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APPLICATION NUMBER:

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SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	January 26, 2016
From	Kimberly Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	206843 S01-03
Applicant	Bristol Myers Squibb
Date of Submission	August 5, 2015
PDUFA Goal Date	February 5, 2015
Proprietary Name / Established (USAN) names	Daklinza (daclatasvir, DCV)
Dosage forms / Strength	30 mg and 60 mg tablets
Proposed Indication(s)	Chronic hepatitis C virus (HCV) genotype (GT) 1, including HCV/HIV-1 co-infection and HCV decompensated cirrhotics and post-transplant population
Recommended:	Approval

1. Introduction

This Cross-Discipline Team Leader review presents the main findings for NDA supplements 001 through 003 to expand labeling of daclatasvir/sofosbuvir (DVC/SOF) to the following subpopulations with the supporting trial data:

- S-001: Post liver transplant patients (ALLY-1)
- S-002: Patients with HCV/HIV-1 co-infection (ALLY-2)
- S-003: Patients with decompensated cirrhosis – Childs-Pugh class A, B and C cirrhosis (ALLY-1)

The data from the two main trials ALLY-1 and ALLY-2 are predominately from subjects with HCV genotype 1 infection. Insufficient data were available for other genotypes (2, 4, 5 and 6) and therefore were not included in labeling or discussed in detail in this review. Please refer to section 7 for further details.

DCV is an inhibitor of NS5A, a nonstructural protein encoded by HCV. DCV binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. DCV was approved on July 24, 2015 for use in combination with SOF for the treatment of HCV genotype 3 infection.

Sofosbuvir (SOF) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. SOF was approved on December 6, 2013, as part of a combination regimen for the treatment of chronic HCV genotype 1, 2, 3, and 4 infection and is the only nucleotide NS5B inhibitor approved. SOF is also a

component of Harvoni (ledipasvir/sofosbuvir) for the treatment of HCV genotype 1, 4, 5, and 6 infection.

Additionally, four Phase 1 drug-drug interaction trials were submitted to support updates to the label regarding DCV coadministration with buprenorphine/naloxone, darunavir/ritonavir, dolutegravir, or lopinavir/ritonavir and various in vitro reports, including evaluating daclatasvir as an OCT1 substrate.

This review highlights the safety and efficacy, virology, and clinical pharmacology findings and overall benefit/risk assessment to support my recommendation for approval of supplemental NDAs 001 through 003.

2. Background

Chronic HCV infection is a serious and life-threatening condition and can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV infection is a global health problem with an estimated 170 million individuals infected worldwide. In the United States, approximately 3 to 5 million people have chronic HCV infection (http://www.epidemic.org/theFacts/theEpidemic/worldPrevalence/).

The majority of cases of chronic HCV infection in the United States (U.S.) are HCV genotype 1 (70-75%, predominately genotype 1a). Approximately 20% are infected with HCV genotypes 2 or 3, approximately 5% with HCV genotype 4, and less than 1% with HCV genotypes 5 or 6.

The treatment of HCV infection has rapidly evolved since the approval of the first direct acting agents (DAAs) in 2011, boceprevir and telaprevir, both NS3/4A protease inhibitors, followed by the approvals of simeprevir (NS3/4A protease inhibitor) and sofosbuvir in 2013. However, these regimens require the use of pegylated interferon and ribavirin (RBV) for the treatment for HCV genotype 1 infection. Since 2013 several other interferon-free DAA regimens were approved for genotypes 1-6, many of which offer SVR12 rates in excess of 90% and include simeprevir+SOF, ledipasvir/SOF (Harvoni), ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak), and DCV/SOF.

HCV co-infection is found in approximately 30% of HIV infected patients in the U.S. The presence of HIV has been shown to accelerate the natural history of HCV infection, even in patients with well controlled HIV infection while receiving antiretroviral (ARV) 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 HCV/HIV-1 co-infected patients is associated with a reduction in mortality and liver-related events. Viekira Pak, Harvoni, simeprevir+pegylated interferon/RBV and SOF+pegylated interferon/RBV all contain dosage recommendations for HCV/HIV-1 co-infected patients with HCV genotype 1 or 4 infection. SOF+RBV regimen has

labeled dosing recommendations for HCV/HIV-1 infected patients with HCV genotype 2 or 3 infection.

Currently, no approved regimens are available for treatment of HCV infected patients with decompensated cirrhosis (Child-Pugh class B or C cirrhosis) and only limited approved options exist for post-liver transplant patients. SOF+RBV is approved for those awaiting liver transplant and Viekira Pak is approved in HCV genotype 1 post-liver transplant patients who have normal hepatic function and mild fibrosis (Metavir Fibrosis score $\leq$ 2). Viekira Pak is contraindicated for Child-Pugh class B or C cirrhotics and the other NS3/4A protease inhibitors are either contraindicated or not recommended for use in Child-Pugh class B or C. DCV/SOF/RBV is the first regimen submitted for approval in subjects with decompensated cirrhosis and therefore received a priority review.

The regulatory history is notable for receiving Fast Track designation on September 8, 2008 and for receiving Breakthrough Therapy Designation (BTD) on April 8, 2014 for HCV genotype 1 patients. On May 11, 2015, the Division communicated the decision to modify the BTD to patients with Child-Pugh class B or C and those who develop genotype 1 HCV recurrence post-liver transplant.

3. CMC/Device

No new CMC data were submitted.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted. PLLR updates to the reproductive toxicology data were made to section 8 of the product labeling. Please refer to Dr. Myers' review for further details.

5. Clinical Pharmacology

Four drug-drug interaction trials evaluating concomitant use of DCV with buprenorphine/naloxone, darunavir/ritonavir, dolutegravir, or lopinavir/ritonavir and various in vitro reports, including evaluating daclatasvir as an OCT1 substrate, were submitted. Please refer to the Clinical Pharmacology review by Dr. Stanley Au for complete details. The main conclusions of the trials are summarized below.

- DCV is not an OCT1 substrate
- No clinically relevant changes in either darunavir, lopinavir or DCV exposures were observed; therefore no dosage adjustment of these drugs is needed.
- No clinically relevant changes in either DCV or dolutegravir exposures; therefore no dosage adjustment is needed.
- Increases in buprenorphine and norbuprenorphine are noted in the presence of DCV; however, no dosage adjustment is needed. Clinical monitoring for buprenorphine associated adverse events is recommended.

6. Clinical Microbiology

Please refer to Dr. Lalji Mishira's assessment of the nonclinical virology data. For further details regarding the resistance analyses from the submitted trials please refer to Dr. Patrick Harrington's review.

