# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 206843Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Risk Evaluation and Mitigation Strategy (REMS) Review

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|---|---|
| Date: | July 16, 2015 |
| Reviewers: | Bob Pratt, Pharm.D.<br>Division of Risk Management |
| Acting Team Leader: | Jamie Wilkins Parker, Pharm.D.<br>Division of Risk Management |
| Acting Deputy Division Director: | Reema Mehta, Pharm.D., M.P.H.<br>Division of Risk Management |
| Subject: | Evaluation to determine if a REMS is necessary |
| Drug Name(s): | Daklinza (daclatasvir) |
| Therapeutic Class: | Hepatitis C virus (HCV) NS5A inhibitor |
| Dosage and Route: | 30 mg and 60 mg tablets |
| Indication: | For use with sofosbuvir for the treatment of patients with genotype 3 chronic hepatitis C virus infection |
| Application Type/Number: | NDA 206843 |
| Applicant/Applicant: | Bristol-Myers Squibb |
| OSE RCM #: | 2014-673 |

# 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) Daklinza (daclatasvir) tablets, NDA 206843. Bristol-Myers Squibb (BMS) originally submitted two NME applications, asunaprevir (ASV) NDA 206844 and daclatasvir (DCV) NDA 206843, on March 31, 2014, both with the proposed indication to treat chronic hepatitis C virus (HCV) infection. Both NDAs shared the same pivotal Phase 3 trial data. On October 6, 2014, BMS withdrew the ASV application as a business decision. As a result, the daclatasvir NDA did not contain adequate evidence to establish the safety and efficacy of daclatasvir without ASV for the treatment of chronic HCV infection. Thus, daclatasvir received a Complete Response (CR) on November 25, 2014.

On February 13, 2015, the Agency received a resubmission of NDA 206843 for daclatasvir from BMS in response to the CR letter dated November 25, 2014. The proposed indication was for the treatment of chronic HCV infection as a component of a combination antiviral treatment regimen in adults, in combination with sofosbuvir in (b) (4) adults with HCV genotype-3 infection (b) (4)

For this NDA resubmission, the Applicant did not submit a proposed REMS.

## 1.1 DISEASE BACKGROUND[1-4]

Infection with the single-stranded RNA virus hepatitis C can result in both acute and chronic hepatitis. Approximately 20 to 30 percent of newly infected persons develop signs and symptoms of an acute illness, which can include fever, fatigue, loss of appetite, and other non-specific symptoms. Although the acute disease is usually self-limited, the immune response is mostly insufficient to eradicate the virus such that acute infection leads to chronic infection in 60 to 80 percent of cases. Chronic HCV infection is associated with ongoing liver inflammation and often follows a progressive course over years to decades, increasing the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

HCV lacks a proofreading mechanism during replication that leads to frequent viral mutations and viral heterogeneity. At least seven distinct HCV genotypes and more than 60 subtypes have been identified, with varying geographic distribution. Genotype 1 is the most common genotype in the United States, with genotypes 2 and 3 less common. The viral diversity and heterogeneity have prevented the development of a vaccine and also affect the completeness of response to antiviral therapy.

The goal of antiviral therapy in patients with chronic HCV is to see an absence of HCV RNA 12 or 24 weeks after the completion of treatment. This is defined as a sustained virologic response (SVR), which is associated with a very low risk of viral reactivation and reduced risk of disease progression. The type and duration of antiviral therapy selected is dependent on the viral

[1] Chopra S. Clinical manifestations and natural history of chronic hepatitis C virus infection. In:UpToDate, Di Bisceglie AM and Bloom A (Eds), UpToDate, Waltham, MA, 2014.
[2] Chopra S. Characteristics of the hepatitis C virus. In:UpToDate, Edward MS, Di Bisceglie AM, and Bloom A (Eds), UpToDate, Waltham, MA 2014.
[3] Feeney ER and Chung RT. Antiviral treatment of hepatitis C. BMJ 2014; 349:g3308.
[4] Liang TJ and Ghany MG. Current and future therapies for hepatitis C virus infection. NEJM 2013; 368:1907-17.

genotype, the patient's baseline disease and host factors, the patient's prior treatment experience and response, and other factors.

HCV has been treated with combinations of indirect acting antivirals and direct acting antivirals. The indirect acting agents typically used include interferon alfa and ribavirin, which have broad antiviral activity but are associated with many toxicities as well as variable efficacy against the different HCV genotypes. Direct acting antivirals are designed to target specific non-structural HCV proteins. Some agents inhibit the NS3/4A serine protease, which cleaves the HCV polyprotein into several polypeptides with distinct functions. Other direct acting antivirals target the NS5A protein necessary for viral assembly and replication, or inhibit the NS5B RNA-dependent RNA polymerase responsible for replication of HCV RNA.

