic encephalopathy, MELD score, Child-Pugh score or ascites while on-treatment; 18 of these 21 subjects (86%) achieved SVR12. No subjects discontinued study drugs due to worsening of encephalopathy, MELD, Child-Pugh score or ascites during treatment.

Multiple analyses were completed to evaluate changes in Child-Pugh and MELD scores as related to potential safety issues (also discussed above in efficacy section). These analyses showed inconsistent results and variability, which increased with worsening Child-Pugh and MELD scores. Overall, no definitive safety signal for worsening of hepatic function or hepatic safety was determined related to use of DCV/SOF/RBV in this limited cohort of subjects. Additionally, the data showed that while some subjects had improvement in Child-Pugh or MELD scores, including those who did not achieve SVR12, others may have worsened despite achieving SVR12. The following table summarizes baseline Child-Pugh category and changes in MELD scores for the 21 subjects with baseline MELD scores ≥ 15. In sum, additional long

term data are needed to evaluate and determine the long term clinical impact and safety of treatment with an effective DAA regimen in patients with advanced decompensated cirrhosis. .

Table 18: Baseline Child-Pugh Category and Changes in MELD Score from Baseline to Follow-Up Week 12 for Subjects with Baseline MELD ≥15

Subject Number	Baseline Child-Pugh	Baseline MELD	Follow Up WK12 MELD	Change in MELD
05	B	15	17	+2
40	B	17	15	-2
34	B	15	8 (relapse)	-7 (no SVR)
62	B	18	17	-1
80	B	19	16	-3
90	B	16	11	-5
99	B	15	12	-3
111	B	16	12	-4
02	C	16	16	0
08	C	17	19 (FUW24)	+2 (relapse @ FUW16 retx and later died)
09	C	16	FUW8: 17 Relapse re-tx	+1 (no SVR)
13	C	17	15	-2
14*	C	19	14	-5 (no SVR; transplant)
15	C	16	19	+3 (no SVR)
50*	C	24	Cir ext FUW8= 10	-14 (transplant)
53	C	27	22	-5
61	C	23	10	-13
84	C	20	FUW4 20/relapse retx	0
85	C	17	17	0
88	C	16	15	-1
100*	C	21	d/c liver transplant	(transplant)

*Subject had transplant; FU=follow-up; Cir ext= cirrhotic extension treatment after transplant; relapse re-tx= retreatment per protocol after relapse
Source: Laboratory datasets ALLY-1

Hepatocellular Carcinoma

At study baseline, 6 subjects in ALLY-1 had known HCC. No subjects were diagnosed with HCC during treatment; however 3 subjects were diagnosed with HCC during the follow up period. One subject (Subject 3-57) had a previous liver transplant due to HCC 2 years prior to baseline, and developed a pulmonary nodule which was

diagnosed as metastatic HCC by biopsy on Day 170. The other 2 cases (Subjects 3-14 and 4-39) were diagnosed approximately 9 weeks and 5 weeks after completing study therapy. None of the cases were considered related to study treatment.

Formal Adjudication of Potential Hepatic Safety Events in ALLY-1

As part of the supplemental NDA application, FDA requested the applicant provide a formal adjudicated evaluation by external expert hepatology consultants (Dr. Willis Maddrey, Dr. Paul Watkins and Dr. Gary Davis) to review cases in the decompensated and post-transplant population that met the following criteria:

- Treatment-emergent deaths (n=0; however the 2 deaths in follow up were submitted for review)
- Increase in ALT or AST >3x nadir or >2x baseline value (n=9)
- Any increase in direct bilirubin > 1 mg/dL from baseline (n=2)
- Any hepatic AE leading to treatment discontinuation (n=2)
- Any discontinuation due to pre-specified laboratory criteria (n=0)
- Subjects requiring liver transplantation (including reason for liver transplantation (n=4; all subjects had HCC)

In total, 12 subjects met one or more of these criteria. The committee was provided with all subjects' study data including, adverse events, clinical exams, laboratory data and narratives for their review. The committee was asked to independently assess the relationship of the events to study drug as a complete regimen and not necessarily the individual drug components. The committee assessed the likelihood of drug causality according to DILIN criteria (Rockey, 2010). The committee then met to review each case to determine and report a consensus with regard to causality. However, one caveat was for the discontinuation of RBV due to anemia which is an expected AE of treatment with RBV and is not hepatic in nature; therefore, those cases were not reviewed by the committee.

One case of the total 12 cases reviewed was considered to be possibly related to study treatment and 11 cases were considered unlikely related to the study treatment. Summary of the case considered possibly related is as follows:

Subject 3-27 is a 65 year old female with significant history of chronic renal disease, anemia, hypertension and liver transplant who had transient elevations of ALT (103 U/L), AST (88 U/L) and Alk Phos (155 U/L) on Day 43. The total bilirubin (8.6 umol/L) remained normal. The liver chemistries resolved without interruption of treatment or with any other intervention (see table below); however, as no cause for the transient elevations was able to determined based on available information, this case was considered possibly drug-related.