The major Clinical Virology issues are: 1) the development of resistance mutations in patients who fail to achieve SVR12, primarily due to relapse, and how resistance emergence can affect the response of subsequent regimens using drugs of the same class and 2) the effect of baseline HCV amino acid polymorphisms on SVR12.

In ALLY-1 and ALLY-2, resistance analyses of both drug targets (NS5A and NS5B) were conducted for subjects who experienced virologic failure and had sequence data available. Among the HCV genotype 1a subjects who received DCV/SOF±RBV for 12 weeks and experienced virologic failure, 82% (9/11) developed a DCV resistance-associated substitution in NS5A. Treatment-emergent substitutions most frequently occurred at position Q30. The following treatment-emergent NS5A substitutions were observed: M28T (18%), Q30E/H/K/R (73%), L31M/V (18%), H54R (9%), H58D (9%) and Y93C/N (18%). The two subjects without treatment-emergent NS5A substitutions had resistance-associated polymorphisms at baseline, and thus 100% of GT1a virologic failure subjects had an NS5A resistance-associated substitutions or polymorphisms at the time of virologic failure.

Five of 10 HCV genotype 1a virologic failure subjects with available data who received DCV/SOF±RBV for 12 weeks had treatment emergent substitutions at NS5B positions potentially associated with SOF resistance. One HCV genotype 1b virologic failure subject who received DCV/SOF/RBV for 12 weeks had a treatment-emergent deletion at NS5A position P32 (P32del) and no NS5B substitutions of concern.

Of the 3 HCV genotype 3 virologic failure subjects across the ALLY-1 and ALLY-2 trials, 2 subjects had virus with treatment-emergent NS5A Y93H, consistent with results from the previously reviewed ALLY-3 trial. Complete sequence data were not available to assess NS5B resistance.

Pertinent results from Dr. Harrington's review regarding the impact of baseline polymorphisms are summarized in section 7 below.

7. Clinical/Statistical- Efficacy

This section summarizes the efficacy analyses conducted by the review team for the two main clinical trials (ALLY-1 and ALLY-2) submitted for review in support of label changes. Please refer to reviews by Dr. Wendy Carter (clinical), Wen Zeng (statistical) and Patrick Harrington (virology) for full details and discussion of efficacy. Each reviewer recommended approval for sNDA 001 through 003.

ALLY-1 and ALLY-2 were open-label, uncontrolled trials. Please refer to Table 1 below for a summary of the clinical trial designs. In both trials, HCV RNA values were measured during these clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL. Sustained virologic response was the primary endpoint for ALLY-1 and ALLY-2 and was defined as HCV RNA below the LLOQ at post-treatment week 12 (SVR12). SVR12 is the currently recommended primary endpoint in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013. SVR (HCV RNA < LLOQ at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a cure for hepatitis C infection; and recent studies have shown that achievement of SVR is associated with halting the progression of liver disease and decreasing the frequency of chronic hepatitis C complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality.

Subjects with cirrhosis were permitted to enroll in the trials. The method for determining cirrhosis (liver biopsy, Fibroscan and FibroTest +APRI) was acceptable. Please refer to the clinical review for details regarding assessment of cirrhosis status for each trial.

ALLY-1 was designed to demonstrate that the proportion of subjects achieving SVR12 in the Cirrhotic cohort (Child-Pugh A, B or C cirrhosis) is higher than the composite historical threshold. Specifically, the lower bound of the two-sided 95% CI of the SVR12 rate for DCV/SOF/RBV was to exceed 41.6% to conclude that 12 weeks of DCV/SOF/RBV is efficacious in patients with Child-Pugh A, B or C cirrhosis. Similarly, the lower bound of the two-sided 95% CI of the SVR12 rate for DCV/SOF/RBV was to exceed 30% to conclude that 12 weeks of DCV/SOF/RBV is efficacious in post-transplant subjects. The thresholds defined for the two trial cohorts are reasonable based on the assumptions provided. Please refer to the statistical review for the justification of the historical control rates selected.

ALLY-2 was designed to demonstrate that the proportion of HCV/HIV-1 co-infected subjects achieving SVR12 with DCV/SOF for 12 weeks is higher than the historical threshold achieved by pegylated interferon/RBV from the APRICOT trial (the standard when the trial was designed) and was estimated at 29%. The lower bound of the two-sided 95% CI of the SVR12 rate for DCV/SOF was to exceed 30% to conclude that 12 weeks of DCV/SOF is efficacious in HCV/HIV-1 co-infected subjects. Since ALLY-2 was designed several genotype 1 HCV/HIV-1 co-infected trial results became available. By today's standards a 30% threshold is low and many DAA regimens exceed SVR12 rates of 90%. Despite this low hurdle to define efficacy as defined in the protocol, DCV/SOF for 12 weeks far exceeded this threshold and the results are further described in detail below.

Table 1: Summary of Trial Designs

Trial	Population	GT	Treatment	# subjects	Control	Historical SVR Threshold Rate
ALLY-1	TN and TE with or without cirrhosis including decompensated cirrhosis and post-transplant	1-6	DCV/SOF/RBV for 12 weeks	113	None	41.6% cirrhotic cohort 30% post-transplant
ALLY-2	TN and TE with or without cirrhosis HCV/HIV-1 co-infection	1-6	DCV/SOF for 8 or 12 weeks	203	None	29%

TN=treatment-naïve, TE=treatment experienced

Results

ALLY-2:

ALLY-2 is an open-label trial in 203 subjects to evaluate DCV/SOF for 8 or 12 weeks in HCV treatment-naïve subjects with HIV-1 co-infection. Subjects were randomized 2:1 to receive DCV/SOF for either 8 or 12 weeks and were stratified by cirrhosis status and HCV genotype. Subjects who are HCV treatment-experienced with HIV-1 co-infection were assigned to 12 weeks of DCV/SOF. The DCV dose was 60 mg; however, dose adjustments (30 mg or 90 mg once daily) were made for strong CYP3A inhibitors or inducers, respectively. Treatment-experience with interferon, RBV NS3/4A protease inhibitors and SOF was permitted; however, previous exposure to NS5A inhibitor was prohibited. Subjects with compensated cirrhosis were eligible to enroll. The majority of subjects enrolled had HCV genotype 1 infection (83%). Ninety-eight percent were on concomitant HIV ARV treatment. No subjects had HCV genotype 5 or 6. Nine percent had HCV genotype 2 infection, 6% had HCV genotype 3 infection and 2% has HCV genotype 4 infection. Insufficient data are available for HCV genotypes 2, 4, 5 and 6 and therefore an indication was not extended to these HCV genotypes.

