

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206843Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

Cross-Discipline Team Leader Review

<b>Date</b>	July 8, 2015
<b>From</b>	Kimberly Struble, PharmD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 206843 (daclatasvir) Resubmission
<b>Supplement#</b>	
<b>Applicant</b>	Bristol Myers Squibb
<b>Date of Submission</b>	February 13, 2015
<b>PDUFA Goal Date</b>	August 13, 2015
<b>Proprietary Name / Established (USAN) names</b>	Daklinza (daclatasvir)
<b>Dosage forms / Strength</b>	Daclatasvir 30 mg and 60 mg tablets
<b>Proposed Indication(s)</b>	Treatment of chronic hepatitis C infection
<b>Recommended:</b>	Approval

## 1. Introduction

This cross-discipline team leader review covers the resubmission for NDA 206843 and presents the main findings for daclatasvir (DCV) when used in combination with sofosbuvir (SOVALDI™, SOF) for the treatment of chronic hepatitis C virus (HCV) genotype 3 infection. 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 is the third direct acting antiviral agent (DAA) in the NS5A drug class submitted for marketing approval, but the first for HCV genotype 3 infection.

The Applicant, BMS, submitted two original NDAs; NDA 206843 for DCV and NDA 206844 for asunaprevir (ASV) on March 29, 2014. The proposed indication for ASV was in combination with DCV for patients with hepatitis C virus (HCV) genotype 1b infection (b) (4)

The proposed indication for DCV was in combination with other agents for the treatment of HCV genotype (b) (4) infections. The pivotal data to support safety and efficacy for each drug came from three Phase 3 trials which evaluated the combination of DCV and ASV or the combination of DCV/ASV/PR. Thus, both NDA's shared the same three pivotal phase 3 trials. On October 6, 2014, BMS withdrew the ASV NDA 206844 as a result of a business decision. Therefore, the DCV NDA did not contain adequate evidence to establish the safety and efficacy of DCV without ASV for an indication for the treatment of chronic HCV infection in combination with other DAA's and therefore received a Complete Response Letter on November 25, 2014.

Before DCV could be approved, FDA informed BMS they must provide additional clinical trial data to support the safety and efficacy of DCV in combination with other

DAA agents for the treatment of chronic HCV infection. Meetings on December 8, 15 and 22, 2014 were held to discuss the contents of a resubmission. During a teleconference on December 17, 2014 FDA agreed to a resubmission for an indication in combination with SOF for chronic HCV genotype 3 infection. A resubmission was permitted versus a new NDA because the original DCV NDA did include a proposal for a DCV/SOF combination regimen in chronic HCV GT 3 infection based on Trial AI444040; however, the efficacy data from this trial were not considered because BMS did not have a right of reference from Gilead. At the time trial AI444040 was conducted SOF was an investigational agent and the trial used a Phase 2 formulation and not the approved formulation of SOF; thus a right of reference from Gilead was needed to link the phase 2 and approved formulations. Because the right of reference was not provided, BMS had to conduct additional studies using the approved SOF formulation to generate efficacy data to support the use of DCV in combination with SOF

This review highlights the safety and efficacy, virology and clinical pharmacology findings. Brief comments regarding chemistry/manufacturing and controls and pharmacology/toxicology are also presented. Please refer to the respective disciplines' original and resubmission NDA reviews for further details.

## **2. Background**

Chronic HCV infection is a serious and life-threatening condition and can lead to cirrhosis, liver failure and hepatocellular carcinoma. Chronic HCV infection is a global health problem with an estimated 170-200 million individuals infected worldwide. In the United States, approximately 4 million people have chronic HCV infection (<http://www.epidemic.org/thefacts/theepidemic/woldPrevalence/>).

HCV genotype (GT) 3 infection is responsible for approximately 20-30% of HCV infections worldwide, and approximately 10% of HCV infections in the US (Gower et al., 2014; Messina et al., 2015). HCV GT3a appears to be the most prevalent GT3 subtype in the U.S. and possibly also worldwide, particularly in HCV-infected intravenous drug users (Clement et al., 2010; Zein 2000; Morice et al., 2006).

A pegylated interferon and ribavirin (PR) regimen for 24 weeks was the standard of care for chronic HCV GT 3 infection until 2011. In 2011 SOF in combination with RBV for 24 weeks was approved for chronic HCV GT3 infection. Efficacy results as measured as proportion of subjects with a sustained virologic response at Follow-up Week 12 (SVR12) for SOF/RBV regimen are 92%-93% in treatment-naïve cirrhotic and non-cirrhotic patients, respectively and 60%-85% in treatment-experienced cirrhotic and non-cirrhotic patients, respectively. Limited FDA approved treatment options exist for HCV GT3 infection and no treatment options are available for those who are unable to receive RBV. DCV/SOF regimen for 12 weeks provides a RBV-free and shorter duration (12 weeks vs 24 weeks for SOF/RBV) option for chronic HCV GT3 infected patients.

Approximately 8,000 subjects received DCV in clinical trials and more than 4,800 subjects received DCV through expanded access/compassionate use programs. The majority of the data in chronic HCV subjects receiving DCV in various regimens was reviewed in the original NDA and is not reproduced in its entirety in this review. The data in the original NDA provide support for the overall safety profile and the SVR12 rates show the contribution of DCV in various regimens and genotypes; all of which are considered supportive data. Overall, safety data from 868 subjects with chronic HCV GT1-4 treated with DCV in combination with SOF with or without RBV (n=363) or DCV/PR (505) for up to 24 weeks was included in the resubmission. This NDA resubmission primarily focuses on the 152 GT3 subjects treated with DCV/SOF from the ALLY-3 trial. Data from other sources, such as AI444040 and DCV/PR based regimens are mentioned where relevant in this review.

Additionally, DCV is approved in Japan and the EU. BMS estimates approximately 25,000 patients have received DCV globally; although, predominately in Japan.

### 3. CMC/Device

Collectively the CMC review team recommends approval. Facilities review and inspections are complete and support approval.

