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*APPLICATION NUMBER:*

**206843Orig1s000**

**SUMMARY REVIEW**

## Decisional Review for NDA 206843

<b>Date</b>	July 23, 2015
<b>From</b>	Debra Birnkrant, M.D.
<b>Subject</b>	Division Director's Summary Review
<b>NDA/BLA # Supplement #</b>	NDA 206843/Resubmission
<b>Applicant Name</b>	Bristol-Myers Squibb Company
<b>Date of Submission</b>	February 13, 2015
<b>PDUFA Goal Date</b>	August 13, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Daklinza <sup>TM</sup> /daclatasvir
<b>Dosage Forms / Strength</b>	60 mg and 30 mg tablets for oral use
<b>Proposed Indication(s)</b>	Indicated for use with sofosbuvir for the treatment of adults with genotype 3 chronic hepatitis C virus infection
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Dr. Wendy Carter
Statistical Review	Drs. Wen Zeng and Fraser Smith supervised by Dr. Dionne Price
Pharmacology Toxicology Review	Dr. Peyton Myers and Dr. Mark Powley supervised by Dr. Hanan Ghantous.
CMC Review	Dr. Chunchun Zhang with Dr. Stephen Miller, CMC- Lead
Microbiology Review	Dr. Patrick Harrington, Dr. Lalji Mishra and Dr. Eric Donaldson, supervised by Dr. Jules O'Rear
Clinical Pharmacology/Pharmacometrics Review	Dr. Stanley Au supervised by Dr. Shirley Seo; Dr. Fang Li supervised by Dr. Jeffry Florian
DDMAC	Dr. Kemi Asante
OSI	Dr. Antoine El Hage
CDTL Review	Dr. Kim Struble
OSE/DMEPA	Dr. Mónica Calderón
OPM/DMPP	Dr. Morgan Walker
OSE/DRISK	Dr. Robert G. Pratt
DPMHM	Dr. Miriam Dinatale
DCRP	Dr. Shari L. Targum

OND=Office of New Drugs  
DDMAC=Division of Drug Marketing, Advertising and Communication  
OSE= Office of Surveillance and Epidemiology  
DMEPA=Division of Medication Error Prevention and Analysis  
DSI=Division of Scientific Investigations  
DDRE= Division of Drug Risk Evaluation  
DRISK=Division of Risk Management  
CDTL=Cross-Discipline Team Leader  
OMP=Office of Medical Policy  
DMPP=Division of Medical Policy Programs  
DPMHM=Division of Pediatric and Maternal Health Memorandum  
DCRP=Division of Cardiovascular and Renal Products

## 1. Introduction

This Division Director's memorandum provides a topline summary of NDA 206843 for Bristol-Myers Squibb Company's New Drug Application (NDA) for daclatasvir (DCV), a hepatitis C virus (HCV) NS5A inhibitor indicated for the treatment of adults with genotype 3 chronic hepatitis C viral infection in combination with sofosbuvir (SOF), a nucleotide analog NS5B polymerase inhibitor. This decisional review summarizes pertinent findings from the NDA resubmission, FDA's multidisciplinary reviews and product labeling.

## 2. Background

It is estimated that chronic hepatitis C (CHC) affects 170 million worldwide and 3.2 million domestically. Chronic hepatitis C virus is now classified into seven genotypes and many subtypes. Hepatitis C genotype 3 is responsible for approximately 20-30% of HCV infections worldwide and about 10% of infections domestically (Gower et al., J. Hepatology 2014; Messina et al., Hepatology 2015). HCV genotype subtype 3a is the most prevalent subtype in the U.S.; genotype and subtype are important determinants of antiviral product efficacy.