The overall SVR12 rates for HCV genotype 1 and 3 infected subjects are summarized below in Table 2. The SVR12 rates were reduced in the 8-week treatment group (76%) compared to the 12 week treatment groups (97%). Therefore, BMS did not propose this duration for labeling, and this arm is not further discussed in this review. The data clearly demonstrate the efficacy of DCV/SOF for 12 weeks in HCV/HIV-1 co-infected genotype 1 subjects. The SVR12 rate was 97% and the lower bound of the

95% CI (92%) far exceeded the historical control rate of 29%. The SVR12 rate for DCV/SOF is comparable to the SVR12 rates following 12 weeks of Harvoni treatment in HCV genotype 1 mono-infected and co-infected patients (96-99%).

Table 2: Outcome Results for HCV Genotype 1 and 3 Subjects Co-infected with HIV-1 Who Received 12 Week Duration in ALLY-2

	Treatment-Naïve DCV/SOF 12 W	Treatment-Exp DCV/SOF 12 W	Total N=127 (%)
Overall GT-1 (n/N)	80*/83 (96%) 95% CI (89.8%, 99.3%)	43/44 (98%) 95% CI (88%, 100%)	123/127 (97%) 95% CI (92.1%, 99.1%)
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%)
Genotype 3	6/6 (100%)	4/4 (100%)	10/10 (100%) 95% CI (69%, 100%)

*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, Clinical and Virology Review

Two subjects experienced virologic relapse, both of whom had HCV genotype 1a and cirrhosis. Notably a minimal number of subjects with HCV genotype 1b (2) or HCV genotype 3 (1) had cirrhosis. SVR12 rates were lower (91%) in HCV genotype 1 subjects with cirrhosis compared to HCV genotype 1 subjects without cirrhosis (98%); of note the overall number of subjects with cirrhosis is low (22). The impact of cirrhosis and baseline NS5A resistance associated polymorphisms, in particular for patients with HCV genotype 1a and cirrhosis is further discussed below.

SVR12 rates were comparable regardless of ARV therapy, HCV treatment-history, age, race, gender, IL28B allele status, or baseline HCV RNA level.

No subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. No change in absolute CD4+ T-cell counts at the end of 12 weeks of treatment was observed.

Despite the limited number of HCV genotype 3 subjects in ALLY-2, dosage recommendations were extended to HCV genotype 3 subjects co-infected with HIV-1. Because DCV/SOF is already approved in HCV genotype 3 subjects, and given the knowledge that the SVR12 rates in HCV/HIV-1 co-infected subjects receiving all oral HCV regimens is similar to HCV monoinfected subjects; the recommendation for genotype 3 HCV/HIV-1 coinfection is to follow dosage recommendations for HCV genotype 3 monoinfected patients. This is consistent with the rationale for dosage recommendations contained in the Harvoni and Viekira Pak package inserts for HCV/HIV-1 co-infected patients.

ALLY-1:

ALLY-1, is an open-label trial to evaluate DCV/SOF/RBV for 12 weeks in 113 HCV infected subjects: 60 cirrhotic subjects with Child-Pugh class A, B, or C cirrhosis (Cirrhotic cohort) and 53 subjects who were post-liver transplant. Please refer to the Clinical Review for a description of the protocol-defined methods to determine presence or absence of cirrhosis and cirrhosis classification.

Treatment-experience with interferon, RBV, NS3/4A protease inhibitors and SOF was permitted; however, previous exposure to an NS5A inhibitor was prohibited. Subjects received an initial RBV dose of 600 mg daily with food; baseline and on-treatment dosing of RBV was modified based on hemoglobin and creatinine clearance measurements. If tolerated, the RBV dose was titrated up to 1,000 mg per day; however; few subjects (3.5%; n=4) in ALLY-1 had RBV dosing increased and maintained above 600 mg. Subjects who relapsed during follow-up were retreated with DCV/SOF/RBV for 24 weeks. The complete SVR12 data on these subjects were not provided and therefore, are not sufficient to provide retreatment dosage recommendations and are not discussed in labeling or this review.

Baseline demographic and characteristics were similar between the cirrhotic and post-transplant cohorts and are consistent with their advanced stage of disease. Subjects with HCV genotype 1-6 were eligible to enroll; however, no subjects with HCV genotype 5 infection were enrolled. The majority of subjects had HCV genotype 1 infection (n=86; 76%);smaller proportions had HCV genotype 2 (n=5; 4%), 3 (n=17; 15%), 4 (n=4; 4%) and 6 (n=1;1%) infection. 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 this review.

HCV Genotype 1

The key efficacy findings from ALLY-1 for subjects with HCV genotype 1 are summarized in Table 3 below. Overall, the SVR12 rate in subjects with genotype 1 was 88%. SVR12 rates were comparable regardless of HCV treatment history, age, gender, IL28B allele status, or baseline HCV RNA level. The pre-transplant cirrhotic genotype 1 cohort had a lower overall SVR12 rate (37/45; 82% [95% CI (68.0%, 92.0%)) compared to the post-transplant cohort (39/41; 95% [95% CI 83.6%, 99.4%)). Additionally, subjects with HCV genotype 1a in the Cirrhotic cohort achieved a lower SVR12 rate (26/34; 76%), compared to the small group of HCV genotype 1b subjects who all achieved SVR12 (11/11; 100%).

Table 3: SVR12 and Virologic Failure Results for HCV Genotype 1 and 3 in ALLY-1

	Cirrhotic	Post-transplant	Total
All GT-1	**37/45 (82%)**	**39/41 (95%)**	**76/84 (88%)**
GT 1a-SVR12	**26/34 (76%)**	**30/31 (97%)**	**56/65 (86%)**
On-Tx Failure	1/34 (3%)	0/31 (0%)	1/65 (2%)
Relapse	7/33 (21%)	1/31 (3%)	8/64 (13%)
GT 1b-SVR12	**11/11 (100%)**	**9/10 (90%)**	**20/21 (95%)**
Relapse	0/11	1/10 (10%)	1/21 (5%)
GT 3-SVR12	**5/6 (83%)**	**10/11 (91%)**	**15/17 (88%)**
Relapse	1/6 (17%)	1/11 (9%)	2/17 (12%)

Source: Adapted from Analysis by Dr. Patrick Harrington and Wen Zeng

The SVR12 results by Child-Pugh category are presented in Table 4 below. Notably, SVR12 rates were lower in subjects with HCV genotype 1 and Child-Pugh C cirrhosis (5/10; 50%) compared to subjects with HCV genotype 1 and Child-Pugh A or B cirrhosis (32/35; 91%). Therefore, the label includes a statement about the reduced SVR12 rates in HCV genotype 1 subjects with Child-Pugh C cirrhosis and a statement that the optimal duration of DCV/SOF/RBV in Child- Pugh C HCV genotype 1 subjects has not been established.