- **General product quality considerations**

DCV dihydrochloride is a new molecular entity. DCV is a tablet for oral administration . Two dosage strengths are proposed, a 30 mg film coated tablet and a 60 mg film coated tablet.

According to the CMC reviewer, Dr. Chunchun Zhang, the data presented in the original NDA and amendments are adequate to assure composition, manufacturing process, and specifications. The expiration dating period of 30 months when stored at 25 degrees Celsius is supported by adequate data. No product quality microbiology issues were identified by Dr. Bryan Riley during the original NDA review. The proposed labeling is adequate pending minor revisions. The specified impurities (genotoxic impurities: (b) (4)) were reviewed and qualified by Dr. Mark Powley with the original NDA.

The dissolution method and dissolution acceptance criteria were acceptable. Adequate data were provided to support the discriminating ability of the dissolution method. A biowaiver was used to support the 30 mg strength table because the 30 mg tablet was not used in phase 3 trials and no PK data on the final formulation were available. The only difference between the 30 mg and 60 mg tablets are tablet weight, color (b) (4). Results from dissolution show the 30 mg tablet is dose-proportional to the 60 mg tablet.

No PMR/PMCs are proposed.

#### **4. Nonclinical Pharmacology/Toxicology**

A comprehensive nonclinical toxicology program was conducted for DCV. The preclinical evaluation includes over 40 studies to assess the safety, pharmacology, pharmacokinetics, general toxicity, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and local tolerance, in mice, rats, dogs, rabbits and monkeys. Repeat dose studies were conducted in mice (up to four weeks), rats (up to 26 weeks), and monkeys (DCV). Dr. Peyton Myers recommended approval for this NDA based on the nonclinical pharmacology/toxicology findings for DCV.

- **General nonclinical pharmacology/toxicology considerations**

The main findings for DCV in the nonclinical studies include liver findings (increased weight and enzyme activity) and an adrenal effect (hypertrophy and vacuolation). With regard to liver findings, in the one month rat study, only minimal and slight increases in ALT and minimal increase in liver weights without any liver histologic changes were noted. No liver effects were seen in rats following six months of DCV. In monkeys dosed for four months, AST and ALT increased with dose and histological changes were noted (mononuclear-cell infiltration in centrilobular areas of the liver, minimal/slight bile-duct hyperplasia and Kupffer-cell hyperplasia/hypertrophy and minimal/moderate rarefaction of cytoplasm in centrilobular hepatocytes). In both rats and monkey vacuolation with increased adrenal weights and discoloration were noted. Additionally, rats had increased urine output with increased water consumption but no kidney related adverse events, changes or histologic findings.

Combination toxicology studies with DCV and PR showed no enhanced toxicity or toxicokinetic interaction.

No irritation effects were noted; however, DCV is a potential dermal sensitizer. In an in vitro study evaluating the absorption of light, DCV was potentially phototoxic; but, in a follow-up study in Long Evans rats, the results were negative. No ocular or other photo-related toxicity was noted in repeat dose studies for DCV.

- **Carcinogenicity and Mutagenesis**

DCV is not genotoxic and no evidence of mutagenic or clastogenic activity was noted in in vivo rat micronucleus assays.

A two-year carcinogenicity study in Sprague Dawley rats and a 6- month study in transgenic (Tg rasH2) mice were conducted for DCV.

In the 2 year study in rats with DCV no drug-related increase in tumor incidence was observed at doses up to 50 mg/kg/day (both sexes). DCV exposures at these doses

were approximately 6-fold (males and females) the human systemic exposure at the therapeutic daily dose. In transgenic mice, no drug related increase in tumor incidence was observed at DCV doses of 300 mg/kg/day (both sexes). DCV exposures at these doses were approximately 8.7-fold (males and females) the human systemic exposure at the therapeutic daily dose.

- **Reproductive toxicology**

Male fertility parameters were affected in rats receiving DCV. Increased mean pre-implantation loss and spermatogenic effects were noted in male rats receiving 200 mg/kg/day. DCV exposures at the 200 mg/kg/day dose in males were approximately 26-fold the human systemic exposure at the therapeutic daily dose. Exposures at 50 mg/kg/day in males produced no notable effects and were 4.7 fold the exposure in humans at the recommended daily dose. DCV had no effects on fertility in female rats at any dose tested. DCV exposures at these doses in females were approximately 24-fold the human systemic exposure at the therapeutic daily dose.

## **5. Clinical Pharmacology/Biopharmaceutics**

Approval is recommended from the clinical pharmacology and pharmacometrics review team. No PMR/PMCs are proposed.

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

The pharmacokinetic properties of DCV were evaluated in healthy and HCV infected subjects. Mean peak concentrations of DCV were observed within two hours post-dose. Following administration of DCV, the terminal elimination half-life was 12-15 hours.

DCV exposures were altered in the presence of food. Administration of DCV after a high-fat meal decreased DCV C<sub>max</sub> and AUC<sub>0-inf</sub>) by 28% and 23%, respectively compared to fasting conditions and the 90% CI for DCV C<sub>max</sub> and AUC<sub>0-inf</sub>) were not within the standard “no effect” limits of 80%-125%. The 90% CI for C<sub>max</sub> was 66%-79% and the 90% CI for AUC<sub>0-t</sub>) was 73%-80%. A food effect was not observed with administration of DCV after a low-fat, low-caloric meal compared to fasting conditions. The exposure-efficacy and exposure-safety data support dosing without regard to food. The ALLY-3 trial was conducted in this manner.

The majority of the DCV dose is eliminated via the fecal route (88%) with 7% eliminated renally.

