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*APPLICATION NUMBER:*

**205123Orig1s000**

**SUMMARY REVIEW**

## Decisional Memorandum to the File

<b>Date:</b>	November 8, 2013
<b>From:</b>	Jeffrey S. Murray, M.D., M.P.H. Deputy, Division of Antiviral Products
<b>Subject:</b>	Summary and Recommendations
<b>NDA/BLA #:</b>	205123 Janssen Research and Development, LLC
<b>Submission Date</b> <b>PDUFA Goal</b>	March 28, 2013 November 28, 2013
<b>Proprietary / Generic (USAN) names</b>	Simeprevir
<b>Dosage forms / strength</b>	150 mg capsules
<b>Proposed Indication(s)</b>	For the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients ( $\geq 18$ years of age) with compensated liver disease (including cirrhosis)

### 1. Introduction

Simeprevir is an HCV NS3/4A serine protease inhibitor, a direct-acting antiviral agent active against hepatitis C virus (HCV) genotype 1. Boceprevir and telaprevir, also HCV protease inhibitors, were approved in May 2011.

The proposed indication for simeprevir is for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with a peginterferon alfa and ribavirin (PR), in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy with or without ribavirin.

Simeprevir has recently received marketing approval in Japan and is currently under consideration by EMA.

Phase 3 trials in the development program were superiority trials (new drug added to PR vs. PR alone) in subjects with chronic hepatitis C who were treatment-naïve or were treatment-experienced (received prior PR) and had relapsed. At the time the phase 3 trials were initiated and well underway, other HCV PIs had not been approved and PR was the standard of care.

With respect to currently approved products, simeprevir may address an unmet medical need, particularly in patients who may be unable to tolerate the hematologic toxicities of the previously approved protease inhibitors, boceprevir and telaprevir.

### 2. CMC

#### 2.1. General Product Quality considerations

For full details of the review of the Chemistry and Manufacturing sections of the NDA, refer to the Office of New Drug Assessment (ONDQA) reviews prepared by Dr. Cruz (for drug product), Dr. Chunchun Zhang (drug substance), and Kareen Riviere (biopharmaceutics). According to ONDQA reviews, this NDA provided sufficient information to assure the identity, strength, purity, and quality of the drug product. An overall facilities recommendation of “Overall Acceptable” was made by the Office of Compliance (20-Aug-2013). All methods were adequately validated and found suitable for their intended purpose. No post-marketing commitments or requirements were recommended.

The drug substance is a white to almost white powder and the drug product is a 150 mg strength hard gelatin capsule. Capsules are to be administered once daily for 12 weeks.

### **3. Clinical Virology**

Please refer to the Virology review prepared by Dr. Damon Deming for details relating to clinical virology and clinical resistance. Important points include:

- In replicon culture studies, the presence of NS3\_Q80K was associated with a 10-fold reduction in susceptibility to simeprevir. Although short-term monotherapy trials showed that simeprevir had antiviral activity against virus with the Q80K polymorphism, phase 3 trial subjects with genotype 1a and the Q80K polymorphism had a considerably lower SVR to simeprevir + PR than patients without the Q80K polymorphism at baseline. The prevalence of the genotype 1a Q80K polymorphism in the U.S. was relatively high (approximately 35% overall in Genotype 1) in the phase 3 trials. Therefore screening for this polymorphism before treatment initiation is recommended.
- Resistance to simeprevir was characterized in biochemical and replicon assays and in the clinic. Simeprevir activity was reduced by the following major amino acid variants at the following positions: 43, 80, 122, 155, 156, and 168, and 170. Cross resistance to boceprevir, telaprevir and other HCV protease inhibitors in development is expected.
- In simeprevir-treated subjects who did not attain sustained virologic response (SVR) for whom samples were analyzed, 91% had post-baseline resistance associated variants (RAVs) detected. The pattern of resistance mutations differs for genotype 1a and 1b.
- Although RAVs appear to diminish over time (by population analysis) when patients have stopped therapy, approximately 30% of patients had one or more RAVS after 88 weeks of follow-up. It is not known how the presence of RAVs or the previous presence of RAVs will affect subsequent treatment with HCV protease inhibitors in the context of other regimens.

