CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205123Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 30, 2013
From	Mary Singer, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205123
Applicant	Janssen Research and Development, LLC
Date of Submission	March 28, 2013
PDUFA Goal Date	November 28, 2013
Proprietary Name / Established (USAN) names	Sovriad or Olysio (pending)/simeprevir
Dosage forms / Strength	150 mg capsules
Proposed Indication(s)	Treatment of chonic hepatitis C genotype 1 infection in combination with peginterferon alfa and ribavirin in adults with compensated liver disease (including cirrhosis)
Recommended:	*Approval*

Cross Discipline Team Leader Review

1. Introduction

Simeprevir (also referred to as TMC435) is a new molecular entity, an HCV NS3/4a serine protease inhibitor; a direct-acting antiviral agent (DAA) developed for treatment of patients with chronic hepatitis C genotype 1 infection in combination with pegylated interferon and ribavirin (PR). Boceprevir and telaprevir are HCV NS3/4a serine protease inhibitors in the same class as simeprevir, which were approved in May, 2011 for use in combination with PR in treatment-naïve and treatment-experienced patients with chronic hepatitis C genotype 1 infection.

In this NDA submission, the applicant submitted data from three phase 3 trials in subjects with chronic hepatitis C genotype 1 who were treatment-naïve and in subjects who had previously relapsed with pegylated interferon and ribavirin therapy. Data from a large phase 2b trial evaluating simeprevir in combination with PR for treatment of treatment-experienced subjects, including prior relapsers, partial responders, and null responders to PR therapy was also included in this submission in order to include both treatment-naïve and treatment-experienced patients in the proposed indication.

2. Background

Simeprevir has not been marketed outside the U.S. to date, although it was recently approved in Japan; and a marketing application is currently under consideration by the EMA.

As with boceprevir and telaprevir, simeprevir was evaluated for treatment of CHC in subjects with HCV genotype 1 in combination with pegylated interferon and ribavirin (PR), with the goal of improving SVR and potentially shortening treatment duration in comparison to PR alone.

Since the approvals of boceprevir and telaprevir in 2011, the standard of care for treatment of chronic hepatitis C in genotype 1 infections has been boceprevir or telaprevir in combination with PR. Boceprevir and telaprevir were approved in the US, while the pivotal trials of simeprevir were underway; however, because the simeprevir trials were already fully enrolled and nearing completion of the treatment phase, and because boceprevir and telaprevir were not widely available in many countries outside of the US, the simeprevir clinical trials were allowed to proceed with the PR control/comparator.

Sustained virologic response (SVR) rates for boceprevir and telaprevir in combination with PR alone were significantly higher than those observed with PR alone (60-70% vs. 40-45%) in treatment-naïve patients with chronic hepatitis C genotype 1 infection. SVR rates were also significantly higher in subjects treated with boceprevir or telaprevir in combination with PR compared with PR alone in subjects who had previously failed PR therapy, including relapsers, partial responders and null responders.

The approved boceprevir treatment regimen is 800 mg (four-200 mg capsules) orally 3 times a day with food in combination with PR; and the currently approved telaprevir treatment regimen is 750 mg (two-375 mg tablets) orally 3 times daily with food in combination with PR.

Boceprevir and telaprevir are both associated with significant anemia greater than that observed with PR alone; and boceprevir has also been associated with increased neutropenia. Telaprevir has been associated with severe rash, including serious and life-threatening skin reactions, namely SJS, TEN and DRESS, some of which have been fatal, necessitating a Black Box Warning for rash in telaprevir prescribing information. Because both boceprevir and telaprevir must be used in combination with PR, they are contraindicated in pregnancy due to teratogenicity associated with ribavirin. Both drugs are associated with multiple clinically significant drug interactions. Boceprevir and telaprevir are contraindicated for coadministration with drugs highly dependent on CYP3A4/5 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events; and with potent CYP3A4/5 inducers that may lead to lower exposures and loss of efficacy.

Priority review designation was granted for this NDA because simeprevir may provide some advantages over boceprevir and telaprevir, including an improved safety profile, particularly with respect to hematological adverse events, and with regard to patient adherence because of simeprevir's once daily dosing in comparison to thrice-daily dosing with boceprevir and twice daily dosing with telaprevir.

The primary endpoint for the simeprevir pivotal clinical trials was sustained virologic response (HCV RNA < 25 IU/mL) measured 12 weeks after the end of therapy (SVR12). Although SVR24 was the primary endpoint in the boceprevir and telaprevir trials, DAVP has determined that very few relapses are reported more than 12 weeks after stopping therapy, and SVR12 and SVR24 are generally equivalent. SVR12 is the currently recommended primary endpoint in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013. Sustained virologic response (HCV RNA < LLOQ) at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a cure for hepatitis C infection; and recent studies have shown that achievement of SVR is associated with halting the progression of liver disease and decreasing the frequency of chronic hepatitis C complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality.

This review will focus on overall efficacy in treatment naïve subjects and relapsers, efficacy in pertinent subgroups (especially in subjects with HCV GT1a with the NS3 Q80K polymorphism at baseline, and the question of whether patients should be screened for the Q80K polymorphism prior to treatment with simeprevir), and efficacy in prior null and partial responders. This review will also focus on the major safety issues identified with simeprevir, namely photosensitivity and rash, as well as on simeprevir dosing in certain subgroups, including those with hepatic impairment, and those of East Asian descent.

3. CMC/Device

See Product Quality Review by Drs. Celia Cruz (for drug product), Chunchun Zhang (drug substance), and Kareen Riviere (biopharmaceutics), through Dr. Rapti Madurawe, Branch Chief, ONDQA DPAII/BranchV, for full details regarding drug product, drug substance and biopharmaceutics.

Simeprevir is a new molecular entity. The chemical name for simeprevir is (2*R*,3a*R*,10*Z*,11a*S*,12a*R*,14a*R*)-*N*-(cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3-thiazol-2-yl)-7-methoxy-8-methyl-4-quinolinyl]oxy]-5-methyl-4,14-dioxo-2,3,3a,4,5,6,7,8,9,11a,12,13,14,14a-tetradecahydrocyclopenta[*c*]cyclopropa[*g*][1,6]diazacyclotetradecine-12a(1*H*)-carboxamide.

Simeprevir for oral administration will be supplied as 150 mg strength hard gelatin capsules.

According to the ONDQA product quality review, this NDA provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The drug master file for the drug substance has been reviewed and found acceptable. 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 postmarketing commitments or requirements were recommended.

At the time the primary reviews were filed in DARRTS, one Biopharmaceutics issue remained regarding the proposed acceptance criteria for dissolution. However, the Applicant provided additional information at DAVP's request, and in a review addendum dated September 26, 2013, Drs. Kareen Riviere and Angelica Dorantes considered the proposed dissolution method and acceptance criteria acceptable for batch release and stability testing; and the simeprevir 150 mg immediate release capsule was recommended for approval from a Biopharmaceutics standpoint. Therefore, from an ONDQA perspective, the simeprevir 150 mg capsule is recommended for approval.

Nonclinical Pharmacology/Toxicology

Please see details of the nonclinical pharmacology/toxicology findings in reviews by Drs. Janice Lansita and Hanan Ghantous. Preclinical findings of concern included the potential for reproductive toxicity, as discussed below.

The major target organs identified in the simeprevir nonclinical studies include the gastrointestinal tract (vacuolation of apical enterocytes, dilatation of lacteals) and the liver (hepatocellular necrosis, centrilobular hypertrophy, increases in ALT, AST, ALP, and bilirubin). Although gastrointestinal adverse reactions were identified in clinical trials, no evidence for liver toxicity has been identified to date. The heart was also identified as a potential target organ (acute endocardial and myocardial necrosis) in the dog at high doses (~28 times the mean AUC in humans at the proposed simeprevir dose of 150 mg/day); however, no cardiac findings were observed in 6- and 9-month oral toxicity studies in the dog at 11- and 4-times the mean human AUC in humans at the recommended daily dose of 150 mg; and no cardiac safety signals have been identified in the clinical trials.

In a rat fertility study, 3/24 male rats showed no motile sperm, small testes and epididymides that resulted in infertility in 2/3 rats at doses approximately 0.2 times the mean AUC in humans. Simeprevir was not teratogenic in rats and mice, at exposures 0.5 times (in rats) and 6 times (in mice) the mean AUC in humans at the recommended simeprevir dose of 150 mg daily.

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. The applicant proposed pregnancy category (b) (4) for simeprevir; however, based on the positive preclinical reproductive toxicology findings in mice and rats, DAVP recommended that the pregnancy category be changed to C. This change was acceptable to the applicant.

Carcinogenicity studies were not required because of the proposed 12 week indication for simeprevir and negative genotoxicity studies.