- **Dose Selection**

The dose selection for DCV is based on a monotherapy trial and four phase 2 trials in subjects with HCV genotype 1 infection. In the multiple dose monotherapy trial (AI444004) a 3.20 log<sub>10</sub> IU/mL decline in HCV RNA was from baseline to day 7 with DCV 60 mg. In the phase 2 treatment-naïve trial (AI444014) DCV 3 mg, 10 mg and 60 mg once daily in combination with PR were compared to placebo + PR for 48 weeks. SVR12 rates were 42% for the 3 mg group, 92% for the 10 mg group, 83% for the 60 mg group and 25% for placebo + PR group. Based on this trial, the 60 mg dose was selected as the highest dose for the next trial in treatment-naïve subjects. In trial AI444010, DCV 20 mg and 60 mg once daily in combination with PR was compared to placebo + PR. The SVR24 rates were 59% and 60% for the DCV 20 and 60 mg groups compared to 38% for the placebo + PR group. These data suggest doses at 20 mg and 60 mg were on the flat part of the dose-response curve. No safety differences were seen between the 20 mg and 60 mg dose groups. BMS conducted a population pharmacokinetic analysis, an exposure-response analysis and a pharmacokinetic viral kinetic analysis to select the dose for Phase 3. The models accounted for genotype, baseline HCV RNA, and cirrhosis status. For genotype 1a subjects with high baseline viral load, the model predicted DCV 60 mg once daily may result in an increase in SVR rate of 1-5% depending on subject compared to the 20 mg dose. To maximize response rates, particularly for difficult-to-treat populations the 60 mg dose was selected. Based on these data, DCV 60 mg once daily was further evaluated in all genotypes.

- **Drug-drug interactions**

DCV is mainly metabolized by CYP3A. DCV is a P-gp substrate. Daclatasvir demonstrated inhibitory effects on digoxin (a P-gp substrate) and rosuvastatin (an OATP 1B1, OATP 1B3, and BCRP substrate) in drug-drug interaction trials. The dosage of DCV is 30 mg once daily when given with strong CYP3A inhibitors and the dosage of DCV is 90 mg once daily when given with moderate CYP3A inducers. Strong CYP3A inducers are contraindicated with DCV.

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

From the original NDA, based on the population pharmacokinetic analyses, age, race, gender, body weight, ALT, AST and CrCL had no clinically relevant effects on the exposure of DCV.

No dosage adjustments are needed for patients with renal impairment.

Using a regression analysis, compared to HCV-uninfected subjects with normal renal function (creatinine clearance [CrCL] of 90 mL/min, defined using the Cockcroft-Gault CrCL formula), the predicted AUC<sub>(0-inf)</sub> of DCV was estimated to be 26%, 60%, and 80% higher in subjects with CrCL values of 60, 30, and 15 mL/min, respectively. DCV

unbound  $AUC_{(0-inf)}$  was predicted to be 18%, 39%, and 51% higher for subjects with CrCL values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function (CrCL of 90 mL/min). Using observed data, subjects with end-stage renal disease requiring hemodialysis had a 27% increase in DCV  $AUC_{(0-inf)}$  and a 20.1% increase in unbound  $AUC_{(0-inf)}$  compared to subjects with normal renal function with creatinine clearance defined using the Cockcroft-Gault CrCL formula.

DCV dosage adjustments are not needed for mild, moderate or severe hepatic impairment. Data in subjects with decompensated cirrhosis are not available.

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

A thorough QT trial was conducted for DCV. No significant QTc prolongation was seen for DCV at doses of 60 mg and 180 mg once daily. The upper bound of the 90% CI for the mean difference between DCV and placebo was below 10 msec. The appropriate moxifloxacin control was included.

## **6. Clinical Microbiology**

Please refer to the reviews by Dr. Patrick Harrington and Dr. Lalji Mishra for a detailed assessment of the cell culture and in vivo clinical virology data. The effect of baseline HCV Y93H polymorphism on SVR12 rates is summarized in section 7 below. This section describes the development of resistance and cross-resistance. An approval action was recommended by the virology reviewers. PMRs are recommended and are summarized in section 13.

Overall in ALLY-3, 17 subjects experienced virologic failure (16 virologic relapse post treatment and one quantifiable HCV RNA at the end of treatment). Fifteen of the 17 subjects (88%) with virologic failure had the Y93H substitution detected at time of failure, of which six subjects had Y93H at baseline (natural polymorphism). One of the two subjects without Y93H at failure developed another NS5A resistance-associated substitution, L31I. Accumulation of additional NS5A substitutions after virologic failure was minimal in subjects with the Y93H baseline polymorphism, indicating that Y93H alone (which causes a > 3,000-fold increase in DCV  $EC_{50}$  value) is likely sufficient to confer clinically relevant resistance to DCV in HCV genotype 3 infection. In comparison for genotype 1b subjects receiving the DCV/ASV based regimen, 94% (113/120) of the virologic failure subjects had virus with two or more DCV resistance-associated substitutions. For subjects with pre-existing NS5A resistance-associated polymorphisms, the consequence of virologic failure in genotype 3 subjects appears different than in genotype 1b subjects. Notably, only 1 subject with virologic failure developed an NS5B substitution (related to SOF) at failure.

No data are available regarding the persistence of NS5A associated substitutions in HCV genotype 3 subjects receiving DCV/SOF. The persistence of NS5A resistance-associated substitutions has been demonstrated in HCV genotype 1a and 1b subjects who experienced virologic failure with DCV-based regimens, in whom key treatment-

emergent NS5A substitutions remained detectable through the end of follow-up (median of > 600 days) in > 90% of subjects

Finally, based on resistance patterns observed in cell culture replicon studies and in HCV genotype 3-infected subjects, cross-resistance between daclatasvir and other NS5A inhibitors is expected. Cross-resistance between daclatasvir and other classes of DAA's is not expected.

## **7. Clinical/Statistical- Efficacy**

This section summarizes the efficacy analyses conducted by the review team for trial AI444218 (ALLY-3), which evaluated DCV 60 mg once daily and SOF 400 mg once daily (DCV/SOF) for 12 weeks in subjects with chronic HCV GT3 infection. Additionally, the clinical virology data with respect to baseline NS5A polymorphisms and outcome is presented in this section. Please refer to reviews by Dr. Wendy Carter (clinical), Wen Zeng (statistical) and Patrick Harrington (virology) for full details and discussion of efficacy. Drs. Carter, Zeng and Harrington each recommended approval for this NDA.