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

The Pharmacology/Toxicology Review was performed by Dr. Janice Lansita who concludes that the sponsor provided sufficient nonclinical safety information in support of marketing approval of simeprevir in the U.S. Important points in the Nonclinical Pharmacology review that are pertinent to labeling discussions include the following:

- Acute endocardial and myocardial necrosis of the left ventricle was seen in several dogs in a 2 week oral toxicity study at exposures approximately 28 times the mean AUC in humans at the recommended daily dose. No cardiac findings were observed in toxicity studies out to 9 months in the dog at 4-11 times the mean human AUC at the recommended dose. Cardiac safety signals that would relate to potential left ventricular endocardial necrosis were not identified in clinical trials.
- Potential reproductive toxicity effects in the pregnant rat and mouse (mortality and post-implantation loss), the fetus (skeletal variations and adverse body weight decrease), as well as in the developing offspring (adverse body weight decrease, small size and motor activity decreases) were observed with no exposure multiples in the rat and a 4-fold exposure multiple in the mouse for the reproductive toxicities. DAVP recommended that the pregnancy category be C. The applicant concurs.
- Carcinogenicity studies are not required for the current indication because the duration of simeprevir therapy is limited to 12 weeks. Simeprevir was not genotoxic in a battery of in vitro or in vivo assays.

## 5. Clinical Pharmacology

For details on Clinical Pharmacology, refer to the review prepared by Dr. Leslie Chinn. Dr. Chinn states that the Office of Clinical Pharmacology (OCP) recommends approval of simeprevir for the proposed indication. One issue that was unresolved at completion of the initial Clinical Pharmacology review was agreement on labeling for dosing patients of East Asian Ancestry.

Important points in the Clinical Pharmacology review are summarized below.

- Mean simeprevir exposures (i.e., AUC<sub>24</sub>) were 3.4-fold higher in Asian subjects in the Phase 3 trials compared to that of the pooled Phase 3 population.
- Mean simeprevir AUC<sub>24</sub> values were 2.4 and 5.2-fold higher in patients with moderate and severe hepatic insufficiency compared to that of the pooled Phase 3 population.
- In exposure-response analyses, higher simeprevir exposure was associated with an increased risk of rash (including photosensitivity) and pruritus

Pending additional data from the applicant, it appears that patients of East Asian Ancestry may need a reduced simeprevir dose (less than 150 mg daily). However, at this time the 150 mg capsule is the only dosing strength included in the NDA. Although final labeling is still not complete, physicians will need to be cautioned regarding the use of simeprevir in patients with East Asian ancestry because an

optimal dose recommendation cannot be made at this time and adverse reactions could occur at greater frequency in these patients if the 150 mg dose is used.

Because simeprevir is intended to be administered with interferon at this time and because interferon is contraindicated in patients with moderate and severe hepatic insufficiency, dose recommendations for simeprevir in patients with moderate and severe hepatic insufficiency will be addressed in the future drug development of simeprevir in the setting of interferon-free regimens.

#### Drug Interactions

Simeprevir is a mild inhibitor of CYP3A and CYP1A2. Drugs that are not recommended for coadministration because of increases in exposures of simeprevir include: erythromycin, darunavir/ritonavir, ritonavir. Drugs that are not recommended for coadministration because of substantial decreases in simeprevir exposure are efavirenz and rifampin. Simeprevir may also increase exposures of other drugs, particularly those metabolized via CYP3A; lower doses for some of these potentially coadministered drugs are recommended in the simeprevir product labeling.

## **6. Clinical/Statistical**

### **6.1. Phase 3/Essential Clinical Studies**

Three phase 3 trials and two phase 2b trials were submitted in support of the proposed indication:

- Phase 3 trials C208 and C216 compared simeprevir added to PR vs. PR alone in treatment naïve patients.
- Phase 3 trial HPC3007 compared simeprevir added to PR vs. PR alone in patients who had previously relapsed to a pegylated interferon-based regimen.
- Phase 2b trial C205 evaluated several doses (75 mg and 150 mg) and treatment durations of simeprevir plus PR in treatment naïve patients.
- Phase 2b trial C206 was the only trial conducted in previous pegylated interferon null and partial responders. Similar to C205, C206 evaluated two doses (100 mg and 150 mg) and several different treatment durations of simeprevir and PR compared to PR alone.

In all studies, simeprevir administered for 12 weeks was added to peginterferon alpha and ribavirin administered for 24-48 weeks (duration depended on early treatment response or prior response) compared to PR alone, the latter being standard of care at the time these trials were initiated. SVR12 was the primary endpoint in the three phase 3 trials and an evaluable endpoint in the phase 2b trials.