HCV Genotype 3

Additionally, dosage recommendations are included in labeling for HCV genotype 3 subjects with Child-Pugh B or C cirrhosis based on an overall SVR12 rate of 83% (5/6). Dosing recommendations were also extended to HCV genotype 3 post-transplant subjects. Despite the limited number of HCV genotype 3 subjects, the rationale for inclusion of dosage recommendations for these HCV genotype 3 subgroups is based on the known efficacy for treatment of HCV genotype 3 from the ALLY-3 trial, the demonstrated efficacy from ALLY-1, and comparable SVR12 rates to HCV genotype 1 infection.

Table 4: SVR12 and virologic failure for HCV GT1 and GT3 subjects in the Cirrhotic Cohort, according to Child-Pugh category.

	Child-Pugh A	Child-Pugh B	Child-Pugh C
Overall GT1	**10/11 (91%)**	**22/24 (92%)**	**5/10 (50%)**
GT1a-SVR12	**7/8 (88%)**	**15/17 (88%)**	**4/9 (44%)**
Virologic Failure/Relapse	1/8 (13%)	2/17 (12%)	5/9 (56%)
GT1b-SVR12	**3/3 (100%)**	**7/7 (100%)**	**1/1 (100%)**
Virologic Failure/Relapse	0	0	0
GT3-SVR12	**n/a**	**3/3 (100%)**	**2/3 (67%)**
Virologic Failure/Relapse	n/a	0	1/3 (33%)

Source: Adapted from Analysis by Dr. Patrick Harrington and Wen Zeng

Both ALLY-1 and ALLY-2 enrolled subjects with compensated Child-Pugh A cirrhosis; however, the regimens differed between the trials. In ALLY-1 subjects received DCV/SOF/RBV for 12 weeks and in ALLY-2 subjects received DCV/SOF for 12 weeks. Both regimens resulted in SVR12 rates of 91% with overlapping 95% CI as shown in Table 5 below. Based on these data we are not able to assess the contribution of RBV to the regimen and therefore, we recommend HCV genotype 1 patients with Child-Pugh A cirrhosis receive DCV/SOF for 12 weeks. We also expect that the benefit of RBV in genotype 1 patients with Child-Pugh A cirrhosis is further minimized if all genotype 1a cirrhotic patients are screened for the presence of NS5A polymorphisms (see below).

Table 5: SVR12 Rates for HCV GT1 Child-Pugh A Cirrhotic Subjects who Received DCV/SOF compared to DCV/SOF/RBV

Trial	**SVR12 and (95% CI)**
ALLY -1 DCV/SOF/ RBV x 12 weeks	91% (10/11) (58.7%, 99.8%)
ALLY -2 DCV/SOF x 12 weeks	91% (20/22) (70.8%, 98.9%)

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

The impact of baseline NS5A polymorphisms on SVR12 rates in HCV genotype 1a subjects with cirrhosis and HCV genotype 3 subjects and baseline NS5A screening considerations

Some patients harbor circulating hepatitis C viruses that have one or more genetic polymorphisms (amino acid substitutions or variants) that could affect drug susceptibility to one or more drugs of a class even without prior exposure to DAAs. Polymorphisms refer to the predominant circulating virus at baseline unlike resistance substitutions which exist as a minority species until selected to circulate as the predominant virus under drug pressure and incomplete viral suppression of a regimen. Baseline genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. Drug resistance-associated polymorphisms occur in a minority of patients, typically 5-15%, but may substantially impact virologic response and/or choice of drug regimen. Dr. Harrington noted in his review that certain NS5A polymorphisms affected treatment response for genotype 1a subjects with cirrhosis. Please refer to his review for complete details.

HCV genotype 1a subjects with cirrhosis

Dr. Harrington's analyses pooled data from ALLY-1 and ALLY-2 to evaluate the impact of baseline positions previously described as possibly being associated with resistance to DCV or other NS5A inhibitors on SVR12 rates; however, for several positions no subjects with NS5A polymorphisms experienced virologic failure. Therefore, Dr. Harrington's subsequent analyses focused on HCV genotype 1a subjects with any polymorphisms at four key DCV resistance-associated positions in NS5A (M28, Q30, L31 or Y93) and excluded subjects who received the suboptimal 8 week treatment regimen in ALLY-1. HCV genotype 1b subjects were evaluated separately and NS5A baseline resistance associated polymorphisms did not appear to impact SVR12 rates; albeit the data are limited (n=9), especially for those with cirrhosis. The overall prevalence of polymorphisms at positions M28, Q30, L31 or Y93 was 9% (19/203) in genotype 1a subjects. SVR12 rates were 76% (13/17) and 95% (142/149) for HCV genotype 1a infected subjects with or without a key DCV NS5A resistance-associated polymorphism, respectively. Of note, the impact of these NS5A polymorphisms at positions M28, Q30, L31, or Y93 was most apparent in subjects with cirrhosis. No subjects with Child-Pugh C had a baseline key DCV associated polymorphism. The SVR12 rates in HCV genotype 1a infected subjects with or without NS5A polymorphisms, according to cirrhosis/post-transplant status is shown in the Table 6 below. Approximately a 60% reduction in the SVR12 rate is seen in subjects with Child-Pugh A or B cirrhosis with NS5A polymorphisms compared to subjects with Child-Pugh A or B cirrhosis without NS5A polymorphisms at the four key positions described above. Notably the data suggests baseline NS5A polymorphisms do not affect SVR12 rates among non-cirrhotic or post-transplant HCV genotype 1a subjects.

Table 6: SVR rates in HCV GT1a infected subjects with or without NS5A polymorphisms, according to cirrhosis/post-transplant status

	SVR12 with Polymorphism(s)	SVR12 without Polymorphism(s)
Subjects with Cirrhosis (Child-Pugh A/B/C)	2/6 (33%)	42/48 (88%)
Subjects with Child-Pugh A/B Cirrhosis[1]	2/6 (33%)	38/39 (97%)
Subjects without Cirrhosis	9/9 (100%)	72/72 (100%)
Subjects Post-Transplant	2/2 (100%)	28/29 (97%)
Child-Pugh A/B (Pre-transplant) or F4 Fibrosis (Post-transplant)	3/7 (43%)	49/51 (96%)

[1]None of the 9 Child-Pugh C subjects in ALLLY-1 had DCV resistance-associated polymorphisms
Source: adapted from Dr. Harrington's Clinical Virology review

NS5B polymorphisms at potential SOF resistance-associated positions were infrequent among subjects with HCV genotype 1 or GT3 infection and if detected at baseline were not clearly associated with treatment failure.