Sustained virologic response (SVR) is the measure of virologic cure used in clinical trials. SVR12 is measured 12 weeks after the end of treatment. FDA considers SVR to be a validated surrogate efficacy endpoint that is correlated with clinically important outcomes such as histologic benefit, a decrease in all-cause and liver-related mortality, and decreases in rates of HCC and hepatic decompensation (Backus, et al, Clin. Gastroenterol Hepatol 2011; Singal, et al, Clin Gastroenterol Hepatol 2010; van der Meer, et al. JAMA 2012; Veldt, et al, Ann Intern Med 2007; Mishra, et al, Hepatology 2015).

Treatment of chronic hepatitis C viral infection (CHC) has improved over the years, especially with the approval of potent direct-acting antivirals (DAA). Specifically, the field is moving towards interferon-free regimens, in general and ribavirin-free regimens for certain genotypes. For genotype 3, current treatment standards are outlined in the 2015 American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) treatment guidelines that were recently published. Current recommendations include use of SOF with pegylated interferon/ribavirin (P/R) for 12 weeks or alternatively, SOF plus ribavirin (RBV) for 24 weeks for genotype 3 subjects.

DCV is the third direct-acting antiviral (DAA) in the class of NS5A inhibitors, but the first for treatment of HCV genotype 3 infection. An NDA for DCV was previously submitted in 2014 along with a separate NDA for asunaprevir, an NS3/4A protease inhibitor for treatment of CHC. A hepatotoxicity signal was seen in clinical trials with the use of the combination, especially in Japanese subjects. BMS withdrew the asunaprevir NDA and FDA issued a Complete Response (CR) for the DCV NDA. Discussions were held and agreements were reached with the Applicant regarding the contents of the resubmission. The DCV NDA was resubmitted in response to the CR and underwent a mandatory 6-month review. The resubmitted NDA encompasses data from a principal Phase 3 clinical trial, ALLY-3 in patients with HCV genotype 3 infection and data from regimens including SOF with or without RBV and P/R for up to 24 weeks that were previously reviewed under the original NDA submission. In addition, data were reviewed for safety from European access programs and post-marketing data from Japan where it is approved. For a complete U.S. regulatory history of the application see the original clinical review and the review of the resubmitted NDA by Dr. Wendy Carter and the CDTL memorandum by Dr. Kim Struble.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), FDA inspected three clinical sites with high enrollment that participated in ALLY-3. Based on the inspection findings, the data generated were found to be reliable and acceptable in support of this application.

As previously stated, DCV is the third NS5A inhibitor in its class. The application was not presented before the Antimicrobial Drugs Advisory Committee because a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

### **3. CMC**

The primary CMC reviewer of the DCV NDA is Dr. Chunchun Zhang. Dr. Stephen Miller served as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity, and quality of DCV. All CMC issues were addressed during the original NDA review cycle. An overall recommendation of Acceptable has been made by the Office of Process and Facilities. Therefore, from a CMC perspective, NDA 206843 is recommended for approval.

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

Please see review of submitted nonclinical toxicology studies by Dr. Peyton Myers and QSAR review by Dr. Mark Powley, supervised by Dr. Hanan Ghantous.

Per Dr. Myers' review, the nonclinical safety profile of DCV has been satisfactorily evaluated in the following studies: safety pharmacology, secondary pharmacology, PK/ADME, single-dose and repeat-dose toxicity, carcinogenicity studies (2 year study in rats and 6 month study in transgenic mice), genotoxicity,

reproductive toxicity, local tolerance, immunotoxicity, and phototoxicity. No significant safety pharmacology signals were detected in studies evaluating cardiotoxicity, CNS toxicity and respiratory effects.

Per Dr. Myers' review, the main findings observed with DCV in the nonclinical studies included liver findings (increased weight, liver histologic changes) in NHPs; no liver effects were notable in the 6 month study in rats. In monkeys dosed 4 months, liver enzymes (AST, ALT) increased with dose with accompanying histological changes (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). Also see Dr. Carter's clinical review of the available hepatic safety data from the DCV/asunaprevir program that suggests that the increased risk for hepatic toxicity in humans, mostly manifested with eosinophilia, with and without pyrexia appeared likely related to asunaprevir.