The phase 3 trials were conducted internationally with 20-30% U.S. representation in C208 and C216 and 18% in HPC3007. Cirrhotic subjects comprised 7-15% of trial participants.

The overall treatment responses for the regimens studied in the phase 3 trials are shown in Table 1. In treatment naïve patients (naïve studies combined) the additional benefit from adding simeprevir to PR was a difference of 30% in the proportion achieving SVR12 and for previous PR relapsers the treatment difference was 43%.<sup>1</sup>

**Table 1: Primary Efficacy Analysis in the Pooled Treatment-Naïve Trials (C208 and C216) and Treatment Experienced (Relapser) Trial (HPC3007)**

Studies (Number of Subjects)	C208 & C216 (N=785)		HPC3007 (N=393)	
	Pooled TMC435	Pooled PBO	TMC435	PBO
Overall SVR12 <sup>a</sup>	419/521 (80%)	133/264 (50%)	206/260 (79%)	48/133 (36%)
On-treatment failure <sup>b</sup>	43/521 (8%)	88/264 (33%)	8/260 (3%)	38/133 (29%)
Viral Relapse	55/469 (12%)	38/171 (22%)	48/249 (19%)	43/90 (48%)

a. SVR12 is defined as the proportion of subjects with HCV RNA < 25 IU/mL detectable or undetectable 12 weeks after the actual end of treatment.

b. On-treatment failure was defined as the proportion of subjects with detectable HCV RNA at EOT.

Subgroup analyses for the primary endpoint (SVR12) using data pooled from C208 and C216 showed statistically significant treatment effects for the following demographic and baseline factors: gender, race, age, body mass index, baseline HCV RNA, IL28B genotype, METAVIR score, HCV subtype (1a/1b), and region (U.S. vs. non U.S.). Notably the subgroup of patients with genotype 1a virus containing the Q80K polymorphism at baseline had a considerably lower treatment effect when adding simeprevir to PR (Table 2).

**Table 2. SVR12 in Treatment-naïve Subjects (Pooled Trials C208 and C216) by Subgroups of HCV GT1 subtype and NS3 Q80K polymorphism**

	Simeprevir +PR N=521	Placebo +PR N=264
HCV Genotype and Subtype	<b>SVR12</b> n/N (%)	<b>SVR12</b> n/N (%)
Overall GT1	419/521 (80)	133/264 (50)
GT1a	191/254 (75)	63/131 (48)
-without Q80K*	138/165 (84)	36/83 (43)
-with Q80K*	49/84 (58)	24/44 (55)
GT1b	228/267 (85)	70/133 (53)

\*Note that presence or absence of Q80K polymorphism at baseline was missing in some subjects.

Table 3 displays the effect of the Q80K polymorphism on the treatment effect in prior relapsers. As with treatment naïve subjects, the effect was substantially reduced; however, a numerical difference was still apparent. However, this subgroup was relatively small and may not represent a real difference.

<sup>1</sup> Treatment differences stated in this review were not calculated according to the applicant's primary analysis stratifying for baseline factors,

**Table 3. SVR12 in HPC3007 (Prior Relapsers) by HCV GT1 subtype and NS3 Q80K polymorphism**

HCV Genotype and Subtype	Simeprevir + PR n/N (%)	Placebo +PR n/N (%)
Overall GT1	206/260 (79)	48/133 (36)
GT1a	78/111 (70)	14/54 (26)
-without Q80K*	62/79 (78)	8/34 (24)
-with Q80K*	14/30 (47)	6/20 (30)
GT1b	128/149 (86)	34/79 (43)

\*Note that presence or absence of Q80K polymorphism at baseline was missing in some subjects.

### 6.2. Other efficacy studies

Previous PR nonresponders (relapsers, null and partial responders) were studied in phase 2b trial C206. Although this trial evaluated several doses and durations, the applicant and FDA reviewers believed that a pooling of treatment arms that included 100 mg and 150 mg doses administered for 12 weeks was appropriate and conservative (in that 150 mg is the recommended dose). The pooled arms were compared to PR alone. In the pooled analyses the difference in response rates (SVR24 for this trial) of adding simeprevir to PR was an overall increase of 47% for all previous nonresponders combined (48% for relapsers, 61% for partial responders and 26% for prior null responders).