Table 19: Liver Chemistries for Subject 3-27 considered possibly drug-related

LFT

	ALP	AST	TBILI	DBILI	ALT
Units	U/L	U/L	umol/L	umol/L	U/L
Range	- 104	- 31	- 20.5	- 5.1	- 33
Day-14	176	47	5.1	1.7	61
Day1	163	74	6.8	1.7	82
Day8	142	21	8.6	3.4	24
Day18	134	15	5.1	1.7	7
Day27	110	15	3.4	1.7	7
Day43	155	88	8.6	3.4	103
Day60	107	14	3.4	1.7	12
Day81	111	13	6.8	1.7	10
Day116	125	20	3.4	1.7	13

Source: Narrative for Subject 3-27 in ALLY-1

The other 11 cases reviewed by the committee were determined to have alternative causes for the events that met the respective criteria. The alternative reasons included: death due to progression of intrinsic liver disease and death due to pre-existing lymphoma with sepsis, and multiorgan failure; elevations of liver chemistries due to biliary obstruction, gastrointestinal bleeding, post-transplant ischemia with reperfusion and post-transplant hepatic artery stenosis; and 2 subjects had spuriously low nadir values for ALT of 7 U/L providing a falsely low nadir with subsequent values meeting the 3x nadir criterion but not being considered clinically significant changes. Therefore, based on review of the data, the overall consensus assessment of the committee was that there was a clear alternative explanation for the hepatic abnormalities of the 11 cases and that overall, there was no consistent hepatic safety signal in all of the cases presented.

The clinical trial data, laboratory values, narratives, adjudication committee information package and the committee report were all reviewed. I agree with the assessment of the 12 cases identified by using the conservative criteria to identify potential cases. There is no consistent hepatic safety signal based on review of the ALLY-1 cases and there were no hepatic safety signals from ALLY-2 or from the other DCV/SOF regimen trials (ALLY-3, AI444040). However, while these trials represent a relatively small database, the DCV trials safety database is relatively large with over 8000 subjects expose. This includes safety data for DCV in combination with multiple different anti-HCV drugs; and to date, there has not been a hepatic safety signal attributable to DCV, or a hepatic safety signal attributable to SOF.

Because of the identification of cases of hepatic decompensation and hepatic failure with related deaths reported with use of Viekira Pak and Technivie in patients with compensated cirrhosis (contraindicated in Child-Pugh class C patients and not recommended in decompensated cirrhosis), Warnings and Precautions language was added to the USPIs and the drugs were contraindicated for patients with Child-Pugh

class B or C cirrhosis. Because of these events, FDA has requested further inquiry into the post-market safety for all DAA regimens with regards to hepatic decompensation and hepatic failure. BMS was requested to provide a full post-market hepatic safety review focusing on cases of worsening hepatic decompensation, new onset decompensation, hepatic failure, transplant or death based on baseline liver status for those with decompensated disease, those with compensated disease and those where baseline liver status is unknown. BMS has submitted an 833 page report that explores post-market hepatic safety of DCV/SOF with and without RBV. The overall conclusion from BMS is that the hepatic benefit risk for DCV remains favorable and there is no additional need for labeling at this time. FDA post-market review of DCV/SOF with and without RBV is ongoing and is not expected to be complete by the action date of the sNDA S001-S003. However, at this time, based on full review of the available clinical trials data and a topline review of the available post-market hepatic safety review, this reviewer concurs with assessment that the hepatic benefit risk continues to be favorable for DCV/SOF with and without RBV and that no specific hepatic warning is currently indicated in the USPI.

Renal Safety

DCV is primarily metabolized by the liver. No renal toxicity was observed in animal studies. Based on results of the mass balance trial, the majority of the dose (88%) of DCV was eliminated through the fecal route with 7% eliminated renally. For DCV, approximately half of the total dose (53%) in feces was identified as daclatasvir parent drug and virtually the entire total dose in urine (6%) was identified as daclatasvir parent drug. Elimination studies determined that the majority of the sofosbuvir dose is recovered in the urine as the metabolite GS-331007. These data indicate that renal clearance is the major elimination pathway for GS-331007. Additionally, sofosbuvir is not recommended for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73m^2) or end stage renal disease due to higher exposures (up to 20-fold) of the sofosbuvir metabolite GS-331007.

Analyses of renal-related AEs and renal laboratory abnormalities were completed to examine safety trends related to DCV/SOF with or without RBV. In ALLY-2, 1 subject reported moderate drug-related acute renal failure that did not lead to discontinuation or change in DCV/SOF. In addition, 2 subjects reported reduced creatinine clearance (1 considered mild and related and 1 considered moderate and not related) and 1 subject reported increased creatinine (moderate and not related). None of these lab-related events led to dose changes or discontinuation of study drugs. In addition, chronic HIV infection is related to renal impairment and dysfunction and cART can also affect renal outcomes.

In ALLY-1, overall few renal-related AEs were reported. Two post-transplant subjects (3-27 and 3-18) reported AEs of renal failure; which were considered moderate (grade 2) in severity and treatment related. Subject 3-18 had RBV dose reduction and continued on DCV/SOF and Subject 3-27 had a RBV discontinuation due to the renal

insufficiency. Additionally, 1 cirrhotic subject (5-62) reported grade 3 azotemia which was considered not related and did not result in any dose changes for study therapy. Lastly, 1 subject (2-67) with a medical history of acute on chronic renal failure since 2003 reported an SAE of acute renal failure which was considered not drug related and lasted 5 days.