In both rats and monkeys, adrenal gland findings included increases in adrenal gland size/weight, morphologic hypertrophy, and/or hyperplasia of cortical cells in the zona fasciculata and/or zona reticularis, increases in urine corticosterone levels (rats), and changes in cytoplasmic vacuolation. In rats, there was also a finding of increased urine output concurrent with increased water consumption in rats (with no associated adverse effects). Adrenal activity was monitored in early clinical trials (cortisol), but no effects were noted.

Carcinogenicity studies in rats and transgenic mice showed no drug-related increase in tumor incidence at exposures that were 6-fold and 8.7 fold the human systemic exposure at the therapeutic daily dose. Also of note, unspecified impurities in drug substance and specified impurities lack mutagenic potential per Dr. Powley's QSAR review. Regarding reproductive toxicity, male fertility parameters were affected in rats at 26-fold the human systemic exposure at the therapeutic daily dose. The risk for fertility effects from these findings is likely low due to the high safety margins as well as the lack of any direct effects of DCV on female fertility parameters or survival status and total number of offspring from the rodent fertility studies.

There are no adequate and well-controlled trials of DCV in pregnant women to inform a drug-associated risk. Therefore, the benefits and risks of DCV should be considered when prescribing DCV to a pregnant woman.

## **5. Clinical Pharmacology**

Dedicated clinical pharmacology trials were conducted in healthy volunteers and HCV-infected subjects to characterize the pharmacokinetics (PK) of DCV. DCV is an inhibitor of P-gp, OATP1B1 and 1B3 and BCRP. Consequently, DCV may increase systemic exposure of products that are substrates of these transporters. DCV is a substrate of CYP3A. For use with strong CYP3A inhibitors such as ketoconazole, it is recommended to decrease the dose of DCV to 30 mg. For use with moderate inhibitors, labeling advises monitoring for adverse events, whereas for use with moderate inducers such as efavirenz, labeling recommends increasing the dose of

DCV to 90 mg. Strong CYP3A inducers such as phenytoin, carbamazepine, rifampin and St. John's wort are contraindicated with DCV. For use with certain anticoagulants, antiarrhythmics and HMG-CoA reductase inhibitors see table 3 in labeling and specific prescribing information for concomitant medications. For use with amiodarone, see Warnings and Precautions, Adverse Reactions, and Drug Interactions sections of the DCV label.

Other pertinent PK data include the following and appear in product labeling:

- No dose adjustment is required for any degree of renal impairment and DCV is unlikely to be removed by dialysis due to protein binding.
- No dose adjustment is required for subjects with mild, moderate or severe hepatic impairment, however data are not available in subjects with decompensated cirrhosis or liver transplant patients.
- DCV does not prolong the QT interval to any clinically relevant extent at a dose that is three times the recommended dose.
- DCV can be dosed without regard to food.
- Based on population pharmacokinetic analyses in HCV-infected subjects it is estimated that female subjects have a 30% higher DCV AUC compared to male subjects. This AUC difference is not considered clinically relevant.
- There was no evidence of drug-drug interactions when DCV was administered with oral contraceptives containing ethinyl estradiol/norgestimate.

Labeling will contain a warning and precaution related to risk of adverse reactions or loss of virologic response due to drug interactions. See section 5.1 of labeling.

Dose selection was based on trials conducted in genotype 1 subjects. The 60 mg dose was selected from phase 2 trial 014 when dosed in combination with pegylated interferon and ribavirin (P/R) for 48 weeks. This dose was evaluated in trial 010 in combination with P/R. Per Dr. Struble's CDTL memorandum, 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 characteristics compared to a 20 mg dose. To maximize response rates, particularly for difficult-to-treat populations the 60mg dose was selected for further evaluation in all genotypes.