The potential reproductive toxicity risks identified in nonclinical studies will be mitigated by appropriate labeling. Currently, simeprevir will be indicated for treatment of CHC in combination with ribavirin and pegylated interferon alfa and ribavirin. Pegylated interferon alfa has potential abortifacient effects; while ribavirin has known fertility, embryocidal and teratogenicity risks and is contraindicated in pregnancy. Therefore, because simeprevir should be used in combination with pegylated interferon and ribavirin, the potential for simeprevir to have an additional impact on pregnancy risk is currently low (because use of pegylated interferon and ribavirin should be avoided in this setting). However, if simeprevir is used without the combination of ribavirin and pegylated interferon alfa, the potential risk of simeprevir on pregnancy and the developing fetus/offspring will change the risk/benefit assessment for use of simeprevir in this population.

4. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology found the application acceptable and at the time the review was finalized recommended approval of simeprevir for treatment of chronic HCV genotype 1 in adults with compensated liver disease who are treatment-naïve or who have failed therapy, pending agreement by the Applicant on dose reduction to 100 mg daily in

patients of East Asian ancestry or moderate hepatic impairment, and agreement that simeprevir use should be avoided in patients who have the Q80K polymorphism. Since that time, further discussions with the Applicant resulted in agreement that the ongoing non-IND trial of simeprevir 100 mg versus 150 mg daily (plus PR) being conducted in China and Korea will provide further information to inform selection of an appropriate simeprevir dose strength in East Asian patients. This study will be completed and submitted to fulfill a postmarketing requirement. Please see details regarding clinical pharmacology in the Clinical Pharmacology review by Drs. Leslie Chinn, Jiang Liu, Jeffry Florian, Jeffrey Kraft, Islam Younis, Michael Pacanowski, Yuzhuo Pan, Ping Zhao, Yoriko Harigaya, and Yongheng Zhang.

Pharmacokinetics

Simeprevir is orally bioavailable, and peak simeprevir plasma concentrations are reached approximately 6 h post-dose (t_{max}). Simeprevir is highly protein-bound in plasma (>99.9%) at pharmacologically relevant concentrations, primarily by albumin. The blood to plasma ratio of simeprevir is approximately 0.66, indicating that simeprevir is largely contained in the plasma rather than the cellular components of the blood. The primary route of simeprevir elimination is hepatobiliary. Following administration of a single dose of ^{14}C-TMC435 200 mg, 91% of radioactivity was excreted in the feces; while urinary excretion was negligible (<0.05% of radioactivity).

Simeprevir exhibits nonlinear pharmacokinetics. This phenomenon appears to be caused by saturation of hepatic uptake (via OATP1B1/3) and metabolism (via CYP3A4) of simeprevir at doses above 100 mg QD in healthy subjects and 75 mg QD in patients with HCV infection.

Simeprevir should be administered with food based on increased exposures under fed conditions relative to fasted conditions.

Exposure-Response Relationships

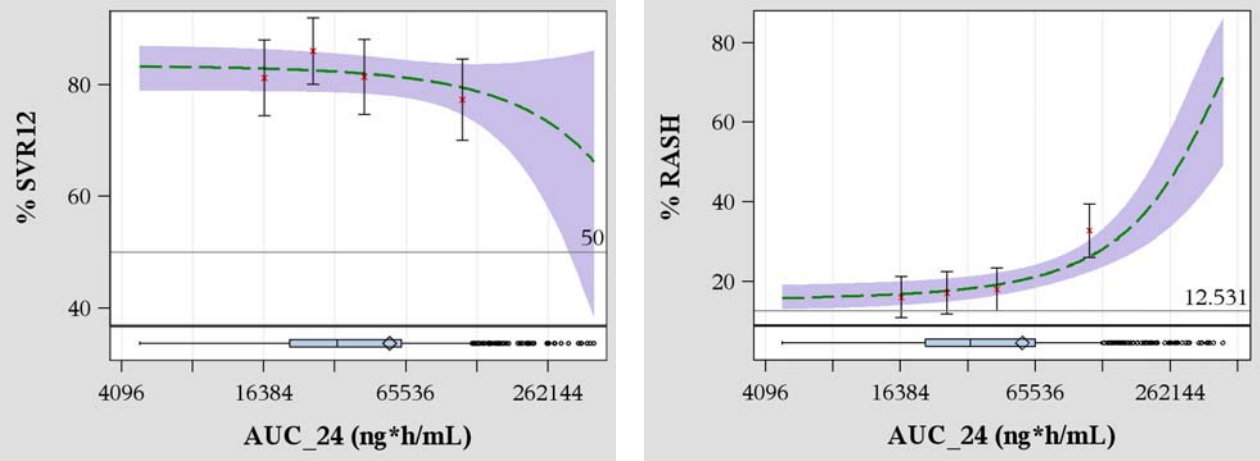
The simeprevir dose and treatment duration were selected by the Applicant based on results from the Phase 2b dose-finding trials C205 (150 or 75 mg QD in treatment-naïve subjects) and C206 (150 or 100 mg QD in treatment-experienced subjects). The Applicant observed that in C205, sustained virologic response rates at post-treatment Week 24 (SVR24) trended higher following administration of simeprevir 150 mg compared to 75 mg in certain patient subgroups (e.g. subjects with HCV Q80K substitution present at baseline and subjects with more severe liver fibrosis and inflammation). The Applicant interpreted the results of C206 to suggest that SVR24 rates trended higher following administration of simeprevir 150 mg compared to 100 mg in the same patient subgroups (though limited in size) identified in C205. There were no meaningful differences in SVR rates with regard to treatment duration (12 or 24 weeks in C205 and 12, 24, or 48 weeks in C206). The Applicant therefore concluded that simeprevir 150 mg QD was the optimal dose and 12 weeks was the optimal duration.

Within the range of exposures observed in the Phase 3 trials, the relationship between efficacy (SVR12) and simeprevir exposures is flat. No clear exposure-response relationships for efficacy (SVR12) was identified for simeprevir based on available data from two Phase 3 trials in treatment-naïve subjects, the phase 3 trial in prior relapsers, or the phase 2b trial in treatment-experienced subjects.

A positive relationship between simeprevir exposure and the incidence of adverse events (including rash, photosensitivity, dyspnea, increased bilirubin, and pruritus) was observed during the simeprevir treatment period.

The following figure shows the exposure-response relationships for SVR12 and rash (see Clinical Pharmacology review).

Figure 1. Simeprevir Exposure-Response for SVR (Left [a]) and Rash (Right [b])



[a] Univariate exposure-SVR relationship was plotted based on the pooled Phase 3 trials for treatment-naïve patients (Study c208 and c216). The predicted lower SVR rate at the high end of simeprevir exposure is likely due to the large uncertainty associated with the small number of subjects and the higher percentage of subjects with metavir score F3-F4 in the upper exposure quartile (METAVIR score was both a factor associated with increased simeprevir exposure and decreased likelihood of treatment response)..
[b] Univariate exposure-safety was plotted based on the pooled Phase 3 trials.

Pharmacokinetics of Simeprevir in Specific Populations

Hepatic Impairment

Mean simeprevir AUC_{24} values were 2.4- and 5.2-fold higher in otherwise healthy subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment compared to healthy subjects with normal hepatic function. Taking into consideration 1) the magnitude of this increase, 2) the positive relationship between simeprevir exposures and adverse events including rash and photosensitivity, 3) the paucity of safety data in the range of exposures expected following administration of simeprevir 150 mg QD to patients with moderate or severe hepatic impairment, and 4) the flat exposure-response relationship for efficacy, which suggests that no therapeutic benefit will be gained from higher exposures, the Clinical Pharmacology reviewers concluded that simeprevir should be administered at a reduced dose in patients with moderate or severe hepatic impairment. Because a lower strength simeprevir capsule was not included in this application, specific dosing recommendations cannot be made for patients with moderate or severe hepatic impairment. However, pegylated interferon is contraindicated in patients with cirrhosis and hepatic decompensation (Child-Pugh score ≥ 6);

and the Applicant will be asked to determine appropriate simeprevir dosing in this population during development of interferon-free simeprevir regimens.

Race
The mean simeprevir AUC_{24} was 3.4-fold higher in Asian subjects in the Phase 3 trials (n=14) compared to the pooled Phase 3 population (C208, C216, HPC3007). Taking into consideration 1) the magnitude of this increase, 2) the positive relationship between simeprevir exposures and adverse events including rash and photosensitivity, 3) the limited amount of safety data available following administration of simeprevir 150 mg QD to East Asian patients, and 4) the flat exposure-response relationship for efficacy, which suggests that no therapeutic benefit will be gained from higher exposures, the Clinical Pharmacology reviewers concluded that simeprevir should be administered at a reduced dose of 100 mg QD (which, based on a Phase 2b study conducted in Japan, provides comparable exposures in East Asian patients as 150 mg QD in the pooled Phase 3 population) to patients with East Asian ancestry. As noted above, further discussions with the Applicant resulted in agreement that an ongoing non-IND trial of simeprevir (plus PR) dosed at 100 mg or 150 mg daily in China and Korea will be completed and submitted postmarketing in order to provide dosing recommendations for Asian patients.