The results below reflect the final analyses proposed for labeling and agreed by FDA and BMS. The primary endpoint was SVR (HCV RNA analyzed using Roche COBAS TaqMan HCV v2.0 assay with limit of quantitation < 25 IU/mL) measured 12 weeks after the end of therapy and is deemed acceptable. SVR12 is the currently recommended primary endpoint in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013. Sustained virologic response (HCV RNA < LLOQ at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a virologic 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.

If an SVR12 result was missing but a HCV RNA value is available past the SVR12 window, then this result was imputed for the primary endpoint. This approach was also used in other HCV applications.

The method for determining cirrhosis was acceptable. For the 32 subjects with cirrhosis at baseline, cirrhosis was identified by liver biopsy in approximately 43%, by Fibroscan (>14.6 kPa) in approximately 32% and by FibroTest  $\geq 0.75$  with APRI > 2 in 22%.

### Trial Design Attributes:

Trial AI444218 (ALLY-3) is an open-label, phase 3 trial to evaluate the safety and efficacy of DCV in combination with SOF for the treatment of patients with chronic HCV GT3 infection. An active or placebo controlled design was not used in ALLY-3.

Per the Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Drugs for Treatment, an immediate versus deferred placebo-control trial design is preferable and in some situations, single-arm trials using a historical control may be appropriate. Dr. Wen Zeng, justified an NI margin based on historical data to assess efficacy. The current standard of care for HCV GT3 infected subjects is SOF/RBV for 24 weeks. Dr. Zeng compared SOF/RBV 24 weeks regimen to: (1) “universal” placebo (assuming SVR12 rate of 10%), (2) 12 weeks of SOF monotherapy from the ELECTRON trial, (3) 12 weeks SOF/RBV from the FISSION trial and (4) 24 weeks of PR treatment from the FISSION trial. Regardless of the methodology used (evaluating treatment-naïve and experienced separately or pooled) for comparison, a conservative estimate of M1, based on the lower bounds of the confidence intervals for the rate differences, ranges from 17% to 34%. As there is clinical benefit for a shorter treatment duration (12 vs 24 weeks compared to SOC) and RBV-free regimen, it is clinically justified to accept an NI margin (M2) of -5% to -10% for the DCV/SOF regimen. As shown below, the trial results demonstrated efficacy through various historical comparisons.

### Results:

Overall, the representation of enrolled subjects for gender and baseline characteristics was reasonable. The treatment-experienced cohort was older than the treatment-naïve cohort (median age 58 years compared to 53 years). Predominantly Caucasians were enrolled (90%) and only 4% of subjects were African American. As mentioned above, only 32 subjects (21%) had cirrhosis at baseline; therefore, limited subjects were available to assess SVR12 rates among the subgroups of subjects who were treatment-naïve or treatment experienced, with baseline cirrhosis. Eleven subjects did not report cirrhosis status and were considered non-cirrhotic for the efficacy analyses because this was a more conservative clinical approach versus excluding these subjects from the analyses.

Results from the phase 3 trial are robust and demonstrate the efficacy of DCV/SOF for the treatment of chronic HCV genotype 3 infection. Overall, 89% of subjects achieved SVR12. The treatment outcomes presented in product labeling are displayed in the table below.

**Treatment Outcomes in ALLY-3**

<b>Treatment Outcomes</b>	<b>Treatment-Naive n=101</b>	<b>Treatment-Experienced n=51</b>	<b>Total n=152</b>
<b>SVR</b>			
All	90% (91/101)	86% (44/51)	89% (135/152)
No cirrhosis <sup>a</sup>	98% (80/82)	92% (35/38)	96% (115/120)
With cirrhosis	58% (11/19)	69% (9/13)	63% (20/32)
<b>Outcomes for subjects without SVR</b>			
On-treatment virologic failure <sup>b</sup>	1% (1/101)	0	0.7% (1/152)
Relapse <sup>c</sup>	9% (9/100)	14% (7/51)	11% (16/151)

a Includes 11 subjects with missing or inconclusive cirrhosis status.

b One subject had quantifiable HCV RNA at end of treatment.

c Relapse rates are calculated with a denominator of subjects with HCV RNA not detected at the end of treatment.

To evaluate efficacy, as stated above, the estimate of M1 based on historical data ranges from 17% to 34%. Dr. Zeng used the SOF/RBV 24 week regimen SVR12 data as the comparison and pooled the treatment-naïve (TN) and experienced (TE) populations (for both DCV/SOF 12 week and SOF/RBV 24 week treatment arms, respectively) and adjusted for treatment history (naïve or experienced) and cirrhosis status at baseline. The result is the following.

(TN+TE): DCV/SOF for 12 weeks -- SOF/RBV for 24 weeks = 2% with 95% CI (-4%, 9%)

The lower bound of the 95% CI (-4%) is higher than the -17% conservative estimate for M1 described above and the -5% to -10% margin which is clinically justified. Thus, the DCV/SOF 12 week regimen is non-inferior to the SOF/RBV 24 week regimen.

Other comparisons also demonstrate efficacy. When comparing DCV/SOF 12 weeks to SOF/RBV 12 weeks, the lower bound of the 95% CI is above zero and demonstrates superiority; thereby establishing the DCV contribution to the regimen [DCV/SOF 12 weeks – SOF/RBV 12 weeks; treatment difference is 34%, 95% CI (24%, 43%). Similar findings are seen when PR 24 weeks is the comparison.

Overall DCV efficacy is demonstrated through various historical comparisons and was either NI to the standard of care: SOF/RBV for 24 weeks or superior to SOF/RBV 12 weeks (to show the contribution of DCV to the regimen) or PR 24 weeks.