### 1.2 PRODUCT BACKGROUND

Daclatasvir is a selective NS5A replication inhibitor of HCV with broad genotype coverage. Daclatasvir monotherapy is not recommended; it is to be used in combination with sofosbuvir (an HCV NS5B polymerase inhibitor) in the treatment of adults with HCV genotype 3 (GT3) infection. It is available as 30 mg and 60 mg tablets. The recommended dose of daclatasvir is 60 mg once daily for 12 weeks.

### 1.3 REGULATORY HISTORY

March 31, 2014: The Agency received two separate original NDA submissions from BMS for ASV (NDA 206844) and daclatasvir (NDA 206843) for concomitant use and in combination with peginterferon and ribavirin (RBV) for the treatment of chronic HCV infection. The Applicant did not submit a proposed REMS for either application.

October 6, 2014: BMS withdrew the ASV application as a result of a business decision.

November 24, 2014: The Agency issued a CR letter for the daclatasvir application because the daclatasvir NDA did not contain adequate evidence to establish the safety and efficacy of daclatasvir without ASV for the treatment of chronic HCV infection.

February 13, 2015: BMS resubmitted the daclatasvir NDA for the treatment of chronic HCV infection in combination with sofosbuvir in treatment-naïve and treatment-experienced adults with HCV GT-3 infection (b) (4)

May 18, 2015: Teleconference with the Applicant to update status of the review. The Agency communicated that, at this time, a REMS is not needed to ensure the benefits of the product outweigh the risks.

There is no Advisory Committee planned for this application.

## 2 MATERIALS REVIEWED

- Redd, N., DRISK, REMS Review for Asunaprevir and Daclatasvir, dated September 5, 2014
- Wilkins Parker, J., DRISK, Addendum to REMS Review for Daclatasvir, dated November 12, 2014
- Daclatasvir, NDA 206843 resubmission, received February 13, 2015 (Serial No. 34)
    - Section 2.5, Clinical Overview
    - Section 2.7.3, Summary of Clinical Efficacy
    - Section 2.7.4, Summary of Clinical Safety

- Connelly, S., Division of Antiviral Products (DAVP) Memorandum: Update summary of arrhythmia events with sofosbuvir-containing therapy, NDA 204671 Sofosbuvir; NDA 205834 Ledipasvir/Sofosbuvir; dated March 20, 2015
- FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug, dated March 24, 2015
- Mid-cycle Meeting slides for NDA 206843 resubmission, dated May 18, 2015
- Carter, W., DAVP, Draft Clinical Review, NDA 206843, dated June 16, 2015
- Daclatasvir, NDA 206843 resubmission, received June 24, 2015 (Serial No. 46)
    - Section 1.14, Labeling

# 3 RESULTS OF REVIEW

## 3.1 OVERVIEW OF CLINICAL PROGRAM

Efficacy and safety of daclatasvir 60 mg daily in combination with sofosbuvir (SOF) 400 mg daily for 12 weeks for the treatment of chronic HCV GT 3 infection was demonstrated in a Phase 3 open-label study (ALLY-3) of 152 subjects. The trial enrolled treatment-naïve (n=101) and treatment-experienced (n=51) subjects, and included 32 subjects with compensated cirrhosis. The primary efficacy endpoint was sustained virologic response 12 weeks after discontinuation of treatment (SVR12). Overall, SVR12 was achieved by 135/152 (89%) of treated subjects. The currently approved standard of care for HCV GT3 is 24 weeks of SOF/RBV combination therapy (which has an overall SVR12 rate of 84%). The overall SVR rate difference for all subjects between 12 weeks of DCV/SOF and 24 weeks of SOF/RBV was 3% [95% C.I. (-4%,9%)]. The lower bound of this confidence interval is higher than the lowest calculated non-inferiority margin of -17%, demonstrating that treatment with DCV/SOF for 12 weeks is non-inferior to SOF/RBV for 24 weeks duration.

Of note, SVR12 rates after the DCV/SOF regimen were approximately 30% lower among subjects with baseline cirrhosis compared to subjects without baseline cirrhosis. The SVR12 rate for the group with baseline cirrhosis was 63% (20/32), whereas the rate was 96% (115/120) for subjects without baseline cirrhosis.

## 3.2 SAFETY CONCERNS

For the purpose of this review, serious adverse events (SAEs) associated with DCV/SOF are defined by the regulatory definition of a serious outcome, such as death, a life-threatening reaction, or hospitalization (among other outcomes). Severe adverse events (AEs) associated with DCV/SOF were defined by the Applicant as Grade 3-4; severe laboratory-related toxicities were graded using the National Institutes of Health Division of AIDS grading scale. The safety population included subjects in the ALLY-3 study and data from additional phase 2 trials.