## **6. Clinical Microbiology**

Please see extensive reviews by Drs. Patrick Harrington, Lalji Mishra, and Eric Donaldson who conducted the review of virology and resistance data, with supervisory concurrence by Dr. Jules O'Rear. Our virology review staff concluded that DCV is approvable with respect to virology for the treatment of Genotype 3 CHC.

DCV is an NS5A inhibitor that interacts with the N-terminus within Domain 1 of the non-structural protein. DCV has a median EC<sub>50</sub> value of 0.2 nM against HCV GT3a replicons without resistance-associated polymorphisms. DCV activity is reduced by the presence of resistance-associated polymorphisms present at NS5A positions 28, 30, 31 or 93 with EC<sub>50</sub> values ranging from 1.3-50 nM.

Clinical virology analyses were conducted in ALLY-3 to evaluate the antiviral efficacy and virological resistance of DCV. Seventeen of 152 genotype-3 infected subjects treated with DCV in ALLY-3 experienced virologic failure. Virus from the 17 subjects had one or more of the following resistance-associated substitutions: A30K/S, L31I, S62A/L/P/T or Y93H. Y93H was the most common substitution at failure occurring in 15/17 subjects of whom 6/15 had the Y93H substitution at baseline. For NS5B resistance-associated substitutions, one subject had treatment emergent S282T at failure.

There is clinical virology evidence that treatment-emergent resistance-associated substitutions in NS5A persist for more than one year. This is based on data from a separate long-term follow-up study primarily in genotype 1 subjects.

SVR rates are impacted by the presence of the NS5A Y93H polymorphism at baseline as outlined in the table below from product labeling.

**Table 7: SVR12 Rates in Subjects with HCV Genotype 3 with/without the Baseline NS5A Y93H Polymorphism, by Cirrhosis Status**

Study Population	SVR12 with Y93H	SVR12 without Y93H
All subjects	54% (7/13)	92% (124/135)
No cirrhosis <sup>a</sup>	67% (6/9)	98% (105/107)
With cirrhosis	25% (1/4)	68% (19/28)

<sup>a</sup> Includes 11 subjects with missing or inconclusive cirrhosis status.

Cross-resistance to DCV is not expected with direct-acting antivirals from other classes. Cross-resistance to other NS5A inhibitors is expected. However, the combination of DCV with SOF has not been studied in subjects who have previously failed an NS5A inhibitor. In ALLY-3 seven patients were previously treated with a SOF-based regimen; 5/7 achieved SVR12.

## 7. Clinical/Statistical-Efficacy

The clinical review was conducted by Dr. Wendy Carter with secondary review provided by Dr. Kim Struble who also served as the CDTL. The Biometrics review was conducted by Dr. Wen Zeng with secondary review provided by Dr. Fraser Smith and supervisory review provided by Dr. Dionne Price.

Principal study ALLY-3 was an open label phase 3 study of DCV in combination with SOF for Genotype 3 subjects who were either treatment naive (n=101) or treatment experienced (n=51), with or without a diagnosis of cirrhosis. ALLY-3 was conducted in the U.S. and Puerto Rico. The trial design was consistent with recommendations in FDA's revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013.

The primary endpoint was SVR using the Roche COBAS TaqMan HCV v2.0 assay (with a LLOQ = 25 IU/mL) at 12 weeks after completion of therapy. The overall SVR12 rate was 89% (135/152) with 95% confidence interval (CI) of (83%, 93%). The SVR12 rate for the treatment naive cohort was 90% (91/101) with 95% CI of (83%, 95%), and 86% (44/51) with 95% CI of (74%, 94%) in the treatment-experienced cohort. Per Dr. Zeng, given the sample sizes in the trial, the SVR12 rates between these cohorts were comparable.