Overall, in ALLY-1 5 cirrhotic subjects (9%) and 5 post-liver transplant subjects (7%) had a decrease in creatinine clearance >25% from baseline at any time while on treatment. However, in all cases these changes were mild and transient in nature and complicated by the pre-existing comorbid conditions as well as advanced cirrhosis.

Generally, the cases of renal AEs and lab abnormalities observed in these trials did not present any renal safety signal attributable to DCV/SOF. Several subjects had reduction or discontinuation of RBV or other interventions (fluid resuscitation) that led to renal improvement while continuing on DCV/SOF treatment. Additionally, the assessment of these cases is complicated by underlying or preexisting comorbid conditions, pre-existing renal insufficiency and concomitant medications making causality assessment to DCV/SOF treatment difficult. Lastly, in the larger DCV safety database to date there has not been a renal signal identified.

However, due to the use of SOF in combination with DCV and the underlying renal metabolism of the primary metabolite of SOF, further post-marketing inquiry has been requested for cases of renal failure. The post-market assessment identified 36 cases reporting a serious, related event mapping to the High Level Terms renal failure and impairment occurring during or after exposure to DCV/SOF. Of these 36 cases, 12 were spontaneous, 1 clinical trial case (observational study), and 23 cases from solicited sources. Most cases were from France (n=19), followed by Germany and Spain (n=4 each), United Kingdom (n=3), Austria (n=2) and Italy (n=1). The regimens included DCV/SOF (n=27), DCV/SOF/RBV (n=7) and DCV/SOF/SMV (n=2).

Many of the cases (n=18) described renal impairment or renal failure at baseline. Most of the cases (n=33) described a history of cirrhosis, with 14 cases further specifying decompensated cirrhosis or a history of decompensated cirrhosis at baseline. Additional significant comorbid conditions included: hypertension (n=20), liver transplant (n=13), diabetes (n=10), HIV coinfection (n=4), kidney transplant (n=3), cryoglobulinemia with nephrotic syndrome, membranoproliferative glomerulonephropathy and pancreas transplant (n=1, each).

Review of the cases demonstrates that there are multiple factors affecting the interpretability of the reports. The patients tend to have significant comorbidities and risk factors (diabetes, hypertension, HIV, liver disease and or renal disease) that may contribute to development of renal dysfunction. The majority of cases had advanced hepatic disease and decompensations at baseline, and other plausible etiologies for the renal events, as derived from case review, are representative for patients with cirrhosis (e.g. hypovolemia-associated renal failure, association with infections, nephropathy, hepato-renal syndrome). Additionally, many of the concomitant

medications treating the comorbid conditions have risks of renal events listed within the respective product labels (e.g. HCTZ, valsartan, cyclosporine, SMP-TMX, clopidogrel, emtricitabine + tenofovir, raltegravir, mycophenolate mofetil, etc.). Additionally, use of SOF and DCV together complicates the ability to assess dechallenge and relatedness specifically to DCV because the drugs generally must be discontinued together. However, there were some cases were DCV was continued while other medications were withdrawn with event resolution (e.g. SOF, RBV, analgesics, HCTZ). The role of DCV causing renal impairment in these cases is unlikely.

Based on the nonclinical, clinical and safety data for DCV in patients with renal impairment, no potential mechanism of action for renal dysfunction related to DCV has been identified. BMS believes DCV remains safe for patients with any degree of renal impairment and does not propose label changes for renal-related events. Based on review of the nonclinical, clinical and safety data available for DCV, I agree with this assessment and believe that no specific renal warnings are indicated in the product labeling. The post-market review of renal data for DCV/SOF is ongoing and FDA will continue to assess the risk of renal safety for a DCV/SOF containing regimen.

Rash related events and Hypersensitivity/Pyrexia with eosinophilia

In ALLY-2 rash-related AEs were reported in 11 (5%) subjects; of whom 6 (3%) subjects were considered to have drug-related rash AEs. all events were grade 1 or 2, none were SAEs and none led to treatment discontinuation of DCV/SOF.

In ALLY-1 rash-related AEs were reported in 8 (7%) subjects; of which 6 (5%) were considered drug-related. All events were grade 1 and 2 and none were reported as SAEs. Rash AEs led to discontinuation of RBV alone in 2 subjects (2%); but no subjects discontinued DCV/SOF due to rash.

Overall, there were no serious rash events and subjects with rash were able to continue both DCV and SOF to complete treatment. Additionally, there were no cases consistent with hypersensitivity or any subjects in either trial who developed pyrexia with clinically significant eosinophilia. One subject in ALLY-1 developed grade 1 pyrexia at Day 80 which led to discontinuation but the event was considered not related to the study regimen by the investigator (AEs of upper respiratory tract infection and fatigue were also reported on the same day) and the subject did not have eosinophilia.

Safety Update Report

The safety update report provided updated safety information from subjects exposed to DCV/SOF with and without RBV. The following main findings were reported:

- One additional death of cerebral hemorrhage considered not related in ALLY-1 during follow up (and after the cut-off date for the safety update report).