Two key factors affected SVR12 rate, the presence of baseline NS5A Y93H polymorphism and cirrhosis. The SVR12 rate for subjects with baseline NS5A Y93H polymorphism was 54% (7/13; 95% CI: 25%, 81%) compared to an SVR12 rate of 92% (124/139; 95% CI: 86%, 96%) for subjects without baseline NS5A Y93H

polymorphism. The review team did consider including a limitation of use statement in section 1 of the product labeling to state SVR12 rates were reduced in subjects with baseline NS5A Y93H polymorphism and to recommend baseline NS5A Y93H polymorphism testing prior to treatment. An assay to detect NS5A Y93H polymorphism in HCV GT 3 subjects is not commercially available. Also HCV GT3 subjects with the Y93H polymorphism is a small minority of the US HCV infected population. In ALLY-3, 9% of the subjects enrolled had the Y93H polymorphism at baseline. Of note, approximately 10% of all US HCV infections are due to GT3; thereby demonstrating the small proportion of HCV GT 3 subjects with the Y93H polymorphism. As Dr. Harrington stated in the clinical virology review, another rationale for not requiring baseline screening or including these data as a limitation of use is because drug resistance-related risks for subjects with the Y93H polymorphism also appear to be small, given that additional major DCV resistance-associated substitutions did not emerge in subjects with the Y93H polymorphism who experienced virologic failure. Finally, a limitation of use statement describing reduced DCV/SOF efficacy in patients with cirrhosis will be included in section 1 of the product labeling, and in ALLY-3 only 3 non-cirrhotic subjects with Y93H experienced virologic failure, representing only 2.6% of the noncirrhotic + cirrhosis-not-reported population. Nevertheless, data on the potential impact of the NS5A Y93H polymorphism on DCV/SOF efficacy for HCV GT3 infected patients will be described in the DCV product labeling in Section 12.4, and referenced in Section 14.

Notably, the SVR12 rate for subjects with cirrhosis at baseline was 63% (20/32) [95% CI: 44%, 79%] compared to 96% (115/120) [95% CI: 91%, 99%] for subjects without cirrhosis; albeit based on a limited number of subjects with cirrhosis (n=32). These data, however, suggest DCV/SOF for 12 weeks may not be optimal for subjects with cirrhosis. Based on these data BMS originally proposed to include the following statement in Section 2 Dosage and Administration of the product labeling: (b) (4)



Therefore, a PMR was issued. The rationale for the PMR was the SVR12 rate was lower and virologic failure was more common in subjects with cirrhosis compared to those without cirrhosis (virologic failure rates of 38% and 4%, respectively), and virologic failure was associated with the emergence of DCV-resistant HCV populations, which are cross-resistant to other drugs in the same class (NS5A inhibitors) and potentially limit re-treatment options. Therefore, the ability to optimize treatment with DCV/SOF in order to limit the rate of virologic failure and treatment-emergent drug resistance is critical, especially for those with cirrhosis because they are potentially more vulnerable to disease progression including development of hepatic cellular carcinoma, liver failure and death. For other HCV combination antiviral therapies and patient populations a longer treatment duration, with or without the addition of the ribavirin, can improve efficacy and reduce the rate of virologic failure, which in turn reduces the rate of drug resistance emergence in the treated population. BMS will conduct a trial to determine if one or more of these approaches improves the efficacy of the daclatasvir plus sofosbuvir regimen in HCV genotype 3 infected patients with cirrhosis. Final protocol details will be discussed later with BMS to determine overall sample size, number of treatment arms, including treatment durations. Results from ongoing trials will help inform the final protocol which is due to the FDA in December 2015.

Other baseline factors such as baseline HCV RNA, gender, age, and IL28B status did not impact SVR12 outcomes.

## **8. Safety**

This section focuses on the safety data from the ALLY-3 phase 3 trial. Overall Dr. Wendy Carter's independent analyses of the safety data confirmed BMS's findings. Please refer to Dr. Carter's review of the original NDA and resubmission to details on events previously reviewed from trials.

### Adequacy of Safety Database:

The primary source of data for DCV/SOF for 12 weeks in HCV GT3 infection is from the phase 3 trial, ALLY-3. In addition, DCV safety was demonstrated in combination with DAA's in various HCV genotypes; however, in regimens for which BMS is not seeking indications and were the subject of the original NDA review for DCV. The totality of safety database for the resubmission NDA was 868 subjects (363 subjects received DCV/SOF ± RBV and 505 subjects received DCV/pegIFN/RBV).

The overall safety database for DCV based regimens and DCV/SOF based regimens for 12 weeks or longer is adequate and consistent with the safety considerations as outlined in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment . Approximately 8,000 subjects were exposed to a DCV containing regimen in the clinical development program. Additionally, 1265 subjects were exposed to DCV 60 mg once daily for 24 weeks in the phase 3 trials (DCV/ASV [DUAL] regimen and DCV/ASV/PR [QUAD] regimens in the original NDA. In total, 2133 subjects (868 + 1265) with chronic HCV infection were treated with the recommended dose of DCV in combination with other DAA's in the pivotal and supportive clinical trials for the original and resubmission DCV NDAs. Additionally, more than 4800 patients have been exposed to DCV under expanded access or compassionate use programs. BMS estimates 25,466 patients have been exposed to DCV, including 4051 global and 21,415 Japanese patients.

The majority of safety data was already reviewed in the original NDA and is not reproduced in entirety in this review. Safety data from all sources show consistent findings with the exception of hepatotoxicity and eosinophilia. These events were seen with ASV/DCV based regimens and not seen with DCV without ASV. See discussion below for further details.

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

No on-treatment deaths were reported in ALLY-3. One SAE of Grade 3 GI hemorrhage was reported in a 58 year old female on Day 15 of treatment with DCV/SOF. She had F3 fibrosis and thrombocytopenia at baseline. I agree with Dr. Carter's and BMS's assessment that the events were unrelated to DCV/SOF and likely related to underlying cirrhosis or portal hypertension with varices undiagnosed at the time of enrollment. No new SAEs were presented in the resubmission from the previously reviewed trials.