Renal Impairment
Mean simeprevir AUC_{24} values were 1.6-fold higher in otherwise healthy subjects with severe renal impairment compared to matched healthy controls, indicating that no simeprevir dose adjustment is needed in HCV-infected patients with mild, moderate, or severe renal impairment. Simeprevir pharmacokinetics were not evaluated in subjects with end-stage renal disease; therefore, no dose recommendation can be made.

Gender and Age
No dose adjustments are recommended for the elderly or female patients.

Drug-Drug Interactions
Based on in vivo drug-drug interaction trials with CYP probes, simeprevir was found to be a mild inhibitor of intestinal CYP3A and a mild inhibitor of CYP1A2. In vitro studies suggested that simeprevir inhibits the uptake transporters, OATP1B1 and NTCP, and the efflux transporters P-gp, MRP2, and BSEP. The therapeutic effect and adverse event incidence rates of drugs which are substrates of these enzymes or transporters may be affected upon coadministration with simeprevir.

Simeprevir is a substrate of CYP3A and to a lesser extent CYP2C8 and CYP2C19. Simeprevir is also a substrate of P-gp, MRP2, BCRP, OATP1B1/3, and OATP2B1. Coadministered drugs that inhibit or induce these enzymes or transporters may affect simeprevir plasma concentrations and/or its efficacy or safety profile.

The Clinical Pharmacology review team recommends against coadministration with strong CYP3A inhibitors based on a drug-drug interaction (DDI) trial with ritonavir in which simeprevir exposures increased approximately 7-fold following multiple dosing. In addition, the Clinical Pharmacology review team recommends against coadministration with moderate

CYP3A inhibitors based on the drug-drug interaction trial with erythromycin, in which simeprevir exposures were increased to the same extent as when administered with ritonavir (i.e. approximately 7-fold increase of simeprevir) and based on PBPK simulations.

The Clinical Pharmacology review team also recommends against coadminstration of simeprevir with strong CYP3A inducers based on a drug-drug interaction trial with rifampin in which simeprevir trough concentrations were decreased by > 90%, with several individual trough concentrations below the simeprevir protein binding adjusted EC_{90}. The Clinical Pharmacology team also recommends against coadministration of simeprevir with moderate CYP3A inducers based on a DDI trial with efavirenz, in which simeprevir trough concentrations were reduced to the same extent as with rifampin.

Drugs that should not be coadministered with simeprevir include erythromycin (due to increased simeprevir and erythromycin concentrations), rifampin and efavirenz (due to decreased simeprevir concentrations), ritonavir (at a dose of 100 mg or higher, due to increased simeprevir concentrations). In addition, the clinical pharmacology reviewers recommend that the doses of the HMG CoA reductase inhibitors be titrated carefully, using the lowest possible dose and maximal daily doses for atorvastatin and rosuvastatin, due to increased exposure of the statins when coadministered with simeprevir. In addition, the maximum atorvastatin dose should be 40 mg daily when coadministered with simeprevir. Caution is warranted for simeprevir use with narrow therapeutic index drugs such as midazolam, tacrolimus, cyclosporine, digoxin and warfarin.

Effect of Simeprevir on QT interval

Simeprevir does not prolong the QT interval. There was no significant relationship between QT interval and plasma simeprevir concentrations at a dose of 150 (therapeutic) or 350 (supratherapeutic) mg QD in the Thorough QT Trial, TMC435-TiDP16-C117. Moxifloxacin 400 mg was used to demonstrate assay sensitivity. The largest upper limit of the 90% CIs of the differences between simeprevir and placebo in QTcF change from baseline were 2.79 ms (150 mg, 3 h postdose) and 3.32 ms (350 mg, 1 h postdose); these fall below 10 ms, the threshold for regulatory concern per ICH E14 guidelines.

Biopharmaceutics Considerations

Simeprevir appears to be a low permeability, low solubility drug, which may classify it as a BCS Class 4 drug. See ONDQA review for further details.

Trial HPC1002 compared the relative bioavailability of the Phase 3 (G007) and to-be-marketed (G019) formulations of simeprevir; as such, this trial was considered to be a pivotal relative BA trial. Although this trial was characterized as a "bridging trial" during formulation development, the Applicant did not consider it to be pivotal based on the differences between the two formulations (b) (4) and did not adhere to the regulatory guidelines that are applicable to pivotal BA/BE trials. Subsequently, the Office of Scientific Investigations (OSI) review team observed the absence of retention samples at the trial site, rendering the results of the trial unverifiable. Additional assessments were performed by the CMC review team and it

was determined that there were sufficient data on the two formulations to deem an in vivo bioequivalence trial unnecessary (please refer to the Biopharmaceutics Review for details).

Although it did not constitute a pivotal BA/BE trial, the Applicant evaluated the relative bioavailability of G007 (the Phase 3 capsule), and F021 (the Phase 2b capsule) in trial C119. The latter formulation was used in a number of clinical trials, including the thorough QT evaluation and several drug-drug interaction trials. Single doses of each simeprevir formulation were administered under fed conditions (high-fat meal) separated by a washout period of at least seven days. The Phase 2b formulation provided comparable simeprevir exposures to the Phase 3 formulation, with least square mean ratios close to 90% and 90% confidence intervals between 80 and 125%.

5. Clinical Virology

See Virology reviews by Drs. Damon Deming and Julian O'Rear for details regarding preclinical and clinical virology findings. Overall, The Virology reviewers concluded that this NDA should be approved with the recommendation that all patients with HCV GT1a infection be screened for the NS3_Q80K polymorphism at baseline, and offered alternative therapy if Q80K is present.

As discussed in detail in Dr. Deming's review, simeprevir is a small molecule inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease. Inhibition of the NS3/4A protease prevents the proteolytic processing of the HCV nonstructural polyprotein, which is required for HCV replication. The antiviral activity of simeprevir was confirmed against a panel of genotype 1a and genotype 1b replicons expressing the NS3 genes of clinical isolates. Simeprevir was not antagonistic with pegylated interferon alfa, ribavirin, or class-representative direct acting antiviral drugs targeting HCV NS5A or NS5B. Simeprevir's antiviral activity on replicons was reduced 2.4-fold in the presence of 50% human serum.

HCV genotype 1a and genotype 1b replicons with reduced susceptibility to simeprevir were selected in cell culture and characterized in a series of nonclinical studies. Reduced susceptibility to simeprevir was frequently associated with substitutions in the NS3 protease at amino acids F43, Q80, R155, A156, and/or D168, and less frequently with substitutions at amino acids Q41, Q89, N174, and N176. Phenotypic analysis of treatment-emergent isolates of early clinical studies indicated that R155K and a series of substitutions at D168 represent the primary pathways to resistance.

Cross-resistance between simeprevir and other NS3/4A protease inhibitors (PIs) is expected, conferred primarily by R155K in genotype 1a virologic failures and D168X in genotype 1b, and patients who fail to achieve SVR after receiving simeprevir may lose the benefit of other NS3/4A PI-containing regimens.

As discussed in Dr. Deming's review, in the phase 3 clinical trials in treatment-naïve subjects (C208 and C216) and prior relapsers (HPC3007), the most frequent treatment-emergent, resistance-associated substitutions identified during the clinical trials were NS3_R155K,

D168E, and D168V for genotype 1a viruses and Q80R, D168E, and D168V for genotype 1b viruses. NS3_R155K and multiple substitutions at NS3_D168 are associated with resistance to NS3/4A protease inhibitors in general, so the majority of subjects who fail simeprevir-containing regimens may have limited re-treatment options available until their resistant virus has fully reverted, which may take years, or new classes of anti-HCV drugs become approved.

Simeprevir treatment was consistently associated with improved SVR responses in the phase 3 trials. However, analysis of the impact of HCV polymorphic variants on efficacy revealed that the SVR rates of subjects infected with genotype 1a NS3_Q80K at baseline were not significantly improved relative to those who received placebo, despite evidence of antiviral activity (i.e., improvements in early virologic responses).

In replicon culture studies, the presence of Q80K was associated with an approximately 10-fold reduction in susceptibility to simeprevir. Results from the simeprevir phase 2b trials, C205 and C206, which were conducted in treatment-naïve and treatment-experienced subjects, respectively, indicated that the 150 mg q.d. dose of simeprevir in combination with P/R (simeprevir + P/R) would likely maintain activity against Q80K variants. However, data from the phase 3 trials showed that simeprevir + PR had significantly reduced efficacy against genotype 1a Q80K variants. Of note, baseline Q80K in subjects with HCV GT1a did not result in a significant reduction in SVR in boceprevir and telaprevir clinical trials.