- SAEs were reported for 1 additional subject during the follow-up period in ALLY-1, and for 7 subjects during relapse retreatment or retreatment follow-up, all considered not related to study treatment by the investigator. The SAEs were similar in nature to previously reported events and do not represent new safety findings
- One addition subject who discontinued RBV due to grade 2 anemia and continued 24-week relapse retreatment with DCV/SOF
- During relapse retreatment or retreatment follow-up in ALLY-1, 5 subjects reported Grade 3 AEs and 1 subject reported a Grade 4 event. All events were considered not related to study treatment by the investigator, with the exception of 1 event (Grade 3 hyperbilirubinemia in a subject with elevated total bilirubin at baseline and throughout the study)
- No additional Grade 3/4 laboratory abnormalities during follow-up were observed in ALLY 2. In ALLY-1, additional Grade 3/4 laboratory abnormalities were observed in 1 subject during follow-up and in 8 subjects during relapse retreatment or retreatment follow-up. In those subjects with available baseline measurements, elevations during retreatment or retreatment follow-up were generally either not emergent or were 1 grade higher than baseline

Overall, no new safety signals were identified based on review of the SUR.

9. Advisory Committee Meeting

No advisory committee meeting was held for these supplements.

10. Pediatrics

No clinical trials of DCV in pediatric subjects have been conducted to date; and therefore, the safety and efficacy of DCV has not been established in the pediatric population.

Waiver Request for Children < 3 years of age (FDA agreed)

FDA has agreed to a full waiver in children < 3 years of age (FDA correspondence October 10, 2013). The rationale for the waiver in children < 3 years of age is that chronic HCV in this age group is relatively benign and spontaneous clearance is possible (24% by age 3 years).

Pediatric Study Plans for DCV

The new indication for GT1 triggers PREA. (b) (4) an appropriate pediatric plan has been submitted which supports

the proposed PREA PMR for DCV in combination with other DAAs for treatment of chronic HCV in pediatric patients from 3 years to <18 years of age. This is the same PMR that was issued during the original NDA; however, a subsequent PMR number will be issued for tracking purposes. The PERC meeting was held on 12/9/2015, and the committee agreed with the pediatric plan and plans for issuing a PMR with the same content as the original PMR for DCV.

11. Other Relevant Regulatory Issues

Ethics and Good Clinical Practices

The Applicant certified all clinical studies included in sNDA S-001 – 003 were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with 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. The trial protocols and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board.

The FDA OSI inspected selected clinical sites, and the submitted data from the site audits are considered acceptable. Please see the OSI consult review for additional details.

The Applicant examined financial disclosure information from all clinical investigators for the clinical trial and completed FDA Form 3454 for Financial Certification. Please refer to Attachment 1 for detailed Financial Disclosure information.

Regulatory Pre-sNDA Communications and Discussions

The original NDA 206843 for daclatasvir tablets was submitted on March 31, 2014. On November 25, 2014 a Complete Response Letter was provided because of the withdrawal of the asunaprevir NDA and subsequent lack of data to support NDA 206843. A resubmission of the application occurred on February 13, 2015. The application was approved on July 24, 2015.

The following highlights the main pre-sNDA communications and discussion:

- On February 27, 2015 BMS submitted a proposal for an ALLY-1/ALLY-2 submission and requested a Type B meeting to discuss the content and format of a proposed sNDA.
- Pre-sNDA Meeting Preliminary Comments were sent to BMS on April 21, 2015
- A Type B pre-sNDA meeting was held on April 29, 2015.
- On May 11, 2015 FDA communicated their decision to modify the Breakthrough Therapy Designation (BTD) indication previously granted for GT-1 patient to a revised BTD indication, which includes patients with Child-Pugh

class B or C cirrhosis and those who develop GT-1 HCV recurrence post-liver transplant.
- On May 13, 2015 BMS response to FDA pre-sNDA Meeting Preliminary Comments were officially submitted to IND 121,165.

Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to the sNDA S001-S003.

Recommendations for Postmarket Study Requirements

A pediatric PMR, with identical content to the prior approved pediatric PMR, will be issued for administrative and tracking purposes.

12. Labeling

The following main clinical labeling issues are summarized here:

- Section 1: The indication is expanded to include DCV for use with SOF, with or without RBV for the treatment of patients with chronic HCV genotype 1 or genotype 3 infection. The Limitations of Use statement regarding lower SVR12 rate for subjects with GT3 and cirrhosis remains.
- Section 2: Section 2.1 is added indicating Testing prior to Initiation of Therapy as follows:

  2.1 Testing Prior to Initiation of Therapy

  NS5A Resistance Testing in HCV Genotype 1a Infected Patients with Cirrhosis
  Consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31, and Y93 in patients with cirrhosis who are infected with HCV genotype 1a prior to the initiation of treatment with DAKLINZA and sofosbuvir with or without ribavirin *[see Microbiology (12.4)]*.

- Section 2.2 Recommended Dosage
  - This section provides the recommended dosing for DCV containing regimens and duration based on genotype and patient population.

Table 1: Recommended Treatment Regimen and Duration for DAKLINZA in Patients with Genotype 1 or 3 HCV

	Patient Population	Treatment and Duration
Genotype 1	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child-Pugh A) cirrhosis	
	Decompensated (Child-Pugh B or C) Cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	
Genotype 3	Without cirrhosis	DAKLINZA + sofosbuvir for 12 weeks
	Compensated (Child- Pugh A) or decompensated (Child-Pugh B or C) cirrhosis	DAKLINZA + sofosbuvir + ribavirin for 12 weeks
	Post-transplant	

- Dosage recommendations states that for patients with HCV/HIV-1 coinfection, the same dosage recommendations should be followed and refers to the Drug Interactions Section for dosage recommendations for concomitant HIV-1 antiviral drugs.
- For HCV genotype 1 or 3 patients with Child-Pugh B or C cirrhosis or post-transplantation patients, the starting dose of ribavirin is 600 mg once daily, increasing up to 1000 mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance.
- For HCV genotype 3 patients with compensated cirrhosis (Child-Pugh A), the recommended dosing of ribavirin is based on weight (1000 mg for patients weighing less than 75 kg and 1200 mg for those weighing at least 75 kg) administered orally in two divided doses with food). This is based on the ALLY-3+ data and this dosing was most commonly used in the ATU and UK cohorts.