No subjects discontinued treatment due to an adverse event; however one subject discontinued treatment at Week 8 due to pregnancy but did achieve SVR12.

The most commonly reported adverse reactions (all grade, all cause) in subjects receiving DCV/SOF were fatigue (20%), headache (20%), nausea (12%), diarrhea (9%), insomnia and nasopharyngitis (both 6%), abdominal pain and arthralgia (both

5%). The adverse reaction profile was similar between subjects with and without cirrhosis, except headache and arthralgia were more common in subjects with cirrhosis. The safety profile from subjects in AI444040 who received DCV/SOF +/- RBV was consistent with the overall findings from ALLY-3. Safety findings from DCV/pegIFN/RBV as described in the original NDA review are consistent with the known safety profile with pegIFN/RBV.

Analyses by sex, age, race and country did not reveal any clinically significant differences or trends in AE reporting or laboratory findings in ALLY-3. However, analyses by race were limited due to the small numbers of non-white subjects enrolled. Of note, females had an approximately 30% higher DCV exposure compared to males but this difference did not lead to any significant differences in adverse events or laboratory abnormalities.

Overall no grade 3 and 4 chemistry laboratory abnormalities occurred in more than 2% of subjects, with the exception of grade 3 and 4 total lipase (2% overall). These increases did not lead to clinical events.

### Special safety concerns

Dr. Carter conducted detailed reviews of adverse events of interest based upon DCV nonclinical data and adverse events for similar drugs in the class, specifically ledipasvir (LDV) which was the first NS5A complex inhibitor approved. The safety profile of SOF is well established in multiple clinical trials and in multiple combinations, including combination with LDV. The most common adverse reactions for SOF are fatigue and headache, and the most common adverse reactions for LDV/SOF are fatigue, headache, nausea, diarrhea and insomnia. These events did not require additional exploratory analyses. This section predominately focuses on (1) hepatotoxicity, (2) hypersensitivity; pyrexia and eosinophilia due findings seen in the phase 3 trials with DCV/ASV based regimens and (3) cardiac toxicity based on postmarketing cases of serious symptomatic bradycardia reported when amiodarone was co-administered with SOF in combination with another DAA including LDV, DCV or simeprevir (SMV). Please refer to Dr. Carter's review of the original NDA and resubmission for details.

### Primary events of interest:

#### ***Hepatotoxicity:***

Based on nonclinical findings (both ASV and DCV had liver findings in animals with histologic changes in some animal species see section 4 above), safety findings from the ASV phase 2 dose-finding trials and the index case of biopsy confirmed drug-induced liver injury with pyrexia, peripheral eosinophilia and eosinophilia and necrosis on liver biopsy, a targeted review for hepatic safety was conducted. Dr. Carter's original NDA review provide an extensive summary of the analyses conducted to further characterize the findings of ALT elevations with and without concomitant

increases in bilirubin and eosinophilia with and without pyrexia and with and without liver involvement.

An exposure-safety analysis showed a higher probability of grade 2-4 increases in ALT seen with higher exposures (both AUC and Cmax) of ASV when given with PR in treatment-naïve genotype 1 and 4 subjects. This finding led to the selection of ASV 100 mg (b) (4) formulation for phase 3 trials because the risk benefit assessment for higher ASV doses (600 mg once daily and 600 mg twice daily) was not favorable in light of the SVR results and increases in ALT and total bilirubin. Similar findings were not observed for the DCV/PR based regimen. Rates of grade 3 or 4 increases in ALT, AST and total bilirubin were similar between DCV/PR and placebo/PR. No DCV/PR subjects met the predefined criteria for potential drug-induced liver injury. Data from AI444040 evaluating DCV/SOF±RBV did not reveal any cases of increased liver biochemistries (ALT, AST or bilirubin) or evidence of hepatotoxicity. BMS convened an external panel of experts to review the totality of the DCV/ASV hepatic safety data. The panel reached consensus and stated the issue of hepatotoxicity appeared related to ASV and not DCV.

No new safety signals with respect to hepatotoxicity were noted for DCV/SOF +/- RBV in either ALLY-3 or AI444040 trial. No hepatic SAES or discontinuations due to hepatic events were seen and no subjects met Hy's Law laboratory or clinical criteria. Non serious events of liver palpable subcostal, hepatic pain and hepatomegaly were seen in trial AI444040. Dr. Carter's NDA resubmission review shows overwhelmingly, subjects treated with DCV/SOF had rapid normalization of their liver biochemistries during treatment. These findings were seen in both cirrhotic and non-cirrhotic subjects. Increases in ALT or AST greater than 3 times ULN occurred in few subjects who developed HCV viral relapse after end of treatment or during the follow-up phase. These changes would be expected for those with relapse because their HCV RNA rebounded and likely does not represent a direct toxicity of DCV/SOF. No significant changes in total bilirubin were noted.

Based on the totality of the data, in my opinion, hepatotoxicity observed with DCV/ASV based regimens, as described in the original NDA, appears related to ASV and not DCV. Of note, hepatotoxicity may be a class effect for HCV protease inhibitors. The simeprevir label recently added a Warning and Precaution for hepatic decompensation and hepatic failure based on postmarketing data. The Viekira Pak label includes a Warning and Precaution for increased risk of ALT elevations (greater than 5 times ULN) which occurred in approximately 1% of all subjects. Notably, more significant elevations were seen in females using ethinyl estradiol-containing medications with concomitant Viekira Pak treatment. Nevertheless, I agree with Dr. Carter's statement that any hepatic concentrated drug may have the potential to cause liver abnormalities in a broad population, particularly one with underlying comorbidities such as chronic HCV. These events will be monitored during postmarketing.

### ***Hypersensitivity, pyrexia and eosinophilia***

All subjects identified with pyrexia and eosinophilia with and without liver involvement received DCV/ASV at the to-be-marketed dosages and were Japanese. Regardless of the presence of pyrexia, eosinophilia findings were transient and occurred most frequently without liver involvement. For the DCV/SOF regimen, no subjects met the criteria for hypersensitivity or had reported pyrexia or evidence of significant eosinophilia. Again, I conclude the data supports ASV as the likely drug contributing to these events, because events of hypersensitivity, pyrexia or eosinophilia were not seen with DCV without ASV.