### 3.2.1 Deaths

There were no deaths on treatment or during the follow-up periods in ALLY-3 or in a phase 2 trial (AI444040) that evaluated DCV/SOF with and without RBV (only daclatasvir-related safety data was reviewed from the phase 2 trial).

### 3.2.2 Nonfatal Serious Adverse Events

One subject in ALLY-3 reported an SAE of grade 3 gastrointestinal hemorrhage that the investigator considered unlikely related to study drugs and more likely related to underlying cirrhosis and/or portal hypertension; the DAVP clinical reviewer agreed with the investigator's assessment. The subject was hospitalized and recovered. This was the only SAE reported on treatment or during follow-up in ALLY-3.

In AI444040, SAEs were reported for 7% (n=15) of subjects overall. Of the 15 subjects with SAEs, 1 subject had an SAE (grade 2 cerebrovascular accident) leading to discontinuation of study therapy, though the subject was a current tobacco smoker with hypercholesterolemia and a reported family history of stroke. Most subjects with SAEs had relevant medical conditions that may have contributed to the event.

### 3.2.3 Severe Adverse Events

Three subjects (2%) in ALLY-3 reported severe AEs, which included the events gastrointestinal hemorrhage (also noted above as an SAE), food poisoning, and arthralgia. The DAVP clinical reviewer stated these AEs were considered unrelated to study drugs. Seven subjects (3%) reported grade 3 or 4 AEs in AI444040, but none were considered related to study treatment.

### 3.2.4 Bradycardia in Association with Concomitant Amiodarone and Sofosbuvir

The Applicant identified five cases of cardiac arrhythmia in their global safety database in patients receiving DCV/SOF (with and without RBV) and concomitant amiodarone. Four of the five cases described severe bradycardia and one report described atrial flutter. One patient required pacemaker insertion for 3$^{rd}$ degree AV block, whereas the other four patients were medically managed. Based on a potential drug-drug interaction, the DAVP clinical reviewer agreed with the Applicant's position that concomitant administration of amiodarone with DCV/SOF may result in severe or life threatening bradycardia. (See Section 4 for further Discussion)

## 4 DISCUSSION

The results of the phase 3 trial of daclatasvir in combination with sofosbuvir provide evidence of efficacy in the treatment of chronic HCV GT3 infection. The once-daily orally administered DCV/SOF combination for 12 weeks offers an improved safety profile compared to the known safety profile described in the prescribing information for interferon alfa- and ribavirin-based HCV regimens, which are difficult for patients to tolerate because of the associated toxicities. The DCV/SOF 12-week regimen also offers the advantage of being shorter than the 24-week regimen of SOF/RBV.

The overall safety profile of DCV/SOF is favorable. The main safety concern is a potential drug-drug interaction with amiodarone and sofosbuvir used in combination with direct-acting antivirals such as daclatasvir (as well as other direct acting antivirals, such as ledipasvir) that may result in serious, symptomatic bradycardia. The manufacturer of sofosbuvir (Gilead Sciences) issued a Dear Healthcare Provider Letter on March 20, 2015, and the Agency issued a Drug Safety Communication on March 24, 2015, that warned of this risk. These communications provided information that included recommendations for patient counseling and to have patients undergo inpatient cardiac monitoring for the first 48 hours of co-administration, after which daily monitoring of the heart rate should occur through at least the first 2 weeks of treatment. The prescribing information for sofosbuvir and for ledipasvir in combination with sofosbuvir

(Harvoni®) was updated with a new Warning and Precaution related to this risk on March 20, 2015; the proposed prescribing information for daclatasvir also includes this Warning and Precaution.

At this time, DRISK does not believe a REMS is necessary to ensure the benefits of DCV/SOF outweigh the risks. HCV is a serious and life-threatening disease that infects an estimated 3 million people in the U.S. There are no Boxed Warnings in the DCV/SOF proposed prescribing information; although there is a serious risk of bradycardia in patients receiving sofosbuvir in combination with a direct acting antiviral and concomitant amiodarone therapy, this risk has been communicated by the manufacturer of sofosbuvir and by the Agency, and it will be reiterated as a Warning and Precaution in the daclatasvir prescribing information.

Furthermore, the most likely prescribers of DCV/SOF are specialists who are familiar with the management of chronic HCV and who understand the risks of treatment using antiviral therapies that have overall more serious risk profiles, and are likely to have been informed of the drug interaction risk with daclatasvir via the Drug Safety Communication and/or the labeling updates to sofosbuvir. Like the HCV antiviral agents already approved, the risks of DCV/SOF may be managed by the prescribing information and routine pharmacovigilance.

## 5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not necessary for daclatasvir. Daclatasvir has proven efficacy and safety for the treatment of chronic hepatitis C virus infection in combination with sofosbuvir in adults with hepatitis C virus genotype 3 infection. Thus, the benefit-risk profile for daclatasvir is acceptable and the risks can be adequately communicated through the professional labeling.