- Section 5.3 is added regarding risks associated with RBV use and refers to the RBV prescribing information for all warnings and precautions
- Section 6 adds ADR and selected laboratory information from ALLY-2 and ALLY-1 to pre-existing safety data from ALLY-3

Table 4: Adverse Reactions (All Severity) Reported at ≥5% Frequency, DAKLINZA + Sofosbuvir, Studies ALLY-3 and ALLY-2

Adverse Reaction	ALLY-3: HCV Genotype 3 n=152	ALLY-2: HCV/HIV-1 Coinfection n=153
Headache	14%	8%
Fatigue	14%	15%
Nausea	8%	9%
Diarrhea	5%	7%

Table 5: Adverse Reactions (All Severity) Reported at ≥5% Frequency in Either Treatment Cohort, DAKLINZA + Sofosbuvir + Ribavirin, Study ALLY-1

Adverse Reaction	Child-Pugh A, B, or C Cirrhosis n=60	Recurrence after Liver Transplantation n=53
Headache	12%	30%
Anemia	20%	19%
Fatigue	15%	17%
Nausea	15%	6%
Rash	8%	2%
Diarrhea	3%	6%
Insomnia	3%	6%
Dizziness	0	6%
Somnolence	5%	0

Table 6: Selected Grade 3 and 4 Laboratory Abnormalities in Clinical Trials of DAKLINZA + Sofosbuvir ± Ribavirin, Studies ALLY-3, ALLY-2, and ALLY-1

Parameter	Percent with Abnormality		
	ALLY-3: HCV Genotype 3 DAKLINZA + Sofosbuvir n=152	ALLY-2: HCV/HIV-1 Coinfection DAKLINZA + Sofosbuvir n=153	ALLY-1: Child-Pugh A, B, or C with Cirrhosis and Post-transplant DAKLINZA + Sofosbuvir + Ribavirin n=113
Hemoglobin (≤8.9 g/dL)	0	0	6%
Alanine aminotransferase (ALT) increased (≥5.1 × ULN)	0	0	2%
Aspartate aminotransferase (AST) increased (≥5.1 × ULN)	0	0	3%
Total bilirubin increased (≥2.6 × ULN)	0	5%[a]	8%
Lipase increased (≥3.1 × ULN)	2%	4%	4%

[a] In the ALLY-2 trial, Grade 3 and 4 increases in total bilirubin were observed only in subjects receiving concomitant atazanavir.

- Section 7.3: statement added to refer to Section 4 Contraindication and Section 12.3 Pharmacokinetics for complete assessment of all drug interaction information.
- Section 14:
  - Outcome table for ALLY-3 will no longer display data by Treatment-Naïve and Treatment-Experienced cohorts but will give only the overall

totals. A statement that SVR rates were comparable regardless of baseline treatment-history is added to the text preceding the table. Clinical trials data from ALLY-2 and ALLY-1 are added to section 14 including outcome tables as follows:

- ALLY-2 [DCV/SOF for 12 weeks]
  - Statement added that available data on subjects with HCV genotype 2, 4, 5, or 6 infection are insufficient to provide recommendations for these genotypes; therefore, these results are not presented in the outcome table.
  - Statement added that SVR12 rates were comparable regardless of antiretroviral therapy, HCV treatment-history, age, race, gender, IL28B allele status, or baseline HCV RNA level. For SVR outcomes related to baseline NS5A amino acid polymorphisms, see Microbiology 12.4.
  - Statement added that no subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. There was no change in absolute CD4+ T-cell counts at the end of 12 weeks of treatment.
  - Statement added that all 10 subjects with HCV GT3 achieved SVR12

Table 14: ALLY-2: SVR12 in Subjects with Genotype 1 and 3 HCV/HIV Coinfection Treated with DAKLINZA in Combination with Sofosbuvir for 12 Weeks

Treatment Outcomes	Total n=137
SVR12	
Genotype 1	97% (123/127)
No cirrhosis[a]	98% (103/105)
With cirrhosis	91% (20/22)
Genotype 3[b]	100% (10/10)
Outcomes for genotype 1 subjects without SVR12	
On-treatment virologic failure[c]	0.8% (1/127)
Relapse[d]	1.6% (2/126)
Missing post-treatment data	0.8% (1/126)

[a] Includes 5 subjects with inconclusive cirrhosis status.
[b] One subject with cirrhosis.
[c] One subject had detectable HCV RNA at end of treatment.
[d] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at the end of treatment.