### ***Cardiac events***

No preclinical cardiac safety signal was observed for DCV. In ALLY-3 no cardiac disorders were reported. Seven patients (3%) in AI444040 reported a cardiac disorder. Of note, subjects receiving RBV reported more events than those not receiving RBV with DCV/SOF (5 vs 2). Most subjects had pre-existing conditions and all events were Grade 1 or 2.

Cardiac events were reviewed in detail as shown in Dr. Carter's review, because in January 2015, the EMA's Pharmacovigilance Risk Assessment Committee asked the manufacturers of SOF and SOF/LDV (Gilead) and DCV to provide a cumulative review of all cardiac arrhythmias, including bradycardia. The EMA considered the possibility of a drug-drug interaction between the HCV agents co-administered with amiodarone. Both Gilead and BMS provided their assessment to FDA. In April 2015, FDA issued a Drug Safety Communication regarding serious reports of bradycardia when amiodarone is used with hepatitis C treatments containing SOF, SOF/LDV or SOF in combination with another DAA, including DCV or SMV. As part of the NDA resubmission BMS conducted a comprehensive review of the cardiac arrhythmias seen with DCV/SOF use. In addition, BMS searched their safety database for events including cardiac failure and cardiomyopathy, evaluated ECGs from patients receiving amiodarone with DCV/SOF and reviewed the phase 3 clinical trials to evaluate cardiac events in subjects receiving calcium channel blockers and/or beta blockers while receiving DCV/SOF (per FDA request). Of note, amiodarone was excluded in most of the clinical trials, but permitted in the expanded access programs.

BMS searched their entire safety database (numbers described above), including the medical literature to identify cardiac arrhythmia events. Overall 30 subjects reported 31 events, of which 17 events occurred in patients receiving DCV/SOF or DCV/SOF/RBV. Among these 17 events, five reports occurred in patients receiving concomitant amiodarone (four cases of severe bradycardia, one case of atrial flutter). Case 21349394 from Dr. Carter's review details a positive dechallenge/rechallenge case. The four cases of severe bradycardia occurred within hours of coadministration up to 12 days. After the report to the EMA and FDA, BMS found a case of cardiac arrest in a subject receiving DCV/SOF and amiodarone. Sudden cardiac arrest occurred 30 minutes after first dose of DCV/SOF while on amiodarone. This 61 year

old female had past medical history of hypertension, atrial fibrillation, coronary arterial disease, ischemic stroke and intra-ventricular hemorrhage along with other comorbidities. Despite the underlying cardiac disorders and other comorbidities in these subjects, strong evidence for an interaction between SOF with another HCV medication such as DCV is evident given the rapid onset and severity of the events. The mechanism for these events is unknown; however, BMS is looking into possible mechanism for this drug-drug interaction including in vitro studies to evaluate transporter effects in amiodarone metabolism and direct interaction with DAA agents on cardiomyocytes which could exacerbate the pharmacodynamic effects of amiodarone. I recommend a PMC to have BMS provide the results of the multielectrode array electrophysiology studies with in vitro incubation of individual agents and/or combination with human stem-cell derived cardiomyocytes to help elucidate potential mechanisms for the bradycardia events described.

At the time of FDA's investigation of serious and life-threatening cases of symptomatic bradycardia reported with coadministration of amiodarone with either SOF/LDV or SOF in combination with another DAA, including DCV or SMV, nine total cases of symptomatic bradycardia were reported during postmarketing. Six cases occurred within the first 24 hours and the remaining three cases within the first 2-12 days. One case was fatal and three cases required pacemaker intervention. In three cases, rechallenge with HCV treatment in setting of continued amiodarone resulted in recurrence of symptomatic bradycardia. All the cases were reviewed by Dr. Shari Targum from the Division of Cardiovascular and Renal Products. She concluded a temporal relationship between the events and initiation of SOF with LDV, DCV or SMV.

The events presented in the resubmission were a subset of the overall nine cases identified in the EMA report and FDA postmarketing reports (as described in the paragraph above) that led to FDA's Drug Safety Communication, Gilead's Dear Healthcare Provider letter and revisions to the SOF, SOF/LDV and SMV label to include Warnings and Precautions. Consequently, the DCV label will include the same Warnings and Precautions. Briefly, from the product labeling highlights section:

Bradycardia when Coadministered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA, particularly in patients also receiving beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended.

Additional analyses were done to explore potential signals for cardiac toxicity; therefore cases of cardiac failure and cardiomyopathy were evaluated. Twenty-six cases were identified, including seven fatal outcomes. The time to onset (provided in 17 cases) ranged from 9 to 185 days (median 51 days) after initiation of DCV

combination therapy. Dr. Shari Targum also reviewed these cases and concluded a safety signal for cardiac dysrhythmia or dysfunction for DCV/SOF in the absence of amiodarone co-administration did not exist. Nevertheless, cardiac related events will be a focus on postmarketing pharmacovigilance assessment.

## **9. Advisory Committee Meeting**

An advisory committee meeting was not held for this application. No controversial safety or efficacy issues were identified that warranted an advisory committee discussion. The issues identified at the preNDA meeting and subsequent meetings were similar issues already addressed in previous HCV NDAs and did not require an advisory committee meeting.

## **10. Pediatrics**

To date, no trials in subjects less than 18 years of age were conducted or are ongoing. A PMR is recommended for ages 3 through less than 18 years and summarized below. A waiver will be granted from birth to less than 3 years of age. A PeRC meeting was held on June 3, 2015 and the committee agreed with the deferral and waiver and the overall pediatric development plan.