### 6.3. Safety

The sponsor evaluated the safety of the combination of simeprevir with PR in 1153 patients with chronic hepatitis C receiving simeprevir at the proposed dose and duration (150 mg for 12 weeks). The majority of the primary safety pool (n=781) was comprised of the three phase 3 trials. As stated in Dr. Sherwat's review the primary safety issues were skin events including rash, photosensitivity and pruritus. For rash of any type there was approximately a 8% difference in incidence for simeprevir + PR compared to PR alone. One percent of subjects discontinued simeprevir due to a rash and less than 1% had a Grade 3 rash event. Photosensitivity conditions including exaggerated sunburn occurred more often (approximately 4% difference in incidence) in subjects receiving simeprevir. Several cases were severe enough to require hospitalization and one resulted in the use of systemic corticosteroids.

In addition to rashes consistent with photosensitivity, there were severe cases of other types of rash including erythema multiforme and severe rashes with concomitant aphthous stomatitis. There were no documented cases of SJS, DRESS or TEN in the drug development program to date.

Dyspnea was another adverse reaction observed with greater frequency in the simeprevir group compared to the placebo group. All of the events were mild/moderate in severity and the vast majority was reversible upon cessation of simeprevir. The etiology of the increased frequency of dyspnea in the simeprevir group compared to placebo group is unknown. Notably, anemia (observed with other HCV protease inhibitors) did not appear to be associated with simeprevir administration.

## **7. Risk Management**

Please refer to the memorandum prepared by Dr. Carolyn Yancey from the Division of Risk Management. DAVP and DRISK agree that no Risk Evaluation Mitigation Strategy (REMS) is needed for this application. The primary safety risks identified (rash and hypersensitivity) can be addressed in the professional labeling. Treatment of chronic hepatitis C is primarily carried out by hepatologists in conjunction with specialized nursing or other health care professional staff. Rash is observed with PR and other direct acting antivirals and hepatologists are accustomed to monitoring patients for these and many other toxicities associated with an interferon-based regimen.

## **8. Summary of Regulatory Issues**

There were two regulatory issues relating to efficacy as described below. These include the endpoint used and the potential need for a companion diagnostic to screen for a viral polymorphism that substantially affects treatment response.

### Endpoint and Type of Approval

The simeprevir NDA was given a priority review and presented before an advisory committee meeting as discussed below. Although the primary endpoint used in the phase 3 trials is a virologic measurement (undetectable virus twelve weeks after the end of therapy, referred to as SVR12), FDA considers this endpoint clinically validated. Therefore approvals using this endpoint will not fall under accelerated approval regulations. The expected regulatory action will be traditional approval. The SVR endpoint has been used in several prior approvals for the treatment of chronic hepatitis C including pegylated interferon plus ribavirin, boceprevir, and telaprevir.

FDA has stated in recent draft guidance that SVR is a clinically validated endpoint based on evidence from multiple observational cohorts. A review by Pearlman and Traub, entitled, "Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More," published in *Clinical Infectious Diseases* 2011 summarizes the association between SVR and clinical outcomes. Nineteen cohorts evaluated clinical outcomes comparing those who achieved SVR vs. those who were nonresponders. Among patients who achieved SVR there were substantial reductions in important outcomes such as progression to decompensated liver disease, hepatocellular carcinoma, liver mortality and all cause mortality.

DAVP considers simeprevir to fill an unmet medical need primarily because it appears to have a more favorable hematologic safety profile than other approved HCV protease inhibitors. Its apparent lack of exacerbation of PR-associated anemia, may allow some patients at risk for complications of severe anemia to receive treatment. In addition, simeprevir is administered once daily and may offer benefits with regard to adherence and ultimately overall response.

#### Q80K Viral Polymorphism and Considerations for a Companion Diagnostic

It is clear that screening for the Q80K polymorphism using one of two commercially available tests (in the U.S.) will optimize the use of simeprevir, by excluding a subset of genotype 1a patients likely to have a substantially reduced response to simeprevir and concomitant emergence of viral substitutions conferring resistance to simeprevir and other protease inhibitors. The commercially available tests are not FDA approved/cleared, but one (b) (4) is a laboratory-developed test that uses the same type of technology as that for genotypic resistance testing for determining susceptibility to HIV drugs. In addition, unlike certain HIV substitutions which can occur in a small percentage of circulating HIV quasi-species, the Q80K polymorphism of HCV genotype 1a appears to be the predominant virus in a patient; therefore, test sensitivity is less of a concern than for similar tests frequently used for HIV resistance testing.