Of the four subjects with baseline NS5A polymorphisms, two subjects subsequently developed additional NS5A substitutions at the time of virologic failure. Also, three subjects had a treatment-emergent NS5B substitution possibly associated with SOF. Therefore, the consequence of virologic failure and treatment-emergent resistance factored into the following labeling consideration for baseline NS5A polymorphisms as summarized below.

Based on the above findings, albeit in limited number of subjects, the review team decided, and BMS concurred, clinicians should consider screening for the presence of NS5A polymorphisms at positions M28, Q30, L31 and Y93 for HCV genotype 1a-infected patients with cirrhosis considering treatment with DCV/SOF±RBV. Please refer to Dr. Harrington's review for a detailed rationale for consideration versus recommendation for pre-screening of NS5A polymorphisms in genotype 1a patients with cirrhosis. In summary, the review team's decision was guided by the following (1) HCV genotype 1a is the most common subtype in the US, (2) treatment options less impacted by baseline NS5A polymorphisms (e.g. Harvoni) are available, (3) consequences of virologic failure as demonstrated by the potential for accumulation of additional treatment-emergent NS5A or NS5B substitutions in those with baseline NS5A polymorphisms, including SOF-associated resistance, (4) potential additional consequences of treatment failure in patients with more advanced disease and (5) two commercially available assays. Furthermore, this decision also took into consideration data from multiple other DCV-based regimen trials which demonstrated an impact of NS5A polymorphisms on treatment efficacy in the context of other HCV genotypes/subtypes (see also the original NDA clinical and virology reviews of DCV/asunaprevir).

HCV Genotype 3

In the original NDA for DCV/SOF for HCV genotype 3, the ALLY-3 trial results showed the presence of the baseline NS5A Y93H polymorphism reduced SVR12 rates in HCV genotype 3 infected subjects with or without cirrhosis. During the original NDA review, this information was included in section 12.4 of the label, but not more prominently (e.g., as a limitation of use) because, at the time, no commercial or FDA-approved assay was available. Additionally, the consequence of further NS5A inhibitor resistance selection was different because additional major DCV resistance-associated substitutions did not emerge in those with the baseline Y93H polymorphism who experienced virologic failure. Also HCV genotype 3 infection is not common in the U.S. SOF/RBV for 24 weeks was the only alternative interferon-free treatment option at that time and DCV/SOF was half the duration (12 weeks) and represented the first HCV genotype 3 treatment that did not include RBV for HCV genotype 3 patients.

During the review of the current NDA supplements, BMS informed the review team that an assay to detect the Y93H polymorphism in HCV genotype 3 subjects is now available, thus leading to review team's evaluation of whether or not to consider screening for the NS5A Y93H polymorphism in HCV genotype 3 subjects. Please refer to Dr. Harrington's review for details on the decision not to include any screening recommendations for the NS5A Y93H polymorphism prior to treatment. In summary, I agree with Dr. Harrington's assessment that screening for the Y93H polymorphism could be considered for HCV GT3 infected patients if or when an optimal alternative treatment regimen becomes available. Given that an ideal, interferon-free alternative treatment regimen for HCV GT3 patients with NS5A Y93H is not approved, it is not critical that a prominent screening recommendation is included in the DCV label at this time. This issue will be revisited in the future as more data are obtained to guide the optimal treatment of HCV GT3 infected patients with the NS5A Y93H polymorphism.

HCV Genotype 3 subjects with compensated cirrhosis dosage recommendations

With this sNDA, the dosage recommendations for HCV genotype 3 infected subjects with compensated cirrhosis was re-examined. As currently noted in the label, the optimal regimen and duration for HCV genotype 3 subjects with cirrhosis has not been established. After review of the available data sources we recommend the addition of RBV to DCV/SOF for 12 weeks in HCV genotype 3 subjects with Child-Pugh A cirrhosis. Our decision to recommend DCV/SOF/RBV for 12 weeks in HCV genotype 3 infected subjects with Child-Pugh A cirrhosis is based on data from ALLY-1, ALLY-3+ (data requested by FDA during sNDA review), and the expanded access programs: French ATU and UK cohort (data requested by FDA during sNDA review) as follows.

- SVR12 rates from ALLY 3+ and French ATU/UK cohort suggest RBV improves SVR12 rates for the DCV/SOF/RBV for 12 weeks in HCV genotype 3 subjects with compensated cirrhosis. Of note the SVR12 rate from ALLY-3 for DCV/SOV for 12 weeks in compensated cirrhotic subjects is 63% (20/32)

  - ALLY 3+: SVR12 - overall 88% (21/24) and 83% (15/18) for compensated cirrhotic subjects
  - French ATU: SVR12 - 100% (4/4) for compensated cirrhotic subjects
  - UK Cohort: SVR 12 - 71% (77/108) overall and 86% (18/21) for compensated cirrhotic subjects
- Comparable SVR12 rates between HCV genotype 1 and HCV genotype 3 patients with compensated cirrhosis receiving DCV/SOF/RBV
  - SVR12 rates for HCV genotype 3 subjects receiving DCV/SOF/RBV for 12 weeks in ALLY-3+ and EAPs combined is 86% (37/43) compared to 91% (10/11) from ALLY-1 in HCV genotype 1 subjects with CPT-A cirrhosis
- RBV is recommended with DCV/SOF for certain HCV genotype 1 patients with cirrhosis. HCV genotype 3 treatment generally results in lower SVR12 rates compared to HCV genotype 1 subjects with cirrhosis. The totality of the data was deemed sufficient to recommend the addition of RBV to DCV/SOF for 12 weeks in HCV genotype 3 subjects with compensated cirrhosis. The limitation of use statement in Section 1 and the statement in section 2 of the label regarding optimal duration of DCV/SOF/RBV in patients with HCV genotype 3 cirrhosis has not been established will remain until the PMR trial (DCV/SOF/RBV for 24 weeks in compensated cirrhotics) is completed and the totality of the data are reviewed to determine if and what further revisions to sections 1 and 2 of the label are needed.