Should DAVP have any concerns or questions, feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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JAMIE C WILKINS PARKER on behalf of ROBERT G PRATT
07/16/2015

REEMA J MEHTA
07/16/2015
I concur.

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Addendum to Risk Evaluation and Mitigation Strategy (REMS) Review

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| Date: | November 12, 2014 |
| Acting Team Leader: | Jamie Wilkins Parker, Pharm.D.<br>Division of Risk Management |
| Subject: | Addendum to determine if a REMS is necessary |
| Drug Name(s): | daclatasvir (DCV) |
| Dosage and Route: | 60 mg orally once daily |
| Application Type/Number: | NDA 206843 |
| Applicant/sponsor: | Bristol-Myers-Squibb |
| OSE RCM #: | 2014-673 (Addendum to 2013-2084) |

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This addendum is to finalize the DRISK review of daclatasvir, as discussed in the Risk Evaluation and Mitigation Strategy (REMS) Review (Subject: Evaluation to determine if a REMS is necessary) dated September 5, 2014. This review covered both daclatasvir as well as asunaprevir (NDA 206844) as the Applications were being concurrently reviewed (the individual products were studied to be used concomitantly and in combination with peginterferon and ribavirin for the treatment of chronic HCV infection).

In the September 5, 2014 review, DRISK's conclusion was that, based on the available information at that time, a REMS was not recommended. However, analysis of the safety signals during the review required further discussion, which was to occur at an Advisory Committee.

On October 6, 2014 (prior to convening the Advisory Committee), Bristol-Myers-Squibb withdrew the Application for asunaprevir, thus leaving daclatasvir without sufficient efficacy or safety data (as asunaprevir and daclatasvir shared the same three pivotal phase 3 trials) to support an approval at this time, and thus will receive a complete response action for this review cycle.

In conclusion, DRISK does not have sufficient safety or efficacy data to make a final decision on the necessity of a REMS for daclatasvir during this review cycle. Should daclatasvir be re-submitted to the Agency for review, we will make a determination at that time, pending sufficient efficacy and safety data for the drug.

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JAMIE C WILKINS PARKER
11/12/2014

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**
**Office of Medication Error Prevention and Risk Management**

# Risk Evaluation and Mitigation Strategy (REMS) Review

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|---|---|
| Date: | September 5, 2014 |
| Reviewer: | Naomi Redd, Pharm.D.<br>Division of Risk Management |
| Acting Team Leader: | Jaime Wilkins Parker, Pharm.D.<br>Division of Risk Management |
| Acting Deputy | Reema Mehta, Pharm.D., M.P.H. |
| Division Director: | Division of Risk Management |
| Subject: | Evaluation to determine if a REMS is necessary |
| Drug Name(s): | Asunaprevir (ASV)<br>Daclatasvir (DCV) |
| Therapeutic Class: | Hepatitis C Virus NS3/4a inhibitor<br>Hepatitis C Virus NS5A inhibitor |
| Dosage and Route: | ASV – (b) (4)<br>DCV – 60mg orally once daily |
| Indication: | Treatment of chronic hepatitis C virus infection |
| Application Type/Number: | NDA 206844 (ASV)<br>NDA 206843 (DCV) |
| Applicant/sponsor: | Bristol Myers-Squibb |
| OSE RCM #: | 2013-2084 |

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# CONTENTS

# 1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for new molecular entity (NME) asunaprevir (ASV) and NME daclatasvir (DCV). Bristol Myers-Squibb submitted two New Drug Applications (NDA) 206844 (ASV) and 206843 (DCV) for the indication of the treatment of patients with chronic Hepatitis C Virus (HCV) infection. Although submitted as separate NDA's, the Division of Anti-Viral Products (DAVP) is concurrently reviewing the applications, as the individual products must be used concomitantly and in combination with peginterferon and ribavirin for the treatment of chronic HCV infection.

The Sponsor did not submit a proposed REMS for either product or risk management recommendations beyond the prescribing information; however, the Sponsor did submit a the Company Core Risk Management Plan (RMP) for both products consisting of routine pharmacovigilance. In these RMPs, the Sponsor notes hepatic toxicity as an important identified risk for ASV, and potential identified risks that include drug induced pyrexia and the development of drug resistance. DCV does not have any important identified risks noted in the RMP, but has potential risks that include hepatic toxicity, hematologic toxicity, development of drug resistance, and embryo-fetal development toxicity.