Although DAVP believes that Q80K screening should be strongly recommended in simeprevir professional labeling, DAVP determined that Q80K screening was not considered “essential,” according to the definition included in the Draft Guidance for Industry entitled, “In Vitro Companion Diagnostic Devices.” Footnote 5 of that draft guidance defines essential: “Generally, this means that the use of the IVD companion diagnostic device with the therapeutic product allows the therapeutic product’s benefits to exceed its risks.” In the phase 3 trials, patients were tested for Q80K but were randomized and treated without respect to the results. All of the primary analyses of these trials confirmed that the benefits of simeprevir outweighed the risks even though patients with the polymorphism were not screened out of treatment. Therefore, DAVP concludes that the test is not “essential,” but has the potential to substantially optimize use. It allows for a simplified treatment algorithm and shorter treatment duration for patients without Q80K as discussed in both Dr. Sherwat’s review and Dr. Singer’s memo. This issue was discussed internally with upper management in the Office of New Drugs and the Center for Drug Evaluation and Research and all concurred with DAVP’s rationale for not requiring a companion diagnostic but strongly recommending screening.

#### **9. Advisory Committee (AC) Meeting**

The Antiviral Drugs Advisory Committee was convened on October 24, 2013. Please refer to Dr. Singer’s Cross-Discipline Team Leader’s memorandum for a synopsis of the meeting. In brief, the AC voted unanimously (19 voting members) for the approval of simeprevir. They also concurred with DAVP’s recommendation for screening all genotype 1a patients for the Q80K polymorphism prior to treatment.

While all committee members acknowledged the considerable reduction in treatment effect the baseline polymorphism conferred, the committee's statistical experts cautioned that these conclusions were based on subgroup analyses and that a positive treatment effect with the polymorphism couldn't be ruled out. The committee also acknowledged that the polymorphism had a biologic basis for the observed reduction in treatment effect as supported by reduced in vitro susceptibility and positioning of the polymorphism in a region where simeprevir interacted with the HCV protease. The committee believed the presence of the polymorphism should prompt prescribers and patients to consider alternative therapy or perhaps defer therapy and that the label should clearly describe the reduction in treatment effect associated with Q80K.

The committee was also asked to comment on the safety profile of simeprevir, primarily focusing on rash events. They concurred that simeprevir appears to be associated with at least two types of rash reactions, one being phototoxicity which was predicted preclinically and was observed in a dedicated photosensitivity study in healthy volunteers. Part of the discussion centered on the management of phototoxicity. The dermatology consultant stated that, given simeprevir is used to treat a serious disease, a physician may consider treating through mild or moderate phototoxicity if a patient could assure that strict adherence to UV light avoidance could be maintained throughout treatment. Others were concerned that some providers might not be able to differentiate a phototoxic rash from other types of rash and may not feel comfortable continuing simeprevir without dermatology consultation. There was consensus that the label should include distinct Warnings regarding the occurrence and management of both phototoxicity and other severe rashes. In addition they concurred with including information on ways to prevent phototoxic reactions.

Finally, the committee was asked to comment on the types of studies/trials that should be completed postmarketing. Data in HIV/HCV co-infected patients, pediatric patients and additional safety data in patients of African ancestry was suggested. In addition, the committee concurred with the Division's recommendations for further exploration of dosing recommendations for patients of East Asian Ancestry and in patients with moderate and severe hepatic insufficiency.

On October 25, the day following the simeprevir AC meeting, the AC convened to discuss another hepatitis C treatment, sofosbuvir. On both days there was an open public hearing prior to the committee discussion of questions. One recurring theme among speakers at the open public hearings was a request to make the wording of indications broad enough such that physicians may not be deterred by third party payers from using new direct-acting antivirals in combinations not included in the Clinical Studies Section of current labeling. The speakers commented that the field of HCV treatment is rapidly progressing and promising data using various direct-acting antiviral combinations are already available or will soon be presented at scientific meetings. The speakers had interest in making sure populations in urgent need of treatment could access optimal combinations. The consumer representative

on the AC also echoed these concerns during the committee discussion on both advisory committee days.

## **10. DSI Audits**

Clinical Inspections found the data acceptable for review. Briefly, two U.S. and two international phase 3 clinical trial sites (both in Poland) were selected for inspection. All four inspections have been completed and no substantive issues were identified.