8. Safety

This section focuses on the safety data from the ALLY-1 and ALLY-2 trials. Dr. Wendy Carter's independent analyses of the safety data confirmed the Applicant's findings with few exceptions and did not affect the overall safety assessment. Please refer to the clinical review for complete details regarding numbers of subjects exposed to DCV-containing regimens and DCV/SOF-containing regimens throughout drug development. In ALLY-1, 113 subjects with chronic HCV infection, including 60 subjects with Child-Pugh Class A, B, or C cirrhosis and 53 subjects with recurrence of HCV after liver transplantation, were treated with DCV/SOF/RBV for 12 weeks. In the ALLY-2 trial, 153 treatment-naive and treatment-experienced subjects with HCV/HIV-1 coinfection were treated with DCV (dose-adjusted for concomitant antiretroviral use)/SOF for 12 weeks.

BMS performed a comprehensive assessment of safety, including, but not limited to a detailed analysis of hepatotoxicity. The submission quality was adequate to perform a thorough safety review and there were no substantive issues with data integrity.

<u>General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests</u>

In ALLY-2, the safety profile of DCV/SOF for 12 weeks was similar to that reported in ALLY-3 for HCV genotype 3 subjects receiving the same regimen. The most commonly reported adverse reactions were fatigue (15%), nausea (9%), headache (8%) and diarrhea (7%). The majority of adverse reactions were mild to moderate in severity. No subjects discontinued therapy for adverse events. No on-treatment deaths were reported. Two deaths occurred during the follow-up period and were considered not related to study treatment (sepsis, progressive liver failure – 12th week of retreatment with DCV/SOF/RBV). Four subjects developed an on-treatment SAE (priapism, chest pain, pre-syncope, pulmonary embolism and hypertensive crisis), none of which were considered related. Few subjects developed Grade 3 or 4 laboratory abnormalities. Five percent of subjects had total bilirubin increases $\geq$ 2.6 x ULN and only occurred in subjects receiving concomitant atazanavir and 4% had grade 3/4 increase in lipase ($\geq$ 3.1 x ULN). No cases met the laboratory criteria for Hy's Law or potential DILI.

In ALLY-1 the most common adverse reactions (frequency of 10% or greater) among the 113 subjects were headache (20%), anemia (20%), fatigue (16%), and nausea (11%). The majority of adverse reactions were mild to moderate in severity. Of the 15 (13%) subjects who discontinued study drug for adverse events, 13 (12%) subjects discontinued ribavirin only and 2 (2%) subjects discontinued all study drugs. No on-treatment deaths were reported. Two deaths occurred during the follow-up period and were considered unrelated to study medications; they included progression of advanced cirrhosis or complications of underlying comorbidities. Overall 13% (15) subjects developed an on-treatment SAE, none were considered treatment related.

Few subjects in ALLY-1 developed Grade 3 or 4 laboratory abnormalities and included Grade 3/4 increases in total bilirubin (8%), lipase (4%), AST (3%), creatinine (3%) and ALT (2%) and Grade 3 decreases hemoglobin (6%) and platelets (4%). More hematologic abnormalities were seen in ALLY-1 compared to ALLY-2 and ALLY-3 as expected given RBV use; however, the majority of the laboratory abnormalities were Grade 1 or 2. Please refer to Dr. Carter's review for discussion regarding anemia and RBV dose and duration during the trial. In ALLY-2, Grade 3/4 increases in total bilirubin and lipase were seen. No Grade 3/4 decreases in hemoglobin or ALT/AST increases were seen in ALLY-2.

Overall, in ALLY-1, seven subjects (6%) had Grade 3 anemia events, none had Grade 4 anemia events and no subjects required use of erythropoietin stimulating agents. One subject required a transfusion at Week 4. 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. Overall 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.

For the cohort of patients with cirrhosis (Child-Pugh A, B or C), the median ribavirin dose was 446 mg daily (range, 101-607). The median time to reduction in the ribavirin dose was 26 days (range, 3-55) and median time to discontinuation of ribavirin was 43 days (range, 8-82). For the post-transplant cohort, the median ribavirin dose was 478 mg daily (range, 99-755). The median time to reduction in the ribavirin dose was 29 days (range, 11-57) and median time to discontinuation of ribavirin was 20 days (range, 3-57).

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, of which 75% achieved SVR12 and 11 subjects (10%) completed less than 6 weeks of RBV therapy, of which 82% achieved SVR12, respectively. Overall these numbers are small and clear conclusions regarding the impact of RBV dose and duration on SVR12 rates cannot be made.

Dr. Carter's targeted safety evaluation included overall hepatic and renal safety, rash related events and hypersensitivity/pyrexia with eosinophilia. Please refer to her review for full details. 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. Because the primary metabolite of SOF is renally metabolized post-marketing review of renal data for DCV/SOF will continue. No serious rash events were reported.

Hepatotoxicity

A comprehensive hepatic safety evaluation was conducted by Dr. Carter, BMS and an independent adjudication committee commissioned by BMS comprised of drug-induced liver injury experts and HCV clinicians to assess the overall hepatic safety profile of DCV/SOF/RBV in ALLY-1. These evaluations were conducted at the request of FDA because this was the first trial submitted to the Division to support labeling for patients with decompensated cirrhosis and review of these data were considered challenging because of the ability to discern if observed safety events were related to the DCV/SOF regimen or underlying advanced cirrhosis. Please refer to Dr. Carter's review for review criteria and further details.

In summary, 12 subjects were identified for further review. The committee independently reviewed all subject data including detailed narratives. The committee independently assessed the relationship of each event to the study regimen. Only one case was considered possibly related to study treatment. A 65 year old female post liver transplant had transient elevations in 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. Because no cause for the transient elevations could be found, the case was considered possibly drug-related. The other 11 cases had alternative causes for the events such as 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. 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 the cases presented.

In summary DCV/SOF has a continued favorable safety profile. No additional DCV/SOF safety related Warnings and Precautions are recommended and no safety related REMS are needed. The addition of ribavirin for 12 weeks in HCV genotype 1 decompensated cirrhotics and post-transplant subjects did not have a negative impact on the overall safety profile. Adverse events and laboratory abnormalities observed are manageable and easily monitored.

9. Advisory Committee Meeting

No meeting was held because we did not require an outside panel of experts to determine safety and efficacy of the proposed regimens.

10. Pediatrics

No clinical trials of DCV in pediatric subjects have been conducted to date; and therefore, the safety and efficacy of DCV have 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) However, 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

Office of Scientific Investigation Inspections

Please refer to the OSI Consult Review for further details. The submitted data from the site audits are considered acceptable.