Because the impact of the Q80K polymorphism in GT 1a subjects was not recognized prior to phase 3 clinical trial results, at the time of the NDA submission, the Applicant proposed an alternative (b) (4) algorithm in lieu of screening for the presence of genotype 1a Q80K virus in prospective patients, who could then be excluded from treatment. (b) (4)

The sponsor's proposed (b) (4) algorithm, in the view of the Virology reviewers, is therefore was not an adequate alternative to screening.

The Division proposed an alternative algorithm based on screening all HCV GT1a patients for the Q80K polymorphism prior to treatment with simeprevir, as further discussed in the clinical-statistical efficacy section below.

6. Clinical/Statistical- Efficacy

See Clinical review by Dr. Adam Sherwat, and Statistical review by Drs. Yanming Yin and Fraser Smith for full details and discussion of efficacy.

Phase 3 Trials in Treatment Naïve Subjects

Two phase 3 clinical trials were performed in treatment-naïve subjects with chronic hepatitis C (CHC) with HCV genotype 1, trials C208 and C216. These were multicenter, international, randomized, placebo-controlled trials in which subjects received simeprevir 150 mg in combination with pegylated interferon and ribavirin (PR) for 12 weeks, followed by PR alone for 12 or 36 weeks based on the response-guided therapy algorithm in which subjects received 12 weeks of PR alone if HCV RNA was < 25 IU/mL (target not detected) at week 4 and undetectable at week 12. Subjects who did not meet these criteria received 36 weeks additional PR alone. The control arm was placebo plus PR for 12 weeks followed by PR alone for an additional 36 weeks. The primary endpoint was SVR12, defined as undetectable HCV RNA at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the end of therapy.

Please see Dr. Adam Sherwat's review for details on patient demographics and baseline characteristics. Most subjects were Caucasian (86-96%), and male (55-69%); and most were non-cirrhotic (7-15% subjects had cirrhosis across trials). Approximately one-half subjects were infected with HCV genotypes 1a and half were infected with HCV genotype 1b at baseline. Across the phase 3 trials, which were conducted in North America, Europe, South America, and the Asia-Pacific region, 20-44% subjects were North American.

Because C208 and C216 were identical in study design, population (treatment-naïve), and primary endpoint (SVR12), efficacy results were pooled. Overall SVR12 was 419/521 (80%) in the pooled simeprevir arms and 133/264 (50%) in the pooled placebo arms, as shown in the following table. Both relapse and on-treatment failures were lower in the simeprevir/PR group than in the placebo/PR group.

Table 1. Primary Efficacy Analysis in Pooled Treatment-Naïve Trials (C208 and C216)

Treatment Outcome	Pooled Simeprevir Arms n/N (%)	Pooled Placebo Arms n/N (%)
SVR12[a]	419/521 (80)	133/264 (50)
On-treatment failure [b]	43/521 (8)	88/264 (33)
Viral Relapse [c]	55/469 (12)	38/171 (22)

[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.
[c] For inclusion in denominator for relapse determination, HCV RNA had to be undetected at end of treatment and there could be no missing HCV RNA during follow-up.

Subgroup analysis showed that in treatment-naïve subjects, SVR12 was higher in subjects treated with simeprevir plus PR than in those treated with placebo plus PR regardless of IL28B genotype, race, gender, age, baseline HCV RNA, and Metavir fibrosis score. SVR12 was somewhat higher overall among subjects with HCV genotype 1b than in those with HCV genotype 1a in the simeprevir/PR group. Among subjects with HCV genotype 1a, SVR12 was substantially reduced in those who had a Q80K substitution at baseline in comparison to those

without the Q80K substitution. In addition, among those with the Q80K polymorphism, SVR12 was not statistically significantly different for the simeprevir treatment group in comparison to placebo, as shown in the following table.

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	**SVR12** n/N (%)	**SVR12** 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.

As noted in Dr. Damon Deming's review, replicon culture studies indicated that Q80K expression was associated with an approximately 10-fold reduction in susceptibility to simeprevir relative to wild-type controls, providing virologic support for the reduced clinical efficacy against Q80K polymorphic variants. The Q80K polymorphism is common in US patients with HCV GT1a (48% US GT1a subjects in the phase 2b and 3 simeprevir trials); while it was present in none of the 113 US GT1b subjects in these trials. Given the high frequency of the HCV GT1a Q80K polymorphism in the US population and its impact on SVR1, DAVP recommends that all GT1a patients be screened at baseline and offered alternative therapy if Q80K is present.

DAVP consulted with CDRH on the issue of a companion diagnostic test for use with simeprevir, as reduced efficacy of simeprevir in subjects with the Q80K polymorphism was recognized late in simeprevir development, and a companion diagnostic test is not currently available. CDRH stated that if the risks outweighed the benefits for use of simeprevir without a companion diagnostic, then FDA approval/clearance of companion diagnostic test by CDRH would be necessary. However, if DAVP recommends (rather than requires) use of a diagnostic test for Q80K with simeprevir, then FDA approval/clearance of a companion diagnostic test would not be needed. DAVP has concluded that because the Q80K polymorphism is present in only a subgroup of US patients with HCV GT1a, and that simeprevir provides benefit from both an efficacy and safety standpoint overall in the HCV GT1 population, screening for the polymorphism should be recommended rather than required. Acceptable commercial HCV sequencing tests are currently available which can be used for Q80K screening in clinical practice. At the CDER Center Director briefing held on September 19, 2013, Dr. Janet Woodcock agreed with DAVP that screening for Q80K should be recommended, but not required. Language will be included in the simeprevir prescribing information Indications and Usage section recommending Q80K screening in patients with HCV GT1a, and alternative therapy should be considered for patients with the Q80K polymorphism present at baseline.

Phase 3 Trial in Relapsers

One phase 3 trial, HPC3007, in subjects who had previously relapsed after treatment with pegylated interferon (with or without ribavirin) was submitted with this application. The study design was the same as that described for trials C208 and C216 above. A total of 462 subjects were enrolled. See Dr. Sherwat's review for details about patient demographics and baseline characteristics. In HPC3007, the SVR12 rate in the simeprevir/PR arm was 79% compared to 36% in the placebo/PR, as shown in the following table. As observed in the treatment-naïve trials, both relapse and on-treatment failure were lower in the simeprevir/PR group than in the placebo/PR group.

Table 3. Primary Efficacy Analysis in HPC3007 (Prior Relapsers)

Treatment Outcome	Simeprevir +PR n/N (%)	Placebo +PR n/N (%)
SVR12[a]	206/260 (79)	48/133 (36)
On-treatment failure[b]	8/260 (3)	38/133 (29)
Viral Relapse[c]	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.
[c] For inclusion in denominator for relapse determination, HCV RNA had to be undetectable at end of treatment and there could be no missing HCV RNA during follow-up.

In the subgroup analysis, SVR12 was higher in the simeprevir plus PR group in comparison to placebo plus PR group regardless of IL28B genotype, race, sex, age, metavir fibrosis score, and baseline HCV RNA. However, as in the treatment-naïve trials, the presence of the Q80K polymorphism at baseline in HCV genotype 1a subjects resulted in significantly reduced SVR12, as shown below.

Table 4. 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.

As discussed above, language will be included in the simeprevir prescribing information Indications and Usage section recommending Q80K screening in patients with HCV GT1a, and that alternative therapy should be considered for patients with the Q80K polymorphism present at baseline.

Phase 2b Trial in Relapsers, Partial Responders and Null Responders
Although their phase 3 trial in treatment-experienced patients (null and partial responders) is ongoing, the Applicant submitted data from a completed phase 2b trial in treatment-experienced subjects, C206 in support of a treatment indication in this population. This trial enrolled prior PR relapsers, partial and null responders. This was a randomized, placebo-controlled 7-arm trial in which subjects received 12, 24, or 48 weeks of simeprevir (either 100 mg or 150 mg daily dose) in combination with PR (PR was administered for a total of 48 weeks in each of the treatment arms). The primary study endpoint was SVR24.

The following table shows SVR24 overall and for each of the subgroups of treatment-experienced subjects (relapsers, null and partial responders). Note that in the ITT population and in each of the subgroups, SVR24 was significantly higher in the simeprevir group than the placebo group.