## **11. Other Relevant Regulatory Issues**

### Office of Scientific Investigation Inspections

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

### Good Clinical Practice

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

### Financial Disclosures

Financial disclosures were reviewed and 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**

Several labeling discussions occurred with respect to Indications and Usage: Limitations of Use, and Dosage and Administration. At the time of this review the final wording for sections 1 and 2 are still under negotiation; however, the issues discussed are described in the sections above. The additional outstanding labeling issues include the sections 8.1 and 8.2. (b) (4)



(b) (4)

(b) (4)

### 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** I agree with the review team's assessment and recommend approval of DCV/SOF for the treatment of chronic hepatitis C genotype 3 infection.

- **Risk Benefit Assessment:**

DCV/SOF for 12 weeks was safe and effective for the treatment of chronic HCV GT3 infection. Overall 89% of subjects in the ALLY-3 trial achieved SVR12. Notably SVR12 rates were higher in non-cirrhotic subjects (96%) compared to cirrhotic subjects (63%). Please refer to section 7 for further details. This finding is not unique to the DCV/SOF regimen. SVR12 rates are lower in cirrhotics (67%) compared to non-cirrhotics (89%) with the current standard of care SOF/RBV for 24 weeks for HCV GT infection. SVR12 rates are similar between DCV/SOF for 12 weeks and SOF/RBV for 24 weeks in cirrhotic subjects; albeit each is based on a limited sample size (n=32 cirrhotic genotype 3 subjects receiving DCV/SOF for 12 weeks and n=58 cirrhotic genotype 3 subjects receiving SOF/RBV for 24 weeks). These data; however, do suggest DCV/SOF for 12 weeks may not be optimal for subjects with cirrhosis. A PMR will be issued to BMS to conduct a trial to determine if a longer duration of treatment or addition of RBV improves SVR12 rates of DCV/SOF for HCV genotype 3 infected subjects with cirrhosis.

In addition to baseline cirrhosis status, the presence of baseline Y93H polymorphism also affected SVR12 rates. The SVR12 rate for subjects with baseline NS5A Y93H polymorphism was 54% (7/13) compared to an SVR12 rate of 92% (124/139) for subjects without baseline NS5A Y93H polymorphism. As a result the review team did not require routine baseline screening for the reasons outlined in Section 7. These data are included in the section 12.4 of the product labeling.

Virologic failure in ALLY-3 was associated with the emergence of DCV resistance-associated substitutions, most commonly NS5A Y93H, which can confer cross-resistance to other NS5A inhibitors and limit re-treatment options.

The resistance-related consequences of virologic failure for subjects with the NS5A Y93H polymorphism, however, are different for genotype 3 subjects compared to genotype 1 subjects with NS5A polymorphisms, as additional major resistance substitutions did not emerge in HCV genotype 3 virologic failure subjects with pre-existing Y93H baseline polymorphism.

Despite the lower SVR12 rates in cirrhotic subjects and impact of baseline Y93H polymorphism of SVR12 rates, DCV/SOF provides an interferon and RBV-sparing alternative for subjects with chronic HCV genotype 3 infection and a shorter duration of treatment compared to the standard of care, SOF/RBV. Overall the SVR12 rates are similar between DCV/SOF for 12 weeks and SOF/RBV for 24 weeks in genotype 3 patients; although based on cross-trial comparisons.

The overall safety profile of DCV/SOF is favorable. The safety profile of DCV was established in several genotypes, including genotype 3 and in several combinations (DCV/ASV +/- PR, DCV/PR and DCV/SOF). Safety data from all sources show consistent findings with the exception of hepatotoxicity and eosinophilia that as seen with ASV/DCV based regimens and not seen with DCV without ASV. See section 8 discussion above for further details.

In ALLY-3, no deaths, no discontinuations due to AEs and only one unrelated on-treatment SAE of GI hemorrhage (due to varices) was reported. The most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. There were no clinically significant trends for laboratory abnormalities. Analyses by sex, age, race and country did not reveal any clinically significant differences or trends in AE reporting or laboratory findings in ALLY-3. Overall toxicity profile was similar between subjects with and without cirrhosis, with the exception of headache and arthralgia which was more frequently reported in subjects with cirrhosis.

Risk of serious, life-threatening bradycardia was identified when amiodarone was co-administered with sofosbuvir in combination with another DAA, including DCV. This event was not seen in clinical trials because amiodarone use was prohibited but was seen in expanded access/compassionate use programs where amiodarone use was allowed. The four cases of severe bradycardia occurred within hours of coadministration up to 12 days. The label includes a Warnings and Precaution for this event. Of note, the SOF, SOF/LDV and SMV labels all include the same Warnings and Precautions for serious bradycardia. Hepatic associated adverse events and laboratory abnormalities were not evident with DCV/SOF.

DCV has the potential for other drugs to affect DCV exposures. Dose modification is needed with strong CYP3A inhibitors or moderate CYP3A inducers. Strong inducers of CYP3A are contraindicated. These types of interactions are seen with other anti-HCV agents and can be managed with careful attention to patient's

current medication list and changing medications during treatment. For a 12 week regimen, drug interactions can be managed.

DCV/SOF appears to provide a number of advantages, including improved tolerability as this represents the first non-pegIFN/RBV containing regimen for chronic HCV GT3 infection, manageable safety profile, and shorter duration than the current standard of care. DCV/SOF regimen provides an unmet medical need for patients who cannot take RBV. The overall benefit risk assessment is favorable for the 12 week DCV/SOF regimen as demonstrated in ALLY-3 trial.

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

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

- **Recommendation for other Postmarketing Requirements and Commitments**

Below is a recommended list of PMRs. Final dates are currently being negotiated with BMS

- Conduct a trial to determine if a longer duration of treatment or addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) of daclatasvir plus sofosbuvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.
- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of daclatasvir in combination with other direct acting antivirals in pediatric subjects 3 through 17 years of age with chronic hepatitis C.
- Characterize the long-term ( $\geq 1$  year) persistence of treatment-emergent, daclatasvir resistance-associated substitutions in HCV genotype 3 infected subjects.

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/s/  
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KIMBERLY A STRUBLE  
07/08/2015