Good Clinical Practice

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

Financial Disclosures

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

12. Labeling

Most of the major changes to the label are mentioned in the sections above with the supporting rationale. The major updates to the label include the following.

- **Section 1: Indications and Usage** - The indication was extended to HCV genotype 1 infection
    - The ALLY-2 results supports use of DCV/SOF for 12 weeks in HCV genotype 1 infected subjects as described in section 7 of this review.
- **Section 2: Dosage and Administration** - The following dosage recommendations were included. Section 7 summarizes the rationale for the DCV/SOF for 12 week regimen in patients without cirrhosis and those with Child-Pugh A cirrhosis.

	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-	DAKLINZA + sofosbuvir + ribavirin for 12 weeks

	Pugh B or C) cirrhosis	
	Post-transplant	

For patients with HCV/HIV-1 coinfection, the above recommendations apply. Please refer to section 7 of this review for rationale regarding the recommended dosage regimen for HCV genotype 1 and rationale for revising the dosage regimen for HCV genotype 3 patients with Child-Pugh A cirrhosis.

Section 2.1 Testing Prior to Initiation of Therapy was added to the label to address consideratrions for screening for the presence of NS5A polymorphisms at positions M28, Q30, L31 and Y93 in patients with HCV genotype 1a and cirrhosis. Please refer to section 7 for our rationale with respect to screening for HCV genotype 1a cirrhotics and HCV genotype 3 subjects.

RBV dosage recommendations in ALLY-1 were 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. This recommendation is included in for HCV genotype 1 patients with Child-Pugh B or C cirrhosis or post-transplantation patients.

We agreed with BMS's proposal to recommend weight-based RBV dosing in HCV genotype 3 cirrhotic patients instead of the RBV dosing used in ALLY-1. The basis for this decision included the fact that weight based dosing was used in subjects with advanced fibrosis and cirrhosis in ALLY-3+ with acceptable tolerability. In addition, investigators predominantly used weight-based RBV dosing in subjects with cirrhosis in the French ATU and UK cohorts. These data contribute to the dosing recommendation, and the tolerability of the higher dose of RBV. Also, the PMR trial, AI444379, in subjects with HCV genotype 3 and cirrhosis will utilize weight-based RBV dosing.

- **Section 6: Adverse Reactions** to include adverse reaction, laboratory abnormality summaries from ALLY-1 and ALLY-2 as described in section 8 of this review:
  - presentation of adverse reaction data from ALLY-1 (text) and ALLY-2 (table)
  - update to selected Grade 3 and 4 laboratory abnormalities table to include findings from ALLY-1 and ALLY-2
- **Section 7 Drug Interactions** Table 7 was updated with relevant findings from the phase 1 trials. Please refer to section 5 of this review for rationale for proposed labeling in section 7 Drug Interactions and section 12 Clinical Pharmacology. The updates included the following:

  - For antiviral medications, in general, Table 7 was reformatted and now organized by concomitant drug class versus including them in the mix of

examples for strong CYP3A inhibitors, moderate CYP3A inhibitors and inducers.
    - Moderate CYP3A inhibitors, including atazanavir (unboosted), fosamprenavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, or verapamil were moved to section 7.4 -Drugs without Clinically Significant Interactions. Originally these agents were in Table 7 and the clinical comment to monitor for DCV adverse events is not clear. Based on section 6 of the label, adverse reactions were minimal and the label does not give instructions in case adverse reactions are observed. Therefore, moderate CYP3A inhibitors were moved to section 7.4 to indicate no dose adjustment is needed.
    - Information was added to section 7.4 for darunavir/ritonavir and lopinavir/ritonavir indicating that clinically relevant changes in exposure were not observed either for the antiretroviral medication or daclatasvir.
    - Per Office of Clinical Pharmacology's current thinking, drugs for which no clinically relevant interaction is anticipated is now included in section 12.3 and not 7.4. I personally disagree with this position because now clinicians need to review sections 4, 7 and 12 for all drug-drug interaction information. However, this is not currently consistent among all drug labels and could lead to confusion among clinicians and potential errors. Therefore, the review team decided to include the following statements in section 7.3 and 7.4, respectively. Further discussions are needed to discuss the merits of consolidating drug-drug interaction data in labeling
        - Please also refer to Section 4 (Contraindications) and Section 12.3 (Pharmacokinetics) for complete information on all drug interactions.
        - Please see section 12.3 for information regarding anticipated interactions that are not clinically relevant.
- **Section 8.1 and 8.2: Pregnancy and Lactation** was revised to conform to PLLR labeling recommendations as described in Dr. Meyers' pharmacology/toxicology review.
- **Section 12 Clinical Pharmacology** tables were updated with results from the four phase 1 trials as summarized in Dr. Au's review. See section 5 of this review for a summary of findings.
- **Section 12.4 Microbiology** was updated to include pertinent HCV genotype subtype, baseline resistance-associated polymorphisms and emergent resistance-associated substitution data from HCV genotype 1 trials. In addition, the subsection "Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response" was expanded to include "Genotype 1a and 1b NS5A polymorphisms" subsections to describe the data from ALLY-1 and ALLY-2. Please refer to discussion in section 7 of this review for details and Dr. Harrington's review.
- **Section 14: Clinical Studies** the major revisions include the addition of results from ALLY-1 and ALLY-2 trials.

- SVR12 data are presented as the total group and by cirrhosis status. Text was included to state SVR12 rates were comparable regardless of antiretroviral therapy (ALLY-2 only), HCV treatment-history, age, race, gender, IL28B allele status, HCV genotype 1 subtype (ALLY-2 only), or baseline HCV RNA level.
- For ALLY-1 descriptive text was included to discuss actual RBV use during the trial. The review team believes the RBV use data is important to show because a high proportion of reductions in RBV dosing occurred in the trial and by Week 6, approximately half of the subjects received 400 mg or less of RBV. The median time to discontinuation of RBV dose was also included. These data are important to highlight because section 2 of the label includes a recommended regimen (DCV/SOF/RBV) and certain patients were unable to receive the initial recommended dose (600 mg) or continue RBV dosing throughout the trial or increase RBV dose above 600 mg throughout the 12 week trial period. This may be due to the advanced disease status of these patients.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** I agree with the review team's assessment and recommend approval of (1) DCV/SOF 12 week regimen for the treatment of HCV genotype 1 patients with or without compensated cirrhosis (Child-Pugh A), (2) DCV/SOF/RBV 12 week regimen for HCV genotype 1 and 3 patients with Child-Pugh B or C cirrhosis or HCV genotype 1 and 3 post-transplant patients. Additionally, I agree with the addition of RBV for 12 weeks to HCV genotype 3 patients with compensated cirrhosis. For patients with HCV/HIV-1 coinfection, I agree the dosage recommendations outlined in section 2 of the package insert should be followed. Data on subjects with HCV genotype 2, 4, 5 and 6 were not sufficient to include in labeling.