Table 5. SVR24 Rates in Phase 2b Trial (C206) by Treatment Arm and Prior Treatment Response

Study				C206			
Subjects per Arm	66	66	65	66	66	68	65
Treatment Arm	PBO	TMC435 100MG/ 12WKS	TMC435 100MG/ 24WKS	TMC435 100MG/ 48WKS	TMC435 150MG/ 12WKS	TMC435 150MG/ 24WKS	TMC435 150 MG/ 48 WKS
----------n/N (%) Subjects Achieving SVR24*----------							
ITT Population	15/66 (23)	48/66 (73)	43/65 (66)	40/66 (61)	44/66 (67)	49/68 (72)	52/65 (80)
Relapsers	10/27 (37)	25/27 (93)	23/26 (88)	20/26 (77)	20/26 (77)	24/27 (89)	23/26 (88)
Partial Responders	2/23 (9)	17/23 (74)	11/23 (48)	12/22 (55)	15/23 (65)	18/24 (75)	19/22 (86)
Null Responders	3/16 (19)	6/16 (38)	9/16 (56)	8/18 (44)	9/17 (53)	7/17 (41)	10/17 (59)

Note that for the proposed duration of triple therapy (12 weeks), SVR24 was similar for the 100 mg or 150 mg simeprevir daily dose. In addition, duration of triple therapy longer than 12 weeks did not result in significantly improved SVR24 rates with 100 mg simeprevir; although there was a trend toward improved SVR24 with increasing treatment duration with 150 mg simeprevir. Based on these data, the Applicant chose a simeprevir dose of 150 mg daily for a duration of 12 weeks in combination with PR as the regimen for further evaluation in phase 3 trials.

In a pooled efficacy analysis, DAVP combined the 12 week triple therapy arms for the 100 mg and 150 mg doses of simeprevir to get a better estimate of SVR overall because of the small numbers in each of the subgroups. Based on exposure-response data from the phase 3 trials, described above, response rates are expected to be similar in this range of simeprevir exposures. The pooled efficacy analysis for C206 is shown in the table below.

Table 6. SVR24 Rates in Study C206 by Pooled Treatment Arm and Prior Treatment Response

Study	C206			
Subjects per Arm	66	66	66	132
Study Arm	PBO	TMC435 100MG/ 12WKS	TMC435 150MG/ 12WKS	**Pooled** TMC435 100MG/12WKS and TMC435 150MG/12WKS
----------n/N (%) Subjects Achieving SVR24*----------				
ITT Population	15/66 (23)	48/66 (73)	44/66 (67)	92/132 (70)
Relapsers	10/27 (37)	25/27 (93)	20/26 (77)	45/53 (85)
Partial Responders	2/23 (9)	17/23 (74)	15/23 (65)	32/46 (70)
Null Responders	3/16 (19)	6/16 (38)	9/17 (53)	15/33 (45)

In relapsers and partial responders, the difference in SVR24 rates between the pooled simeprevir groups and placebo group reached statistical significance. In null responders, the difference in SVR24 rates (26%) between the pooled simeprevir groups and placebo group (45% vs. 19%, respectively) did not reach statistical significance (P-value = 0.11). However, the lack of statistical significance in the null responder population likely relates to the small sample size of the groups and greater than predicted SVR24 rates in the null responder placebo group (which was more than twice that of the SVR24 rate in the partial responder placebo group).

Additional indirect evidence for efficacy in partial and null responders comes from the harder to treat subgroups in the phase 3 treatment naïve trials, C208 and C216, as discussed in Dr. Jiang's pharmacometrics review. The Division's previous experience in evaluating the treatment-naïve and treatment-experienced populations has indicated that PR treatment-experienced subjects are present in the treatment-naïve population (Florian J et al. *Hepatology 2012*, Liu J et al. *Clinical Infectious Diseases 2012*, and Liu J et al. *Hepatology 2012*). Population mapping based on baseline factors can be used to identify a subset of the treatment-naïve subjects in the simeprevir Phase 3 trials that matches the PR treatment-experienced population, i.e., the putative PR-experienced cohort embedded in the Phase 3 trials of treatment-naïve population. The subjects in the putative PR-experienced cohort are the harder-to-treat subjects with IL28B genotypes CT and TT, advanced liver fibrosis (e.g., metavir score F3-F4), and/or high baseline HCV RNA (e.g., baseline HCV RNA ≥ 800,000 IU/mL). Significantly higher SVR rates with simeprevir/PR versus placebo/PR in the harder-to-treat subpopulation supports effectiveness of simeprevir in the PR treatment-experienced population, as most patients who previously failed PR therapy have one or more of the characteristics listed above. As shown in the following table, SVR12 rates for the harder-to-treat subjects with simeprevir 150 mg for 12 weeks were significantly higher compared to

those with the PR treatment. These data also confirm that IL28B non-CC genotype, advanced liver fibrosis or cirrhosis (metavir score of F3 or F4), baseline HCV RNA ≥ 800,000 IU/mL are predictors of diminished virological responses to simeprevir/PR triple therapy, as shown previously for PR alone and for other HCV protease inhibitor-based therapy in combination with PR.

Table 7. Comparison of SVR Rate between Simeprevir/PR and PR Treatment in Treatment-Naïve Subjects Who Had Baseline Harder-to-Treat Factors

Baseline Factors		SVR12, n/N (%)	
		Placebo	Simeprevir
IL28B	CC	64/79 (81)	144/152 (95)
	CT	61/147 (42)	228/292 (78)
	TT	8/38 (21)	47/77 (61)
Liver disease status	F0-F2	107/192 (56)	317/378 (84)
	F3-F4	26/72 (36)	89/130 (68)
Baseline HCV RNA	< 800 KIU/mL	54/70 (77)	96/104 (92)
	≥ 800 KIU/mL	79/194 (41)	323/417 (77)
nonCC & F3-F4 & BL HCV ≥ 800 KIU/mL		3/38 (8)	37/73 (51)

In addition, as discussed in Dr. Jiang Liu's review, results of the Japanese Phase 3 trials, for which summary data but no datasets were submitted, also support the use of simeprevir in combination with PR in prior PR non-responders. In these trials, the SVR rates for the trials exceeded the historic 16% of SVR rate assumed for PR treatment:

- SVR12 response rate was 53% (28/53) and 36% (19/53) for simeprevir 100 mg q.d. administered for 12 weeks and 24 weeks respectively in HPC3004; and
- SVR12 response rate was 39% (10/26) for simeprevir 100 mg q.d. administered for 12 weeks in HPC3010.

Note that the majority of subjects in the Japanese phase 3 trials were infected with HCV genotype 1b. However, because SVR12 rates were similar in subjects infected with HCV genotype 1a or 1b in the pivotal phase 3 trials for this application, the Japanese data can be considered supportive. Based on the totality of the evidence, DAVP concluded that simeprevir in combination with PR was efficacious in treatment-naïve subjects, prior relapsers, as well as in prior partial and null responders.

Efficacy Issues: Screening for HCV NS3 Q80K Polymorphism Prior to Treatment with Simeprevir and Proposed Treatment Algorithms

The Q80K variant is a common polymorphism in U.S. HCV 1a-infected subjects, and simeprevir has reduced activity against Q80K variants. Screening for baseline HCV Q80K polymorphism was raised as a potential issue by DAVP at the pre-NDA meeting with the Applicant. At that time the Applicant indicated that development of a companion diagnostic test for Q80K screening would not be feasible. However, with the NDA submission, the Applicant proposed a treatment algorithm (b) (4)

(b) (4)

DAVP concluded that rather than use the Applicant's proposed treatment algorithm, patients should be screened for the HCV Q80K substitution prior to treatment with simeprevir and PR. Patients with HCV GT1a with the Q80K polymorphism should be offered alternative therapy. Pretreatment screening would greatly simplify the treatment algorithm for patients and medical providers. (b) (4)

Considering the (b) (4)

availability of alternative treatment options to simeprevir where Q80K is not an issue (i.e. boceprevir or telaprevir plus PR), prescreening for Q80K prior to treatment with simeprevir/PR may offer a simpler and clinically more practical option as follows:

a. Treatment-naïve and prior relapse patients receive a fixed 24-week course of PR in conjunction with 12 weeks of simeprevir.
b. Prior partial- and prior null-responders receive a fixed 48 week course of PR in conjunction with 12 weeks of simeprevir.
c. All patients treated with simeprevir/P/R with quantifiable (≥25 IU/mL) HCV RNA levels at Week 4 should stop treatment (simeprevir and PR).

The Applicant found this approach acceptable, and these recommendations will be included in the simeprevir prescribing information.

7. Safety

The safety database for simeprevir 150 mg daily in combination with PR for 12 weeks is adequate. The primary safety pool which included the 3 phase 3 trials, C208, C216, and HPC3007, included 781 subjects who received simeprevir 150 mg/day for 12 weeks in combination with PR and 397 subjects who received placebo plus PR for 12 weeks. In addition, safety data from the phase 2b trials, C205 and C206 in which subjects received 100 mg or 150 mg/day simeprevir for at least 12 weeks in combination with PR was considered supportive.

See Dr. Adam Sherwat's clinical review for detailed review of safety. The major safety issues identified in the simeprevir development program were rash and photosensitivity reactions. Hyperbilirubinemia is associated with simeprevir use, but as discussed below was not associated with hepatotoxicity in the clinical trials, and appears to be related to inhibition of hepatic transporters. The following is a brief summary of simeprevir safety from clinical trial data submitted with this NDA.