## 1.1 DISEASE BACKGROUND

Hepatitis C is transmitted through blood from an infected person primarily through percutaneous exposure such as injection drug use, needle-stick injuries, inadequate infection control in health-care settings, and less commonly through sexual transmission. Infection with HCV can result in symptomatic acute infection and spontaneously clear without treatment, however 75-85% of these cases develop into chronic infection. Chronic HCV infection is insidious, progressing slowly without any major physical signs or symptoms for several decades, and may not be recognized until screening test reveal positive infection, or persistently elevated hepatic enzymes during routine examinations.[1] Many of these patients often progress to liver disease that may result in advanced cirrhosis and liver cancer.

Chronic HCV has become a global health epidemic since it was identified in 1989. It is estimated that 130-170 million people worldwide are infected with chronic hepatitis C, with 5-7 million of these infections occurring in the United States (US).[2] One third of HCV infections in the US occur in high-risk populations such as incarcerated persons and the homeless; with 75% of cases diagnosed in people born between 1945 and 1965.[2] In the HIV infected population, co-infection with HCV is found in approximately 10-30% of these patients, consequently resulting in increased risks of progression to end-stage liver disease and death.[3]

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[1] http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#- accessed August 1, 2014

[2] Ansaldi F et al. HCV in the new era *World J Gastroenterol*; August 7, 2014; 20(29): 9633-9652

[3] Neukam J et al. Latest pharmacotherapy options for treating HCV in HIV infected patients. *Expert Opin. Pharmacother.* 2014; 15(13) e-ISSN 1744-7666

The genetic diversity of HCV poses a significant challenge for effective therapy. Seven different genotypes (1-7) are classified in HCV, with at least 67 subtypes.[2] Genotype 1 (subtypes 1a and 1b- (GT1a and GT1b)) are more prevalent worldwide, and constitute the majority of cases in the United States, Europe, Australia, and Japan. Subtype 1b is more prevalent in Europe and Asia, while subtype 1a is more common in Northern Europe and the United States. Approximately 65-75% of genotype 1 infections in the US are subtype 1a, with subtype 1b constituting the remaining 25-35%.[4] These diverse genotypes respond differently to current treatment regimens, and in general, patients with genotype 1 infection are more difficult to treat compared to other genotypes.

The goal of treatment for HCV is for patients to obtain a sustained virologic response (SVR), which is defined as lack of detection of HCV RNA in blood plasma, usually within 6-12 months of therapy. The cornerstones of chronic HCV treatment have been use of pegylated interferon and ribavirin. However, these treatments often yield untoward side effects such as depression, anemia and other blood dyscraias, flu-like symptoms, as well as gastrointestinal side effects; making it difficult for patients to adhere to therapy and obtain significant treatment response. Over the last 3 years, several improvements in the treatment of chronic HCV have yielded newer classes of antivirals that have specific targets in the HCV replication cycle. These classes are collectively known as direct acting antivirals (DAAs), and can be classified into NS3/4A protease inhibitors (bocepravir; Victrelis and telaprevir; Incivek). In 2013, another NS3/4A protease inhibitor, simeprevir (Olysio) was approved, and a first in class NS5B polymerase inhibitor, sofosbuvir (Solvaldi) was added to the armamentarium of treatments for chronic Hepatitis C. When used in combination with interferon and ribavirin, these agents have greatly advanced the likelihood of success of virologic response rates in challenging HCV patient populations. However, there continues to be tolerability issues with these treatments, in part due to the interferon and ribavirin that are still required to achieve substantial virologic response rates. Response rates can also be suboptimal due to low treatment adherence and drug resistance. There still remains a need for a regimen in this patient population that is ribavirin and interferon free, that presents high efficacy across various HCV genotypes, with better safety and tolerability, as well as shorter duration of treatment.

### 1.2 ASUNAPREVIR AND DACLATASVIR PRODUCT BACKGROUND[5,6]

Asunaprevir is a NS3 protease inhibitor (b) (4) . ASV is being developed in combination with the Sponsor's NS5A inhibitor daclatasvir, (b) (4) The recommended dose for ASV is (b) (4) and 60mg once daily for DCV. These products are not developed as a fixed dose combination product; rather ASV and DCV are individual

[4] FDA Internal Consultant Backgrounder, July 2014

[5] Clinical Overview, Asunaprevir

[6] Clinical Overview, Daclatasvir

products that should be used concomitantly. Recommendations for use of ASV and DCV proposed in these submissions include:

- Use of ASV + DCV for the treatment of chronic HCV patients (b) (4) [redacted]
- Use of ASV and DCV (b) (4) [redacted]

### 1.3 REGULATORY HISTORY

Breakthrough therapy for use of DCV and ASV in combination for chronic HCV (dual program) was granted on February 3, 2014. The applications for these drugs were submitted on March 31, 2014. The review classification for both applications is Priority, and the PDUFA action date is November 28, 2014. Other pertinent regulatory history is as follows:

- June 26, 2014: FDA Midcycle Meeting
- July 10, 2014: Midcycle teleconference with the Sponsor; of note, issues surrounding hepatotoxicity and eosinophilia with pyrexia were discussed as potential approvability issues, and that decisions regarding whether a REMS may be necessary was still being evaluated.
- July 22, 2014: DAVP/DRISK meeting to discuss the review team's current assessment of the safety issues
- August 13, 2014: DAVP/DRISK meeting to discuss progress on safety findings, and the role of DRISK at upcoming Antiviral Advisory Committee meeting
- November 17, 2014: pending Antiviral Advisory Committee meeting

## 2 MATERIALS REVIEWED

- March 31, 2014, Original NDA submissions for 206844 (ASV) and 206843 (DCV)
  - Section 2.5, Clinical Overview
  - Section 2.74, Summary of Clinical Safety
  - ASV and DCV Risk Management Plans
- June 26, 2014, slides from Midcycle Meeting
- July 21, 2014 Midcycle Communication to Sponsor meeting minutes
- July 25, 2014, FDA Internal Consultant Backgrounder - Briefing Document for external review of efficacy and safety data for ASV and DCV
- August 29, 2014, DAVP Clinical Review NDA 206843 and 206844, Wendy Carter, D.O.

## 3 RESULTS OF REVIEW

### 3.1 OVERVIEW OF CLINICAL PROGRAM

The clinical programs for these applications contain several ongoing studies assessing the efficacy and safety of ASV and DCV for the treatment of chronic HCV. ASV (b) (4) [redacted]

[redacted], with DCV having been exposed to over 6,000 patients in the same study phases.

The DUAL (ASV and DCV as combination without interferon and ribavirin) and QUAD (ASV and DCV in combination with ribavirin and peginterferon) programs are the clinical programs being used to support submission of these applications. All of the Phase 3 trials are based on 24 week data.

Phase 3 data to support use of DCV 60 mg once daily and ASV [redacted] for the DUAL program in genotype 1b patients are from 2 non-randomized, open label, clinical trials. Study AI447026 (7026) was completed in Japan with 222 patients. Study AI447028 (7028) was a global, multi-centered, study that initially began as a randomized, placebo-controlled study for the first 12 weeks (in the treatment-naïve cohort) and then rolled in to an open label study; there were 645 in the study arm and 102 in the placebo arm).

The QUAD regimen includes the use of DCV 60 mg once daily, ASV 200 mg twice daily, peginterferon alfa, and ribavirin for treatment of patients with genotypes 1a, 1b, and 4. This regimen is supported by study AI447029 (7029); which is also a global, multi-centered, phase 3, non-randomized, open-label clinical trial (n = 398).

Demographics differed slightly across the Phase 3 trials. Study 7026 included all Japanese patients, 65% were female, 40% were age 65 or older, and 10% were classified as cirrhotic at baseline. In global studies 7028 and 7029 participants were largely comprised of Caucasian patients (70% for study 7028 and 76% for study 7029), with females making up 52% of the population for study 7028 and 31% in study 7029. Twenty-one percent were age 65 or older in 7028 (9% in study 7029), with 32% of these patients having cirrhosis at baseline (23% for study 7029).

***Key Efficacy Findings***

***DUAL Program (Studies 7026 and 7028) –*** This is an all oral, interferon and ribavirin sparing regimen being developed for use in genotype 1b patients, including those patients who are treatment naïve or have failed prior interferon and ribavirin therapy. FDA analyses of efficacy at 24 weeks found an overall SVR rate of 81-90%; dependent on the patient HCV genotype and prior response to therapy.[4] Prior non-responders (included patients with prior non-response to interferon and ribavirin, as well as partial responders) were on the lower end of efficacy, with 81% of these patients in study 7026 achieving SVR, and 82% of patients achieving SVR in study 7028. There were no baseline demographic factors or characteristics which had a significant effect on efficacy outcomes; however, baseline NS5A polymorphisms at resistance-associated amino acid positions were determined to have a clinically significant impact on efficacy.[4] Based on analyses of NS5A sequence data, there was a clear association between the detection of DCV resistance-associated polymorphisms and treatment outcome, particularly for L31 polymorphisms (including F, I, M, or V) and Y93H. These NS5A positions are known to be key sites for the emergence of DCV resistance.[4] Approximately 10% of U.S. subjects had the L31F/I/M/V or Y93H polymorphism(s) naturally at baseline, and detection of these polymorphisms was associated with high rates of virologic failure in the Phase 3

DUAL trials (nearly 60%).[4] Based on these results, to optimize treatment efficacy FDA believes that HCV GT1b patients considering treatment with the ASV/DCV DUAL regimen should be screened for the presence of NS5A L31F/I/M/V or Y93H polymorphisms, and those with the polymorphisms should consider alternative treatments.[4] However, at the present time there are no NS5A sequencing assays are commercially available for routine clinical use.