- **Benefit Risk Assessment:**

  The data submitted provides sufficient evidence to recommend DCV/SOF for 12 weeks for the treatment of HCV genotype 1 patients with compensated (Child-Pugh A) cirrhosis or without cirrhosis and to recommend DCV/SOF/RBV for 12 weeks for the treatment of HCV genotype 1 patients with decompensated (Child-Pugh B or C) cirrhosis or HCV genotype 1 recurrence post-transplant patients. Also the totality of the data is sufficient to extend dosage recommendations for HCV genotype 3 subjects with HIV-1 co-infection, decompensated cirrhosis (Child-Pugh B and C), and recurrence post-liver transplantation.

The data from ALLY-2 clearly demonstrate the efficacy of DCV/SOF for 12 weeks in HCV/HIV-1 coinfected genotype 1 subjects with or without compensated (Child-Pugh A) cirrhosis. The SVR12 rate was 97% [95% CI: 92.1%, 99.1%) and the lower bound of the 95% CI far exceeded the historical control rate of 30%. Additionally, the results for ALLY-2 are consistent with other DAA HCV programs with respect to SVR12 rates in both mono-infected and HCV/HIV-1 co-infected subjects and the SVR12 rates exceed 90%.

Sufficient data from ALLY-1 were provided to recommend DCV/SOF + ribavirin for 12 weeks in HCV genotype 1 subjects with decompensated (Child-Pugh B and C) cirrhosis. Currently no approved HCV DAA regimens include dosage recommendations for this population who are in need of treatment. Differences in SVR12 rates were noted in ALLY-1. The pre-transplant cirrhotic genotype 1 cohort had a lower overall SVR12 rate (82% [95% CI (67.9%, 92%)) compared to the post-transplant cohort (95% [95% CI 83.6%, 99.4%)). Additionally, subjects with HCV genotype 1a achieved a lower SVR12 rate (77%), compared to the small group of HCV genotype 1b subjects who all achieved SVR12 (11/11; 100%). Notably, SVR12 rates were lower in subjects with HCV genotype 1 Child-Pugh C cirrhosis (50%) compared to subjects with HCV genotype 1 Child-Pugh A and B cirrhosis (91%). The reason for the difference in efficacy is not fully understood and could be a combination of small sample size, host and virologic factors. No HCV genotype 1 subjects with Child-Pugh C cirrhosis had a key baseline NS5A resistance-associated polymorphism; therefore, this was not the reason for the lower SVR12 rate. Nevertheless, treatment options do not exist in this population and modest efficacy was established. If left untreated, SVR12 rates are virtually zero. Therefore a statement is included in labeling that the optimal duration of DCV/SOF/RBV for treatment of patients with HCV genotype 1 decompensated Child-Pugh C cirrhosis has not been established.

Data were limited for HCV genotype 3 infection in ALLY-1 and ALLY-2; however, as stated in section 7 of this review, the totality of the data supports use for treatment of the labeled HCV genotype 3 populations.

ALLY-3+ and the compassionate use programs (French ATU and UK cohort) were submitted by BMS at the request of FDA to further evaluate revisions to the HCV genotype 3 Child-Pugh A dosage recommendations. These data provide evidence that the addition of RBV to DCV/SOF for 12 weeks improves SVR12 rates in HCV genotype 3 subjects with Child-Pugh A cirrhosis. The optimal regimen and duration still remains to be determined and BMS is committed to completing the PMR trial to determine if DCV/SOF/RBV for 24 weeks improves SVR12 rates and minimizes relapse and consequently the development of resistance. Unfortunately, BMS declined to enroll HCV genotype 3 subjects with decompensated cirrhosis (Child-Pugh B or C) into this trial. However, data from multiple sources will be taken into consideration to

determine if revised further dosage recommendations for these HCV genotype 3 subpopulations are needed.

Overall the safety profile was favorable for both DCV/SOF and DCV/SOF/RBV for 12 weeks. Grade 3 or 4 adverse events were infrequent. Only two subjects in ALLY-1 discontinued DCV/SOF/RBV for adverse events and 13 subjects prematurely discontinued RBV only. No subjects in ALLY-2 discontinued study medications for adverse events. The most commonly reported adverse events were similar between trials; however, the frequency of certain events were higher in ALLY-1 compared to ALLY-2; although the severity of events were mild to moderate in each trial. As expected, decreases in hemoglobin ($\leq$ 8.9 g/dL) were seen with the DCV/SOF/RBV regimen (6%) compared to 0% in ALLY-1. Grade 3/4 increases in ALT, AST, total bilirubin and lipase were numerically higher in ALLY-1 compared to ALLY-2 and may in part be due to advanced disease state of subjects in ALLY-1. The addition of RBV to the regimen overall did not adversely affect the safety profile and the events are manageable and do not preclude the use of SOF/DCV/RBV for 12 weeks.

An independent adjudication committee concluded no consistent hepatic safety signal was found and I agree with this assessment based on review of the ALLY-1 data and executive summary of the requested post marketing safety assessment with regards to hepatic decompensation and hepatic failure.

In summary, the overall benefit/risk assessment is favorable. DCV/SOF with or without RBV has demonstrated efficacy in HCV genotype 1 and 3 infection including subjects with Child-Pugh A, B and C cirrhosis and HCV genotype 1 and 3 post-transplant subjects. DCV/SOF/RBV is the first approved regimen for patients with decompensated cirrhosis (Child-Pugh B or C), albeit with the limitations noted in the labeling. Insufficient data were provided to indicate DCV/SOF for 12 weeks in HCV genotypes 2, 4, 5, and 6. Baseline NS5A resistance testing should be considered for HCV genotype 1a subjects with cirrhosis to increase the likelihood of virologic cure and to decrease the risk of development of additional resistance-associated substitutions. As stated previously in this review, baseline resistance testing is not considered at this time for HCV genotype 3 subjects until alternative interferon/ribavirin-free treatment options are approved.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Based on the safety profile of DCV/SOF with or without RBV, the Division does not recommend a Risk Evaluation and Management Strategy (REMS).

- Recommendation for other Postmarketing Requirements and Commitments

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

- **Recommended Comments to Applicant**

  No additional comments for the Applicant at this time

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

/s/

KIMBERLY A STRUBLE
01/26/2016