- ALLY-1 [DCV/SOF/RBV for 12 weeks]
  - Statement added regarding RBV dosing: Subjects received an initial ribavirin dose of 600 mg daily with food; baseline and on-treatment dosing of ribavirin was modified based on hemoglobin and creatinine clearance measurements. If tolerated, the ribavirin dose was titrated up to 1,000 mg per day

- Description of RBV dosing in the trial as follows: A high proportion of reductions in RBV dosing occurred in the trial. By Week 6, approximately half of the subjects received 400 mg or less of RBV In total, 16 subjects (15%) completed less than 12 weeks and 11 subjects (10%) completed less than 6 weeks of RBV therapy, respectively. For the cohort of patients with cirrhosis (Child-Pugh A, B or C), the median time to discontinuation of ribavirin was 43 days (range, 8-82). For the post-transplant cohort, median time to discontinuation of ribavirin was 20 days (range, 3-57).
- Statement added that available data on subjects with HCV genotype 2, 4, 5, or 6 infection are insufficient to provide recommendations; therefore, these results are not presented in the outcomes table.
- Statement added that SVR12 rates were comparable regardless of age, gender, IL28B allele status, or baseline HCV RNA level.
- Statement added that no HCV genotype 1 subjects with Child-Pugh Class C cirrhosis had baseline NS5A amino acid polymorphisms.
- Statement added that SVR12 rates were comparable between genotype 3 (5/6 with Child-Pugh B or C cirrhosis and 10/11 post-liver transplant) and genotype 1 subjects with or without decompensated cirrhosis.

Table 15: ALLY-1: SVR12 in Genotype 1 Subjects with Child-Pugh A, B, or C Cirrhosis or with HCV Genotype 1 Recurrence after Liver Transplantation Treated with DAKLINZA in Combination with Sofosbuvir and Ribavirin for 12 Weeks

Treatment Outcomes	Child-Pugh A, B, or C Cirrhosis n=45	Post-Liver Transplant n=41
SVR12		
Genotype 1	82% (37/45)	95% (39/41)
Child-Pugh A	91% (10/11)	-
Child-Pugh B	92% (22/24)	-
Child-Pugh C	50% (5/10)	
Genotype 1a	76% (26/34)	97% (30/31)
Genotype 1b	100% (11/11)	90% (9/10)
Outcomes for subjects without SVR12		
On-treatment virologic failure	2% (1/45)[a]	0
Relapse[b]	16% (7/44)	5% (2/41)

[a] One subject had detectable HCV RNA at end of treatment.

[b] Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at end of treatment.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval of this application is recommended based on the clinical review of available data. The data submitted from ALLY-1 and ALLY-2 supports the use of DCV in combination with SOF with and without RBV for 12 weeks for the treatment of chronic hepatitis C genotype 1, including for subjects with HCV/HIV coinfection, those with

Child-Pugh class A compensated cirrhosis and Child-Pugh Class B decompensated cirrhosis and those with recurrence of HCV genotype 1 post-transplantation. Data from ALLY-2 and ALLY-1 also supports the dosage recommendation of DCV/SOF± RBV for 12 weeks for treatment of HCV genotype 3 HCV/HIV coinfected subjects.

Benefit Risk Assessment
The overall benefit risk assessment is favorable for DCV/SOF with and without RBV based upon the demonstrated efficacy results and observed safety profile of DCV. Additionally, DCV/SOF/RBV for 12 weeks will be the first approved treatment regimen for HCV GT1 patients with decompensated cirrhosis, a subpopulation of HCV patients in need of treatment options.

Benefit Risk assessment for DCV/SOF 12 week regimen

Data from ALLY-2 support the use of DCV/SOF for 12 weeks in HCV genotype 1 patients without cirrhosis and those with Child-Pugh A cirrhosis. The overall SVR12 rate for HCV genotype 1 was 97% (123/127), with 96% (100/104) of HCV GT1a subjects achieving SVR12 and 100% (23/23) of HCV GT1b subjects achieving SVR12. Subjects with compensated cirrhosis achieved a SVR12 rate of 91% (20/22). Two subjects experienced virologic relapse, both of whom had HCV GT1a and cirrhosis. Minimal numbers of subjects with HCV GT1b had cirrhosis. All 13 subjects with prior treatment experience (10 boceprevir or telaprevir + pegIFN/RBV, 3 SOF/RBV) achieved SVR12.

ALLY-2 enrolled 10 subjects with GT-3 HCV; all achieved SVR12 (10/10, 100% 95% CI (69%, 100%)). DCV in combination with SOF is currently indicated for treatment of HCV GT-3; because HCV/HIV coinfected subjects have had comparable response rates to monoinfected subjects across multiple DAA development programs the data in coinfected subjects can support monoinfected populations and vice versa. Therefore, SVR12 data from ALLY-2 also supports use of DCV/SOF for treatment of GT-3 HCV/HIV coinfected patients.

Baseline resistance associated NS5A polymorphisms are associated with lower SVR12 rates in subjects with HCV genotype1a and cirrhosis. Prior to initiating therapy with DCV/SOF, clinicians should consider screening for the presence of NS5A polymorphisms at amino acid positions M28, Q30, L31 and Y93. Clinicians can use this information to make the most informed treatment decision for each individual patient.