Four deaths were reported in the phase 2 and 3 trials; however, none of the deaths was immediately temporally related to receipt of simeprevir, and none were considered related to simeprevir by investigators or DAVP clinical reviewers. Reported causes of death were bacterial meningitis and brain hemorrhage, pneumonia and septic shock, colon cancer, and presumed cardiopulmonary event (sudden death). In the pooled phase 3 trials, serious adverse events (SAEs) were reported in 2% subjects in the simeprevir/PR group and 3% of those in the placebo/PR group during the first 12 weeks of treatment. SAEs reported in more than 1 subject in the simeprevir/PR group (n=781) included depression (2 subjects), syncope (2 subjects), and photosensitivity reaction (2 subjects). No SAEs of depression, syncope or photosensitivity were reported in the placebo/PR group (n=397). SAEs considered at least possibly related to simeprevir by investigators were depression (1 subject) and photosensitivity (2 subjects). However, depression (or exacerbation thereof) and other psychiatric adverse events are part of the well-characterized safety profile of interferon therapy, and thus the SAE of depression in a subject with underlying depression, was confounded.

Discontinuations due to adverse events were reported in 14/781 (2%) simeprevir/PR-treated subjects and 5/397 (1%) placebo/PR-treated subjects. The most common AE resulting in discontinuation was rash (5 subjects) in the simeprevir/PR group compared to none in the placebo/PR group. Grade 3 AEs were reported in 172/781 (22%) and 94/397 (24%) subjects in the simeprevir/PR and placebo/PR groups, respectively; while Grade 4 AEs were reported in 23/781 (3%) and 11/397 (3%) of subjects in the simeprevir/PR and placebo/PR groups, respectively. The most common Grade 3 or 4 AEs were hematologic, including neutropenia (9%), and thrombocytopenia (1%) in both treatment groups, and hyperbilirubinemia (1%) in the simeprevir/PR group.

The most common adverse events reported at least 3% more frequently in the simeprevir/PR group in comparison to the placebo/PR group were rash (28%), influenza-like illness (26%), pruritus (22%), nausea (22%), myalgia (16%), dyspnea (12%), increased bilirubin (8%), and photosensitivity (5%). See Dr. Sherwat's review for further details.

There was no evidence for increase in the frequency or severity of hematological laboratory parameters, including neutropenia, anemia, or thrombocytopenia, nor was there an increase in the frequency or severity of renal laboratory parameters or electrolytes for the simeprevir/PR group in comparison to the PR group. See review of hyperbilirubinemia below for discussion of hepatic laboratory abnormalities.

Adverse Events of Clinical Significance Identified in the Simeprevir Development Program:

Rash and Photosensitivity Reactions
In the phase 2b and 3 trials, rash (pooled MedDRA preferred terms, including photosensitivity reactions and rash) was reported as an AE in 28% subjects in the simeprevir/PR group and 20% subjects in the placebo/PR group during the first 12 weeks of treatment. The most commonly reported AEs in this category were rash (14%), erythema (3%) and photosensitivity reaction (3%) subjects in the simeprevir/PR group and rash (11%), erythema (3%), and eczema (2%) subjects in the placebo/PR group. Among subjects who developed rash in the simeprevir/PR group, 56% had onset of rash during the first 4 weeks of therapy. A similar pattern was observed in the placebo/PR group.

Photosensitivity
Photosensitivity reactions were reported during the early clinical experience with simeprevir, and a dedicated photosensitivity study was performed in healthy subjects. Immediate photosensitivity reactions were reported in 33% subjects in the simeprevir group, and in no subjects in the ciprofloxacin (positive control) group or placebo group. A positive association was noted between simeprevir exposure and development of immediate photosensitivity reactions. Delayed photosensitivity reactions were observed in the ciprofloxacin group, but not in the simeprevir group. The Applicant interpreted these results as showing that simeprevir was not associated with photosensitivity. However, interpretation of this study by reviewers in the Division of Dermatology and Dental Products (DDDP) differed significantly. See further discussion of photosensitivity below regarding DAVP's consultation with the DDDP.

During the phase 2b and 3 clinical trials, subjects were asked to adhere to sun-protection measures. In these trials photosensitivity was reported in 38(5%) subjects in the simeprevir/PR group and in 3 (1%) subjects in the placebo/PR group during the first 12 weeks of treatment. Two SAEs of photosensitivity were reported in the simeprevir/PR group, in both cases resulting in hospitalization, and in one case treatment with systemic steroids was needed. No SAEs of photosensitivity were reported in the placebo/PR group. There were no Grade 4 events, but one Grade 3 AE of photosensitivity was reported in the simeprevir/PR group.

Rash
In the phase 3 trials, when rash was assessed separately from photosensitivity reactions, rash was reported in 25% simeprevir/PR and in 19% placebo/PR-treated subjects during the first 12 weeks of therapy, suggesting that simeprevir (and not just PR) is associated with rash. No Grade 4 rashes were reported; but there were 4 subjects in the simeprevir/PR group and no subjects in the placebo/PR group that experienced a Grade 3 rash. Discontinuations due to rash were reported in 7 simeprevir/PR-treated subjects and 1 placebo/PR-treated subject during the

first 12 weeks of therapy. Several subjects who discontinued simeprevir developed associated mucosal lesions (apthous stomatitis, mouth ulcers), and the possibility of erythema multiforme could not be excluded. However, no cases of Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) were reported.

Similarly in the pooled phase 2b trials, an increase in rash and severity of rash was observed in the simeprevir/PR group in comparison to the placebo/PR group. Similar proportions of subjects discontinued due to rash, and 2 of the discontinuations in the simeprevir/PR group were due to SAEs (one due to cutaneous vasculitis and one due to drug eruption). There were no Grade 4 AEs or reports of SJS, TEN or DRESS in phase 2b trials.

In clinical trials of simeprevir/PR conducted in Japan by the Applicant, in which simeprevir was dosed at 100 mg daily for 24 weeks, there were no reports of SJS, TEN or DRESS. However, 3 subjects experienced erythema multiforme (EM), two during treatment with simeprevir/PR and the third during treatment with PR alone.

The Division of Dermatology and Dental Products was consulted regarding rash and photosensitivity observed with simeprevir in the clinical trials. At DAVP's request, the Applicant provided available photographs and biopsy results for severe photosensitivity and rash AEs. Although the Applicant did not consider the findings in the dedicated photosensitivity study to be significant or indicative of simeprevir photosensitivity, the Dermatology reviewers concluded that the finding that 33% simeprevir-exposed subjects in the study exhibited immediate photosensitivity was clinically significant. The Dermatology reviewers, Drs. Brenda Carr, and Jill Lindstrom, agreed with the Division that a clear signal for photosensitivity was identified in the simeprevir clinical development program, a risk which could potentially be mitigated by advising sun-protection measures, including UV light avoidance, in the patient and prescribing information. The pattern of photosensitivity observed with simeprevir suggests phototoxicity rather than photoallergy. Phototoxocity classically manifests as exaggerated sunburn, which was the apparent presentation in affected subjects in the simeprevir clinical trials. Drs. Carr and Lindstrom also recommended that the risk of photosensitivity and rash be communicated separately in the Warnings and Precaution section of the prescribing information as their risk mitigation strategies are sufficiently distinct to warrant separate discussion in the label. See section 12 below on labeling for further discussion of this issue.

Hyperbilirubinemia and Hepatobiliary Adverse Events

Hyperbilirubinemia associated with simeprevir was identified as an issue early in clinical development. In the phase 3 trials increased bilirubin (analyzed as grouped MedDRA preferred terms including hyperbilirubinemia, increased blood bilirubin, jaundice, unconjugated bilirubin increased, conjugated bilirubin increased) was reported as an adverse event in 61/781 (8%) simprevir/PR-treated subjects and in 11/397 (3%) placebo/PR-treated subjects. Grade 3 or 4 AEs under the grouped term, increased bilirubin was reported in (2%) and 1% of subjects treated with simeprevir/PR or placebo/PR, respectively during the first 12 weeks of treatment.

A marked increase in frequency of graded bilirubin elevations in the simeprevir/PR group (49%) compared to the placebo/PR group (26%) was noted. This difference was primarily driven by grade 1 and 2 laboratory abnormalities, and included elevations in both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, peaking by Week 2. By four weeks following completion of simeprevir treatment (i.e. Week 16), levels were shown to return to near baseline values.

Overall, elevations in bilirubin were not accompanied by ALT or AST elevation. ALT levels decreased similarly in the simeprevir/PR and placebo/PR groups during treatment. In addition, no definitive Hy's law cases (i.e. ALT or AST > 3 x ULN, total bilirubin > 2 x ULN without increase in alkaline phosphatase and without another explanation for increased liver enzymes) attributable to simeprevir were identified in the clinical development program.