The SVR12 rate was lower for subjects with cirrhosis compared to those without cirrhosis: 63% (20/32) with 95% CI of (44%, 79%) for subjects with cirrhosis at baseline and 96% (115/120) with 95% CI of (91%, 99%) for subjects without cirrhosis at baseline. As the confidence intervals for cirrhotics and non-cirrhotics did not overlap, this finding may suggest that the DCV/SOF 12-week regimen may not be the optimal regimen for subjects with cirrhosis. The Applicant agreed to conduct an additional trial to address a more optimal treatment regimen in cirrhotic subjects as part of a post-marketing requirement. Further, the SVR12 rate for subjects with the Y93H baseline polymorphism was also lower: 54% (7/13) with 95% CI of (25%, 81%) and 92% (128/139) with 95% CI of (86%, 96%) for subjects without the Y93H baseline polymorphism, respectively. The prevalence of the Y93H polymorphism in ALLY-3 was only about 9% and the prevalence of Genotype 3 in the U.S. population is also less than 10%. In addition there is not a commercially available assay to detect the NS5A Y93H polymorphism in HCV genotype 3. Therefore, for these reasons, it is not recommended to screen for the Y93H baseline polymorphism in product labeling.

The ALLY-3 protocol did not define an NI margin for determination of efficacy. Dr. Zeng calculated potential NI margins based on historical data from multiple trials including the VALENCE trial where genotype 3 subjects received SOF with RBV for 24 weeks. Dr. Zeng determined that the NI margin (M1) could be as low as -17% without any clinical consideration for M2. The stratum-adjusted SVR12 risk difference between the new regimen (DCV/SOF 12 weeks) and the SOC (SOF/RBV 24 weeks) is about 2% with 95% CI of (-4%, 9%) using the Mantel-Haenszel approach. The lower bound of the 95% CI is -4% which is well within the derived NI margin (M1) of -17% and a clinically justified NI margin (M2) of -5 to -10% for the shorter and ribavirin-free DCV/SOF regimen. Therefore, we concluded that the DCV/SOF regimen is non-inferior to standard-of-care.

Overall, both the Clinical and Statistical reviewers' independent analyses confirmed the Applicant's conclusions of effectiveness based on ALLY-3 with support from other



trials where approximately 1900 subjects with CHC have been treated with the recommended dose of DCV in combination with other anti-HCV drugs.

## **8. Safety**

Safety information from the overall DCV development program was reviewed including previously reviewed data from the original DCV NDA. The safety database for the NDA contained over 1900 subjects. These subjects 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. More than 4800 patients have been exposed to DCV under expanded access or compassionate use programs. Further, BMS estimates 25,466 patients have been exposed to DCV, including 21,415 Japanese patients.

The majority of safety data was already reviewed in the original NDA. Safety data from all sources showed consistent findings with the exception of hepatotoxicity and eosinophilia events seen with asunaprevir/DCV based regimens and not seen with DCV without asunaprevir.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug in the same class and may not reflect the rates observed in practice. The following wording and table appear in product labeling:

Approximately 1900 subjects with chronic HCV infection have been treated with the recommended dose of DCV in combination with other anti-HCV drugs in clinical trials.

In the ALLY-3 study, 152 treatment-naive and treatment-experienced subjects with HCV genotype 3 infection were treated with DCV 60 mg once daily in combination with SOF for 12 weeks. The most common adverse reactions (frequency of 10% or greater) were headache and fatigue. All adverse reactions were mild to moderate in severity. One subject experienced a serious adverse event that was considered unrelated to DCV, and no subjects discontinued therapy for adverse events.

Adverse reactions considered at least possibly related to treatment and occurring at a frequency of 5% or greater are presented in Table 2.