Generally, DCV/SOF is well tolerated. In ALLY-2, 69% of subjects reported an on-treatment AEs of any grade. Most AEs were mild or moderate in severity and none led to treatment discontinuation. The most common ADRs (≥5%) for the 12 week duration arms were headache (9%; 13/153), fatigue (15%; 23/153), nausea (9%; 14/153), and diarrhea (7%; 10/153). There were no on-treatment deaths and no SAEs considered related to study treatment. Treatment emergent laboratory

abnormalities were generally grade 1 or 2 and did not lead to treatment interruption or discontinuation, or medical intervention. No unexpected safety signals were observed in this trial.

DCV is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of DCV. Strong inhibitors of CYP3A may increase the plasma levels of DCV. Dose adjustment of DCV to 90 mg or 30 mg once daily is recommended for moderate or strong CYP3A inducers or strong inhibitors, respectively. DCV can affect other drugs because it is an inhibitor of P-gp, OATP 1B1 and 1B3 and breast cancer resistance protein (BCRP). DCV may increase systemic exposure to drugs that are substrates of P-gp, OATP 1B1 and 1B3 or BCRP which could increase or prolong their therapeutic effect or adverse reactions. The prescribing information provides clinical recommendations for established or potentially significant drug interactions between DCV and other drugs. Dose adjustments for commonly prescribed antiretrovirals are provided in the product labeling.

In summary, the efficacy and safety data from ALLY-2 supports a positive benefit risk assessment for the regimen. DCV/SOF for a 12 week duration treatment is well tolerated with manageable adverse reactions and drug-drug interaction profile. This regimen provides another once daily oral DAA therapeutic option for patients infected with HCV genotype 1, including those with HIV co-infection and those with compensated Child-Pugh A cirrhosis.

Benefit Risk assessment for DCV/SOF/RBV 12 week regimen

Data submitted for support of the sNDA for the DCV/SOF/RBV regimen comes from the ALLY-1 trial which enrolled subjects with Child-Pugh class A, B or C cirrhosis with baseline MELD scores ≥8 and those with HCV recurrence after liver transplant. The efficacy data from ALLY-1 supports an indication for treatment of HCV GT1 patients with decompensated cirrhosis Child-Pugh class B or C, or HCV GT1 post- transplant patients. The overall SVR12 rate in HCV GT1 subjects from ALLY-1 was 88% (76/86) with 95% CI (79.7%, 94.3%). Consistent with findings in other DAA programs, the pre-transplant cirrhotic subjects had a lower overall SVR12 rate of 82% (37/45; 95%CI (68%, 92%)) compared to the post-transplant cohort SVR12 rate of 95% (39/41; 95%CI (83.5%, 99.4%)). Additionally, subjects with HCV genotype 1a achieved a lower SVR12 rate of 77% (26/34), compared to the small group of HCV genotype 1b subjects who all achieved SVR12 (11/11; 100%). SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B status or baseline HCV RNA level.

In total there were 16 subjects with Child-Pugh class C designation at enrollment; however, only 10 of these subjects were HCV genotype 1 (9 were genotype 1a and 1 genotype 1b). The SVR12 rate for these 10 subjects was 50% (5/10) with 95% CI (18.7%, 81.3%). Based on the available limited data, the review team could not

determine an optimal regimen and duration of DCV/SOF/RBV for treatment of HCV genotype 1 Child-Pugh class C cirrhotic patients. However, the ALLY-1 data provides evidence of efficacy in this advanced, decompensated patient population without currently approved therapeutic options. Efficacy is also demonstrated in the Child-Pugh class B subjects with HCV GT1; the SVR12 rate was 92% (22/24). Based on the totality of data in subjects with decompensated cirrhosis, DCV/SOF/RBV provides an effective treatment option for patients without any currently approved therapy. It is important to note that none of the Child-Pugh class C subjects had baseline NS5A resistance associated polymorphisms; and therefore, it remains unknown what impact pre-screening for NS5A baseline polymorphisms in this more advanced decompensated cirrhotic subgroup will have. The high failure rate in this limited subgroup may be a result of other baseline or host disease factors, including the advanced stage of liver disease.

The collective data from ALLY-1, ALLY-3, ALLY-3+ and the EAPs provides evidence for 12 weeks of DCV/SOF/RBV for treatment of subjects with HCV GT-3 and compensated cirrhosis (Child-Pugh class A), decompensated cirrhosis (Child-Pugh class B or C) and for those with recurrence post-liver transplant. The overall SVR12 rate for subjects with HCV GT3 in ALLY-1 was 86% (5/6) for those with decompensated cirrhosis and 91% (10/11) for those post-transplant. A comparable SVR12 rate of 86% (37/42) was observed in ALLY-3+ and in the EAPs in subjects with HCV GT3 and compensated cirrhosis; similarly, the SVR rate was 68% (59/87) in HCV GT3 subjects with decompensated cirrhosis treated in the UK cohort. These data, along with the knowledge that cirrhosis is an independent baseline risk factor for a higher chance of virologic failure, supports the decision to add RBV to the regimen for the HCV GT3 subjects with compensated Child-Pugh A cirrhosis. These data also supports extension of the indication to include treatment of HCV GT3 patients with decompensated cirrhosis and those with recurrence post-liver transplant.

A PMR to evaluate a 24 week duration of DCV/SOF in HCV GT3 subjects with cirrhosis was issued with the original approval. The optimal regimen and duration for treatment of HCV GT3 subjects with cirrhosis has not yet been determined; therefore, the Limitations of Use statement which states that SVR rates are reduced in HCV GT3 subjects receiving DCV/SOF for 12 weeks will remain in the label.