## **11. Conclusions and Recommendations**

### **11.1. Regulatory Action**

I concur with FDA reviewers and the Advisory Committee that simeprevir should be approved for the treatment of genotype 1, chronic hepatitis C, in combination with pegylated interferon and ribavirin in adult patients. The committee also voted unanimously that benefits greatly outweigh risks and that simeprevir should receive marketing approval. I concur that the treatment effect is robust, substantial, and highly statistically significant. Substantial treatment effects from adding simeprevir to PR were observed across multiple subgroups including race, gender, baseline viral load, IL28B genotype, and METAVIR fibrosis scores. However, presence of genotype 1a Q80K polymorphism at baseline substantially reduced the treatment effect of simeprevir added to PR such that no statistical difference was observed for this subgroup. The indication should include previously untreated patients and patients who have previously failed treatment with an interferon with or without ribavirin.

Adverse reactions associated with adding simeprevir to PR are manageable and severe reactions are relatively infrequent. A major advantage of simeprevir is its apparent lack of exacerbating anemia associated with PR. However, simeprevir can cause phototoxic skin reactions so UV light avoidance is necessary. In addition infrequent but sometimes severe cases of other types of skin rashes may occur, including erythema multiforme. For severe or worsening skin rashes discontinuation of simeprevir is necessary. Continuing or restarting simeprevir in the setting of a phototoxic skin reaction may be considered only if there are no other suitable treatment options and the patient can adequately avoid UV light exposure throughout the entirety of treatment duration. Consultation with a dermatologist would be prudent if considering continuation in these cases.

Overall, the benefits of simeprevir for the treatment of chronic hepatitis C outweigh the risks.

### **11.2. Postmarketing Trials**

#### **Postmarketing Requirements**

1. The applicant will be required to conduct pediatric trials under PREA but these trials will be deferred. Specific trial designs will be decided when

the development plan for simeprevir as part of interferon-free regimens has progressed in adults, such that the best regimen(s) can be studied in children.

2. The applicant will be required to submit a complete study report and datasets for the ongoing phase 3 trial in Chinese and Korean subjects evaluating safety, efficacy and pharmacokinetics of simeprevir 100 mg and 150 mg daily in combination with PR for treatment of chronic hepatitis C genotype 1. This trial is needed to establish safe and effective dosing in patients of East Asian descent because of the observed increased simeprevir exposures in Asian patients and the observed association between simeprevir exposure and adverse events (e.g., rash and photosensitivity).
3. The applicant will be required to conduct replicon culture studies to determine the phenotypic susceptibility of simeprevir against several substitutions including: L356F, V406I, V629I individually and in combination with Q80K and also R24W, K213R, T358F, P574A, P574S, T610I, and V629I .

### **Recommended Postmarketing Commitments**

1. To submit the requisite chemistry and manufacturing data (b) (4) should the results of the above trial (Postmarketing Requirement 2) deem a lower dose is needed in patients of East Asian ancestry.
2. To submit the final study report and datasets for trial HPC3001, entitled, “A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFN $\alpha$ -2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior pegylated interferon alfa and Ribavirin Therapy,” as confirmatory evidence of efficacy of simeprevir in conjunction with PegIFN $\alpha$ -2a and ribavirin in the partial and null responder patient populations.

### **11.3. Labeling**

As discussed above, the critical labeling issues centered on recommendations regarding screening for the Q80K polymorphism and safety Warnings regarding rash and photosensitivity events. With respect to Q80K screening, the reduction in SVR associated with this polymorphism will be included as a limitation in the Usage Section and data showing reduction in response with this polymorphism will be clearly displayed in the Clinical Trials Section. A strong recommendation for screening for this polymorphism and considering alternate therapy (which a physician could reasonably consider to include deferred treatment) will be included in the Indication and Usage sections. The Warnings and Precaution Section of the label will include two warnings relating to skin reactions, one for photosensitivity

and one for other types of skin rashes. Management and prevention will be addressed.

As stated in section 5, Clinical Pharmacology, of this memorandum, the product labeling will include statements regarding the lack of definite dose recommendations for patients of East Asian ancestry and how the currently available dose of 150 mg could lead to high exposures and increased frequency and/or severity of adverse reactions such as rash and phototoxicity.

One unresolved issue at the writing of this memorandum is the exact wording of the indication. DAVP is considering the advantages/disadvantages of an indication that is written more broadly in terms of how simeprevir is used in combination with other agents. Regardless of the exact wording of the first sentence of the indication, the label will need to be clear regarding the data that supported the basis of approval. Dosing and administration will generally follow that evaluated in clinical trials with the exception of slight modifications to futility rules and PR duration according to treatment response. The latter is discussed in Dr. Sherwat's clinical review.

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/s/  
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JEFFREY S MURRAY  
11/05/2013