**Table 2: Adverse Reactions Reported at  $\geq 5\%$  Frequency, DAKLINZA + Sofosbuvir for 12 Weeks**

Adverse Reaction	n (%) n=152
Headache	21 (14%)
Fatigue	21 (14%)
Nausea	12 (8%)
Diarrhea	7 (5%)

No cardiac safety signals were observed in nonclinical studies. Further, in ALLY-3 no cardiac disorders were reported. However, cardiac events from BMS' entire safety data base and literature were reviewed in detail in Dr. Carter's review because of an identified potential drug-drug interaction (DDI) with use of amiodarone co-administered with SOF in combination with another HCV DAA, including DCV. The potential DDI resulted in severe, life-threatening bradycardia.

Specifically, BMS identified 17 cardiac reports that occurred in patients receiving DCV/SOF or DCV/SOF/RBV. Of these 17 events, five reports occurred in patients receiving concomitant amiodarone; amiodarone was excluded from use in most clinical trials evaluating DCV, but was allowed in expanded access programs. Of these 5 reports, four reports were of severe bradycardia that occurred within hours of coadministration to up to 12 days later; there was also a report of atrial flutter. BMS subsequently submitted a case of cardiac arrest in a 61 year old female subject receiving DCV/SOF and amiodarone whose past medical history included hypertension, atrial fibrillation, coronary artery disease, ischemic stroke and intra-ventricular hemorrhage along with other comorbidities. Cardiac arrest occurred 30 minutes after the first dose of DCV/SOF while the subject was on amiodarone; she survived the cardiac arrest. Despite the underlying cardiac disorders and other comorbidities in these subjects, a drug interaction was suspected given the rapid onset of the events associated with dosing. These cardiac events were also reviewed in consultation with the Division of Cardio-Renal Products. Also, these events along with other cases associated with use of SOF in combination with another DAA and amiodarone served as the basis for the Dear Healthcare Provider Letter sent by Gilead Sciences, FDA's Drug Safety Communication and changes to the SOF, SOF/ledipasvir and simeprevir labels.

The following wording will appear in the Warnings and Precautions section of DCV labeling:

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with another HCV direct-acting antiviral, including DAKLINZA. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (ledipasvir/sofosbuvir). Bradycardia has generally occurred within hours to days, but cases have been observed up

to 2 weeks after initiating HCV treatment. Patients also taking beta blockers or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this bradycardia effect is unknown.

Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. For patients taking amiodarone who have no alternative treatment options and who will be coadministered DAKLINZA and sofosbuvir:

- Counsel patients about the risk of serious symptomatic bradycardia
- Cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking sofosbuvir in combination with DAKLINZA who need to start amiodarone therapy due to no other alternative treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long elimination half-life, patients discontinuing amiodarone just prior to starting sofosbuvir in combination with DAKLINZA should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pain, confusion, or memory problems [see *Adverse Reactions (6.2) and Drug Interactions, Table 3 (7.3)*].

BMS is evaluating possible mechanisms for this potential drug-drug interaction including amiodarone's direct interaction with DAAs on cardiomyocytes that could exacerbate the pharmacodynamic effects of amiodarone. Data from these studies will be submitted in response to post-marketing requirements.

#### Laboratory Abnormalities

Transient, asymptomatic lipase elevations of greater than 3 times the upper limit of normal (ULN) were observed in 2% of subjects in ALLY-3.

Of note, females had an approximately 30% higher DCV exposure compared to males but this difference did not appear to lead to any significant differences in adverse events or laboratory abnormalities.

## Deaths

No deaths were reported in ALLY-3. Two deaths were reported in subjects treated with DCV/pegIFN/RBV during the follow-up period. Subject AI444011-16-81 died due to sepsis, hemorrhagic shock, liver and renal failure during follow-up 83 days after the last-dose of DCV. Subject AI444011-58-69 died due to hemoperitoneum as a complication of hepatocellular carcinoma 232 days after the last dose of DCV. In addition, one subject exposed to placebo + pegIFN/RBV also died. These deaths are unlikely to be related to use of DCV because of both the nature of the events, the comorbidities of the target population (e.g. hepatocellular carcinoma), the timing of the events (mostly during follow up period) and the concomitant use of pegIFN/RBV.