Alkaline phosphatase elevations were reported in 4% subjects in the simeprevir/PR group and 1% subjects in the placebo/PR group. Most elevations were Grade 1 or 2; and alkaline phosphatase elevations peaked at week 8 and declined to baseline levels after week 12 of treatment.

Two subjects in the simeprevir/PR group and none in the placebo/PR group experienced a hepatobiliary SAE. One subject, a 54 year white old female with diabetes experienced adverse events of jaundice and abdominal pain, starting on study day 31 of simeprevir/PR and was diagnosed with bile duct obstruction which required ERCP and cholecystectomy. This subject had several risk factors for gallstones, including age, female sex, and diabetes, and thus the case was confounded. In addition, this was the only such case in the simeprevir clinical development program. Therefore, it seems unlikely that the gallstones and biliary obstruction were related to simeprevir, although chronic hyperbilirubinemia has been associated with biliary stones. The other hepatobiliary SAE in a subject receiving simeprevir/PR was the report of a "hepatic lesion" in a 45 year old female hospitalized with liver laceration, shoulder pain and chest contusion due to motor vehicle accident. This SAE was clearly not related to simeprevir/PR.

Discontinuations due to hepatobiliary adverse events were reported in 1 subject in simeprevir/PR group and one in the placebo/PR group, both due to increased blood bilirubin or jaundice.

The bilirubin elevations associated with simeprevir are considered to be due to decreased bilirubin elimination secondary to inhibition of the hepatic transporters, OATP1B1 and MRP2. OATP1B1 transports both unconjugated and conjugated bilirubin; MRP2 transports conjugated bilirubin. As noted in the Clinical Pharmacology review, simeprevir is an inhibitor of both OATP1B1 and MRP2, and the bilirubin elevations observed during clinical trials could be the result of hepatic transporter inhibition.

Overall, no hepatic safety signal was identified with simeprevir in the clinical trials, and the bilirubin elevations observed do not appear to be clinically significant and resolve after stopping simeprevir therapy.

Safety Conclusions
Simeprevir is associated with both photosensitivity reactions and rash. DAVP is considering including separate Warnings for Photosensitivity and Rash in the simeprevir prescribing information because management of these cutaneous reactions differs. The Advisory Committee will be asked to provide advice on this issue. See section 11 on Labeling below.

In comparison with the currently approved HCV protease inhibitors, boceprevir and telaprevir, the safety profile of simeprevir is improved. Although rash and photosensitivity were observed in clinical trials of simeprevir, there have been no cases of serious cutaneous adverse reactions, such as SJS, TEN or DRESS to date in clinical trials, including those conducted in Japan; whereas telaprevir carries a Boxed Warning regarding serious skin reactions, including SJS, DRESS and TEN. Boceprevir has also been associated with SJS and DRESS in the postmarketing period. In addition, both boceprevir and telaprevir have been associated with significant anemia. Although anemia has been reported with pegylated interferon and ribavirin, additional decreases in hemoglobin were observed with boceprevir and telaprevir in combination with PR, requiring ribavirin dose reductions and sometimes blood transfusions and/or erythropoietin stimulating agents (off-label use) for management. In the clinical trials, simeprevir was not associated with increased rates of anemia beyond that observed with PR, nor was it associated with increased rates of other hematologic abnormalities, such as neutropenia or thrombocytopenia; whereas boceprevir has been associated with increased neutropenia, and to a lesser extent, thrombocytopenia.

8. Advisory Committee Meeting

The Advisory Committee (AC) meeting was held on October 24, 2013. The following questions were discussed at the AC meeting:

1. **DISCUSSION:** Please comment on the safety profile of simeprevir focusing on rash and photosensitivity reactions reported during the clinical trials.

> a. Does the committee agree that a discussion of the photosensitivity reactions, including a recommendation for sun-protection measures, should be included in the Warnings and Precautions section of the simeprevir prescribing information?
>
> ***Reviewer Comment:*** *The committee agreed that photosensitivity reactions and sun-protection measures should be included in the Warnings and Precautions section of simeprevir prescribing information. Dr. Michael Bigby, Associate Professor of Dermatology, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA noted that a drug does not necessarily have to be discontinued for a phototoxic reaction if sun exposure can be stopped.*
>
> b. There are apparent differences related to both the clinical presentation and prevention/management strategy for photosensitivity reactions versus rash. Does the

committee agree that a separate discussion of rash should be included in the Warnings and Precautions section of the simeprevir prescribing information?

Reviewer Comment: *A broad range of opinions were expressed by the committee regarding this question. Some committee members thought it might be important to state that expert opinion should be obtained regarding rash. The dermatologist, Dr. Michael Bigby, commented that the data on drug eruptions in this drug development program were not that robust, that there were no severe AEs such as SJS, TEN, and DRESS, and that erythema multiforme, which is usually not drug related, should not necessarily be considered a severe skin reaction.. He stated, however, that reactions like SJS and TEN are very rare and may not be seen during the drug development program. Dr. Bigby also noted that there would be no downside to having a warning for rash similar to that included in the telaprevir prescribing information. Some committee members thought it might be confusing to have two separate warnings for photosensitivity and rash; while others thought it would be better to have two distinct warnings.*

2. **VOTE:** Considering the overall risks and benefits, do the available data support approval of simeprevir in combination with pegylated interferon and ribavirin for treatment of HCV genotype 1 infection?

VOTE: Yes/No/Abstain

Reviewer Comment: *The committee voted 19 yes/0 no/0 abstentions on this question. The discussion centered on the positive benefit-risk profile of simeprevir and ease of administration in comparison to the currently available HCV protease inhibitors.*

3. DISCUSSION: DAVP intends to recommend screening all subjects with GT1a infection for the Q80K viral polymorphism prior to initiation of simeprevir (in combination with pegylated interferon and ribavirin) and that alternative treatment options be considered for patients with this baseline polymorphism. Does the committee agree with DAVP's proposed approach to managing the reduction in efficacy apparent in the setting of the Q80K polymorphism?

Reviewer Comment: *In general, the committee agreed with DAVP's plan to recommend screening for the Q80K polymorphism. Some members thought that alternative treatment options, including no treatment, should be recommended rather than considered for patients with the Q80K polymorphism at baseline; however, others thought that because simeprevir/PR treatment is effective in some patients with the Q80K polymorphism at baseline, its use should not be restricted, and that a risk/benefit assessment should be performed on a patient by patient basis.*

4. **DISCUSSION:** Are there postmarketing studies that should be conducted to further define risks or to optimize use of simeprevir?

Reviewer Comment: *The committee noted that more data is needed in a number of patient populations, including African Americans, Hispanics, Asians, prior PR nonresponders (null and partial responders), cirrhotic patients, HIV/HCV-coinfected patients, pediatric patients, and patients with co-morbidities (including chronic renal failure). Others thought that additional safety studies to further evaluate rash, photosensitivity, and dyspnea might be important. However, others noted that the HCV treatment paradigm is rapidly changing, and interferon-free regiments may become the standard of care; and thus the patient populations mentioned should be studied with an interferon-free regimen.*

9. Pediatrics

The Applicant requested a waiver of pediatric studies in patients less than 3 years old, and a deferral in patients ≥3 to < 18 years of age. The Division agreed with the request for waiver in pediatric patients under the age of 3 because the rate of spontaneous clearance of HCV in pediatric patients is somewhat variable and can not be predicted for individual patients and because pediatric hepatologists disagree on the appropriate age to begin therapy, and because the number of patients < 3 years of age who might be enrolled in clinical trials is relatively small and widely dispersed across the US, Europe and Asia. The Division also agreed with the request for deferral in pediatric patients ≥3 to < 18 years old because adult studies are ready for approval, and for the following additional reasons:

1. Children with a chronic HCV infection are often asymptomatic and usually experience slow disease progression;
2. The safety concerns associated with current pegylated interferon-based regimens (potential impact on growth, etc.), may outweigh the benefit of immediate treatment and a potential cure with an interferon-based regimen in children ≥ 3 to < 18 years of age, particularly with the prospect of interferon-free regimens in the foreseeable future;

Preliminary data from simeprevir-containing interferon-free regimens are promising and show high SVR rates in HCV-infected adults. For these reasons, the Division considers it appropriate to request a deferral for the study of simeprevir in combination with pegylated interferon and ribavirin in the pediatric population (≥ 3 to < 18 years of age) until further data on simeprevir-containing interferon-free regimens, with or without RBV, for the treatment of chronic HCV infection in adults become available.

The Pediatric Review Committee meeting for simeprevir is scheduled for October 30, 2013.