***QUAD Program (Study 7029)*** **-** This regimen combines the use of ASV and DCV with peginterferon alfa and ribavirin for the treatment of genotype 1 or genotype 4 patients who failed prior interferon and ribavirin based therapy, in addition to treatment naïve patients. FDA analyses of the efficacy of the QUAD regimen in prior peginterferon and ribavirin non-responders demonstrated overall, 94% of patients achieved a sustained virologic response at 12 weeks (SVR12). However, the proportion of subjects with genotype 1a who achieved SVR12 was lower at 87%, compared to 99% of genotype 1b patients, and 98% for genotype 4 patients.[4] FDA analyses determined there were no statistically significant baseline factors or polymorphism issues that affected outcome for the QUAD regimen.

***Study AI447017 –*** this is an additional supportive study (as well as study AI447011) for phase 3 trials 7028 and 7029, that provides efficacy and safety data in GT-1 patients who are ineligible or intolerant to interferon, prior non-responders to interferon based therapy, and patients without cirrhosis. Additional safety data were gleaned from review of this trial by FDA clinical reviewers.

### 3.2 SAFETY CONCERNS

FDA safety analyses were assessed in all patients in the Phase 3 clinical trials, and to determine if there were differences in adverse events reported in the DUAL regimen versus the QUAD regimen. Adverse events leading to discontinuation occurred overall in 39 patients (3%; excluding the placebo group), and common adverse events reported in more than 10% of the patient population included: nasopharyngitis (31%), headache (17%), pyrexia (13%), diarrhea (11%), nausea (6%), fatigue (5%), and dizziness (1%).[4] Known adverse events specific to peginterferon and ribavirin such as rash/pruritus, fatigue, depression, and flu-like symptoms were more commonly reported in those patients receiving the QUAD regimen versus the DUAL regimen. However, in the Japanese DUAL trial (study 7026) more patients experienced pyrexia, and in some cases, concomitant eosinophilia versus the comparator arm. There were also higher rates of elevated ALT and AST in study 7026 compared to studies 7028 and 7029.

In the RMP for ASV, hepatic toxicity is noted as an important identified risk, and drug induced pyrexia and development of drug resistance are noted as a potential risk. For DCV, the sponsor do not note any important identified risks, but note hepatic toxicity, hematologic toxicity, development of drug resistance, and embryo-fetal development toxicity as important potential risks. At this time, the Sponsor has proposed to manage these events in labeling. However, FDA clinical reviewers believe that the risks of eosinophilia with pyrexia, more specifically in Japanese patients, and that assessment of

hepatic toxicity for ASV warrants further risk assessment by the Agency before a determination regarding risk mitigation can be made.

### 3.2.1 Eosinophilia with pyrexia[4, 7]

Collectively, there were 37 patients evaluated for pyrexia and eosinophilia from FDA's analysis. The multi-national, multi-center sites for studies 7028 and 7029 had 9 patients with this phenomenon, of which, the majority of these patient's events were found to be related to peginterferon dosing or upper respiratory infections. In the Japanese study (7026), 28 patients were found to have pyrexia and eosinophilia; most of these cases were without elevated hepatic enzymes. Six of these patients had high eosinophils and pyrexia concurrently, with 2 of the six also having grade 2-3 elevations in ALT and AST. Liver functions returned to normal in these patients while continuing on study drug. There were no deaths reported from these events, however, 2 patients discontinued the study drug due to hepatic dysfunction.

### 3.2.2 Hepatic toxicity[4]

Two prominent findings during the development of ASV and the ASV/DCV DUAL program prompted further review of hepatic safety. The first finding was transaminase elevations observed with higher doses of ASV in Phase 2 studies. These increases were commonly seen in patients receiving ASV at doses higher than 200 mg twice daily. The second finding was a case of confirmed liver damage with eosinophils (confirmed via liver biopsy) in study 7026.

Overall, the proportions of treatment emergent laboratory elevations of ALT and AST were low, and similar between the DUAL treatment arms for studies 7026and 7028, and the QUAD treatment in study 7029. Table 1 below provides an overview of hepatic biochemistry profiles for these studies:

The proportion of subjects with treatment emergent Grade 1-4 elevations of ALT and AST were higher in the Japanese DUAL study 7026, compared to the global DUAL study 7028's treatment and placebo arms and the QUAD treatment regimen in 7029. Eighteen patients (n =18/1265; 1.4%) from the Phase 3 trials discontinued due to hepatic-related adverse events, however 94% of these 18 total discontinuations were patients from the Japanese study 7026. In the analysis of 17 of the 18 patients (1 patient from 7029 is excluded due to liver related adverse events), 3 patients did not achieve a SVR; however, the remaining 14 patients did achieve SVR despite early discontinuation from the study.