The baseline resistance associated NS5A polymorphisms and consideration for pre-treatment screening for HCV genotypes 1a with cirrhosis for the DCV/SOF/RBV regimen. Likewise, the drug-drug interactions and dose adjustments for DCV are the same for the DCV/SOF/RBV regimen.

The DCV/SOF/RBV regimen was well tolerated in the advanced cirrhotic cohort and post-transplant subjects in ALLY-1. The most common ADRs (10% or greater) were headache, anemia, fatigue and nausea. The majority of ADRs were mild to moderate in severity. Fifteen (13%) subjects experienced an SAE; all were considered unrelated to treatment. Of the 15 (13%) subjects who discontinued study drugs due to adverse events, 13 (12%) subjects discontinued RBV only and 2 (2%) subjects

discontinued all study drugs. There were no on-treatment deaths. Rash occurred infrequently overall with 6 (5%) subjects reporting a rash-related ADR. Review of hepatic safety data did not reveal any new liver-related safety signals for DCV.

The most frequently reported grade 3 or 4 treatment-emergent laboratory abnormalities were decreased hemoglobin (6%), increases in ALT (2%), AST (3%), total bilirubin (8%) or lipase (4%). Compared to the DCV/SOF regimen without RBV, there were more clinically significant events of decreased hemoglobin and elevated total bilirubin resulting from RBV-induced hemolysis. However, the frequency of decreases in hemoglobin to 8.5-9.0 g/dL were comparable (11%; 12/113) in ALLY-1 to those observed in pegIFN/RBV trials (11%; ribasphere tablets package insert). However, the frequency of Hb < 8.5 g/cL was higher in ALLY-1 at 7% (8/113) compared to pegIFN/RBV trials (2%; ribasphere tablets package insert); likely reflecting the advanced cirrhotic population enrolled in ALLY-1 who were excluded from the pegIFN/RBV pivotal trials.

RBV dosing, dose reduction and early discontinuation related to anemia or rash may have impacted SVR rates, particularly in the more advance Child-Pugh C group. However, data from ALLY-1 are limited and confounded by the variability of the tailored RBV dosing schedules and lack of comparator in both the advanced cirrhosis cohort and the post-transplant cohort. The ability to draw definitive conclusion is limited. Regardless, RBV dosing recommendation will be for 600 mg once daily with food, increasing up to 1,000 mg daily as tolerated. The starting dose and on-treatment dose of ribavirin can be decreased based on hemoglobin and creatinine clearance.

The efficacy data and safety profile of DCV/SOF/RBV presented above support the indications for treatment of HCV genotype 1 patients with decompensated Child-Pugh B or C cirrhosis, HCV genotype 1 patients who have recurrence post-liver transplant, genotype 3 patients with Child-Pugh A, B or C cirrhosis and HCV GT3 post-transplant. Currently, there are no approved DAA regimens for treatment of patients with HCV GT1 or GT3 decompensated cirrhosis Child-Pugh class B or C. DCV/SOF/RBV provides a therapeutic option for once daily all oral treatment for these patient populations with an unmet medical need. Additionally, DCV/SOF/RBV provides another therapeutic option for HCV genotype 1 patients who have recurrence post-transplant and for those with HCV genotype 3 with and without cirrhosis (Child-Pugh A, B and C).

In conclusion, the benefit-risk assessment for DCV in combination with SOF, with and without RBV is positive and supported by the totality of the data. DCV has been well tolerated, even in the more advanced population of patients who have decompensated cirrhosis or are post-liver transplant. Discontinuations of DCV/SOF are infrequent and RBV has been tolerated by the more advanced population; albeit at lower doses in ALLY-1. DCV/SOF with or without RBV provides another once daily oral treatment option for patients with HCV GT1 and GT3.

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Clinical Investigator Financial Disclosure
Review Template

Application Number: 206843

Submission Date(s): 8/05/2015

Applicant: Bristol Myers Squibb Company

Product: Daclatasvir

Reviewer: Wendy Carter, D.O.

Date of Review: 8/27/2015

Covered Clinical Study (Name and/or Number): AI444215, AI444216, AI444043, AI444064, AI444093, AI444273

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 812 unique individuals served as either PIs or Sub-Is in the covered studies		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: *1; One investigator for AI444043 received $1,600.00 in compensation on a BMS Advisory Board and while this amount does not exceed the 25,000 category, it was reported due to his institutions* (b) (6) *requirement that any interaction regardless of compensation amount be recorded. Additionally, while this investigator did have an* (b) (6) Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: *1; One investigator in AI444216 held $100,000 of common stock in BMS. This investigator enrolled* (b) (6) *in the trial.*		
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) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

BMS has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21CFR Part 54. The Applicant provided certification (Form 3454) which indicates that the vast majority of investigators and sub-investigators who participated in BMS studies had no financial arrangements with the Applicant. There were two investigators who had disclosable information, (b) (6) Based on the low proportion of investigators with a financial interest and the objective nature of the pivotal and supportive trial designs (open label, same regimens, with central laboratory HCV RNA PCR based efficacy endpoints), the likelihood that trial results were substantively biased based on financial interest is minimal.

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

/s/

WENDY W CARTER
01/27/2016

KIMBERLY A STRUBLE
01/27/2016