## 9. Advisory Committee Meeting

The application was not presented before the Antimicrobial Drugs Advisory Committee because it was the third drug in the class of NS5A inhibitors. Further, a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

## 10. Pediatrics

The review team met with the Pediatric Review Committee (PeRC) on June 3, 2015. The PeRC agreed with the Division to grant a deferral for a study in pediatric patients aged 3 through 17 years because the product is ready for approval in adults. A PMR for pediatric studies will be triggered under the Pediatric Research Equity Act (PREA) at the time DCV is approved.

## 11. Other Relevant Regulatory Issues

Recommended Postmarketing Requirements include the following to which the Applicant agreed:

### Required Pediatric Assessments under PREA

2930-1 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.

Final Protocol Submission:	10/31/2019
Study/Trial Completion:	07/31/2023
Final Report Submission:	12/31/2023

## Postmarketing Requirements

2930-2 Conduct an observational study to characterize the long-term (> 1 year) persistence of treatment-emergent daclatasvir resistance-associated substitutions in hepatitis C virus genotype 3 infected subjects who failed treatment with daclatasvir-containing treatment regimens.

Final Protocol Submission:	completed
Study Completion:	09/2017
Final Report Submission:	9/2018

2930-3 Evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between amiodarone and HCV direct acting antivirals including daclatasvir using a multielectrode array electrophysiology study in human stem-cell derived cardiomyocytes.

Final Protocol Submission:	completed
Trial Completion:	12/2015
Final Report Submission:	02/2016

2930-4 Evaluate the effect of individual direct acting antivirals, including daclatasvir on the plasma protein binding of amiodarone using the TRANSIL® high sensitivity binding assay to help elucidate the potential mechanism of an interaction between amiodarone and HCV direct acting antivirals.

Final Protocol Submission:	completed
Trial Completion:	12/2015
Final Report Submission:	02/2016

2930-5 Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with daclatasvir plus sofosbuvir to determine if a longer duration of treatment or the addition of ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations.

Final Protocol Submission:	12/2015
Trial Completion:	05/2017
Final Report Submission:	11/2017

## 12. Labeling

Final negotiations related to labeling have been completed.

### **13. Decision/Action/Risk Benefit Assessment**

This NDA examined the use of DCV in combination with SOF for the treatment of CHC in subjects with genotype 3 with and without cirrhosis. This combination was shown to be efficacious and well-tolerated with a manageable safety profile. Overall SVR rates were 89% and even higher, 96%, in subjects without cirrhosis. Overall SVR rates in cirrhotic subjects (n=32) were 63%. Treatment-experienced cirrhotic subjects had an SVR rate of 69%. Due to lower rates of SVR in subjects with cirrhosis, the Applicant agreed to conduct a post-marketing clinical trial to examine whether a longer duration of treatment or the addition of RBV will improve SVR rates, which could reduce the risk of virologic failure and drug resistance emergence. Drug-drug interactions are complex, but product labeling adequately conveys this issue and other safety considerations including bradycardia in the setting of administration of DCV with SOF and amiodarone. Although the original NDA that contained DCV data with asunaprevir showed hepatotoxicity, we agree with BMS' external panel of experts who concluded that hepatotoxicity appeared to be related to asunaprevir. It should also be noted that any drug that concentrates in the liver may have the potential to cause hepatotoxicity, particularly one with underlying comorbidities such as chronic HCV infection.

In sum, I am in agreement with the conclusions of the multidisciplinary review team that the benefit-risk assessment favors approval of DCV in combination with SOF for CHC genotype 3 subjects. The approved regimen of DCV with SOF for 12 weeks in genotype 3 subjects will meet an unmet medical need, particularly in subjects who are interferon ineligible or unable to tolerate P/R regimens.

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/s/

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DEBRA B BIRNKRANT  
07/23/2015