Because of these hepatic events, the Sponsor implemented monitoring rules in their clinical protocols to assess potential drug-induced liver injury (pDILI), which they defined as concurrent ALT $\geq$ than 5 times baseline or nadir value, and $\geq$ 10 times the upper limit of normal, and total bilirubin more than 2 times the upper limit of normal while on study. Cases were to be reported as serious adverse events. Four patients met these criteria, and when FDA analyses used the Hy's Law criteria, 9 patients met these criteria. Three of these patients discontinued early, and the remaining 6 completed the

[7] Midcycle Meeting Slides – clinical review; June 26th, 2014

study. In these 6 patients, ALT improved to near or below baseline, and 8 out of the 9 patients achieved SVR12. There were some confounding factors in these cases such as underlying cirrhosis (3 cases), and concomitant events or comorbidities of non-TB mycobacterial infection (3 cases). There were no deaths related to any of the hepatic events reported.

## 4 DISCUSSION

Although treatments for chronic HCV infection are evolving, there still remains a medical need for patients with advanced liver disease, patients who are intolerant or unsuitable for interferon therapy, and patients with other HCV genotypes. ASV and DCV are two DAAs being proposed for the treatment of chronic HCV infection in two settings. The DUAL program (use of ASV 100mg twice daily + DCV 60mg once daily) presents a peginterferon and ribavirin free regimen for genotype 1b patients who are treatment naïve or failed prior interferon and ribavirin therapy. At 24 weeks, 81-90% of patients achieved a sustained virologic response; however, baseline NS5A polymorphisms at resistance-associated amino acid positions were determined to have a significant impact on efficacy. The QUAD program (ASV 200mg twice daily + DCV 60mg once daily + peginterferon + ribavirin) also yielded impressive results, with overall SVR12 rates at 94%, but with slightly lower response rates at 87% in genotype 1a patients.

The clinical development program demonstrated that overall adverse events were generally low and tolerable; however, the identification of eosinophilia with pyrexia and hepatic toxicity (including DILI and Hy's Law's cases) necessitates further investigation. Grade 3 or higher elevations in ALT and AST were 5% and 4% respectively in the Phase 3 clinical programs. The proportion of Japanese subjects meeting the criteria of pyrexia with eosinophilia within 2 weeks in the DUAL trials was 7% (16/222) for study 7026 and 12% (4/33) for another supportive trial, AI447017.

The Sponsor submitted a RMP for both products which includes a pharmacovigilance plan. For ASV, the following important identified risk is hepatic toxicity, and potential risks include drug induced pyrexia and the development of resistance. The sponsor does not note any important identified risk in the RMP for DCV, but note important potential risks that include: hepatic toxicity, hematologic toxicity, development of drug resistance, embryo-fetal development toxicity, and drug interactions for DCV; and drug-induced pyrexia, development of drug resistance, drug interactions, and hepatic toxicity for ASV.

(b) (4)

Current therapies approved for chronic HCV include many of the same risks as outlined above which are mitigated through product labeling. However, the nature of the risks for hepatotoxicity and eosinophilia with pyrexia seen with ASV and DCV requires further evaluation. There remains uncertainty whether the safety findings represent a single clinical syndrome, or distinct events and whether only ASV or the combination of DCV and ASV are associated with these events. Furthermore, clarity regarding whether there is a possible increased risk associated with certain demographic factors such as race require further review. Because unanswered safety concerns still remain for these drugs, no recommendation for regulatory action has been made at this time. The clinical team continues to review these applications based on the safety signals associated with these drugs, and have requested an internal consult to FDA reviewers John Senior, Mark

Avigan, and Bob Temple for further review of these issues. Several questions arise regarding the approvability of these compounds in light of these evolving safety issues, and there is a meeting of the Anti-Viral Advisory Committee planned for November 17, 2014 to gain additional insight on these events.

Based on the current assessment of the available data, DRISK agrees with the Sponsor that additional risk mitigation beyond the product labeling are not necessary to mitigate the aforementioned risks. However, since further risk assessment is ongoing, a final determination of the need for a REMS will be determined once the risk assessment for hepatotoxicity and eosinophilia with pyrexia is completed by the Agency.

## 5 CONCLUSION

At this time, DRISK does not recommend a REMS for ASV or DCV. Analysis of the safety signals during this review requires further discussion, most of which surround approvability issues, and will happen at the Advisory Committee. DRISK will make a final determination of the need for a REMS once the risk assessment for hepatotoxicity and eosinophilia with pyrexia is completed by the Agency.

Should DAVP have any concerns or questions, feel that a REMS may warranted for this product, or new safety information becomes available, please send a consult to DRISK. DRISK will follow this review with a final, confirmatory memorandum pending the outcome of the Advisory Committee meeting.

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