The Applicant plans to evaluate simeprevir in combination with other DAAs in pediatric patients ≥ 3 to < 18 once an interferon-free DAA combination regimen containing simeprevir has demonstrated efficacy and safety in adults. The Division plans to include two PREA postmarketing requirements for evaluating simeprevir as part of a combination regimen for treatment of pediatric patients ≥ 3 to < 18 years old at the time of approval as follows:

- Conduct a trial to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as a measure) of simeprevir as a component of

a combination antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

- Collect long-term safety data for subjects enrolled in the pediatric simeprevir safety and treatment trial. Data collected should include at least (b) years of follow- up in order to characterize the long-term safety of simeprevir in pediatric patients, including characterization of simeprevir resistance-associated substitutions in viral isolates from subjects failing therapy.

10. Other Relevant Regulatory Issues

Office of Scientific Investigation Inspections
Two domestic and two international phase 3 clinical trial sites (both in Poland) were selected for inspection. Sites were selected for inspection on the basis of relatively large enrollment of subjects, high treatment responses, protocol violations, and significant primary efficacy results pertinent to decision-making. All four of the site inspections have been completed and no substantive issues were identified. In his review, Dr El-Hage noted that while minor regulatory violations were identified during the inspection of Drs. Lawitz and Felizarta sites, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the violations on overall data integrity to be significant. Overall, the data submitted from these four sites were considered acceptable in support of the pending application. See review by Dr. Antoine El-Hage for full details.

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

Financial Disclosures
Financial disclosures were reviewed for all investigators involved in the phase 2b and 3 trials used for assessment of efficacy and safety in the Division's review. See Dr. Adam Sherwat's review for full details. Dr Sherwat concluded that based on the information provided, the likelihood that the trial results were substantially biased due to financial interest is low.

11. Labeling

Proprietary Name: Initial review of the proposed proprietary name, Sovriad, was considered unacceptable because it could result in medication errors due to confusion with another product that is also under review; and therefore the ultimate acceptability of the proposed name, Sovriad was dependent on which application was approved first. The Applicant subsequently resubmitted Sovriad as the proposed proprietary name in addition to an alternate name, Olysio. DMEPA has determined that the proposed proprietary name, Olysio, is acceptable, and is currently awaiting comment from the review team before finalizing their review and notifying the Applicant.

Prescribing Information: Simeprevir prescribing information is currently under negotiation with the Applicant. To date, the Applicant has agreed with DAVP's proposed labeling changes. The substantially completed labeling is currently under review by the Office of

Prescription Drug Promotion. DAVP proposed the following major changes to the Applicant's proposed prescribing information for simeprevir.

1. Indications and Usage:
DAVP proposed simplified language for the indication, as follows:
"TRADENAME is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis)."

In addition, the following information was proposed under "points to consider":

"Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. TRADENAME efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to those without the Q80K polymorphism, and alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism."

2. Dosage and Administration
The Applicant's proposed treatment algorithm (b) (4) was removed and the Division's proposed tables showing the recommended simplified treatment algorithm (based on Q80K screening) and stopping (futility) rules were included, as follows:

Table A: Duration of Treatment with TRADENAME, Peginterferon alfa and Ribavirin

	Treatment with TRADENAME, peginterferon alfa and ribavirin[1]	**Treatment with peginterferon alfa and ribavirin**[1]	**Total Treatment Duration**[1]
Treatment-naïve and prior relapser patients[2] **including those with cirrhosis:**	First 12 weeks	Additional 12 weeks	24 weeks
Prior non-responder patients[2] **(including partial and null responders) including those with cirrhosis:**	First 12 weeks	Additional 36 weeks	48 weeks

[1] Recommended duration of treatment if patient does not meet stopping rule (see Table 2).
[2] Relapse or non-response following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin [*see Clinical Studies (14)*].

Table B: Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response

HCV RNA	**Action**
Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue TRADENAME, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin (treatment with TRADENAME is complete at Week 12)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin

2.4 Hepatic Impairment

In section 8 (Use in Specific Populations), the Applicant had proposed no dose adjustment for simeprevir in patients with mild (b) (4) hepatic impairment; and no dose recommendation for patients with severe hepatic impairment. Because of the clinical pharmacology findings of increased simeprevir exposures in HCV-uninfected subjects with moderate or severe hepatic impairment compared to healthy controls, and the exposure-response relationship for adverse events such as rash and photosensitivity, DAVP proposed the following language for section 2:

"No dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher simeprevir exposures [see Pharmacokinetics (12.3)]. In clinical trials, higher exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. The safety and efficacy of TRADENAME have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C)."

2.5 Race

DAVP proposed the following language for simeprevir dosing in Asian patients based on the clinical pharmacology findings of increased simeprevir exposure in subjects of East Asian descent compared to the pooled Phase 3 population (which was primarily Caucasian) and the exposure-response relationship for adverse events, such as rash and photosensitivity:

"Patients of East Asian ancestry exhibit higher simeprevir exposures due to higher simeprevir exposures [see Pharmacokinetics (12.3)]. In clinical trials, higher exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients with East Asian ancestry."

5. Warnings and Precautions

The Applicant had not proposed including Photosensitivity and/or Rash in this section. In light of the association of photosensitivity and rash with simeprevir in the clinical trials, DAVP proposed the following language:

5.2 Photosensitivity

Photosensitivity reactions have been observed with TRADENAME in combination with peginterferon alfa and ribavirin, including serious reactions which resulted in hospitalization [see Adverse Reactions (6.1)]. Photosensitivity reactions occurred with greatest frequency during the first 4 weeks of treatment with TRADENAME in combination with peginterferon alfa and ribavirin, but can occur at any time during treatment. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, and dorsa of the hands). Manifestations may include burning, erythema, exudation, blistering, and edema.

Avoid exposure to sun and use sun protective measures during treatment of TRADENAME in combination with peginterferon alfa and ribavirin. Avoid use of tanning devices during

treatment of TRADENAME in combination with peginterferon alfa and ribavirin [see Patient Counseling Information, Photosensitivity (17.2)]. TRADENAME should be discontinued if a photosensitivity reaction occurs and patients should be monitored until the reaction has resolved.

After discussion with the Advisory Committee, DAVP will propose a separate Warning for rash in the prescribing information for simeprevir, as follows:

Rash has been reported with TRADENAME in combination with peginterferon alfa and ribavirin. Rash occurred with greatest frequency during the first 4 weeks of treatment with TRADENAME in combination with peginterferon alfa and ribavirin, but can occur at any time during treatment. Severe rash and rash requiring discontinuation of TRADENAME has been reported. Patients with mild to moderate rashes should be followed for progression of rash or development of mucosal lesions (e.g. oral lesions, conjunctivitits) or systemic symptoms. If rash progresses or becomes severe, TRADENAME should be discontinued. Patients should be monitored until the rash has resolved.

In addition, DAVP proposed a Warning regarding Sulfa Allergy, as follows:

5.3 Sulfa Allergy

"TRADENAME contains a sulfonamide moiety. There are insufficient data to demonstrate any association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of TRADENAME."

Carton and Container Labeling
ONDQA reviewers found the proposed Carton and immediate container labeling acceptable. DMEPA is currently negotiating with the Applicant on some minor container labeling issues.

Patient Labeling
Patient labeling (Patient Package Insert) is currently under review by the Patient Labeling Team in the Office of Prescription Drug Promotion, CDER Office of Medical Policy. DAVP has proposed language on use of sunscreen and other measures to prevent photosensitivity reactions. DAVP does not consider a Medication Guide necessary for simeprevir.

8. Use in Specific Populations
Because of the pharmacology/toxicology findings of potential reproductive toxicity in the rat and mouse, DAVP recommended that simeprevir be classified as a pregnancy category C drug. This language was proposed as follows:

8.1 Pregnancy

Pregnancy Category C: TRADENAME

There are no adequate and well-controlled studies with TRADENAME alone or in combination with peginterferon alfa and ribavirin in pregnant women.

In addition, sections 8.6 Race, and 8.8 Hepatic Impairment were modified for consistency with section 2, Dosage and Administration.

12. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:** *APPROVAL* is recommended for simeprevir in combination with pegylated interferon alfa and ribavirin for treatment of patients with chronic hepatitis C genotype 1 and compensated liver disease, including cirrhosis.

- **Risk Benefit Assessment:** Efficacy of simeprevir for treatment of CHC (HCV genotype 1) in combination with PR was demonstrated in phase 3 trials of treatment-naïve subjects and in prior PR relapsers, and in a large phase 2b trial in subjects who were nonresponders (null or partial responders) to prior PR therapy. The major clinically significant safety issues associated with simeprevir use include rash and photosensitivity. These risks and mitigation thereof will be addressed in simeprevir labeling. Additional risks of simeprevir in combination with PR include those associated with pegylated interferon and ribavirin. These risks are addressed in the prescribing and patient information for the approved pegylated interferon and ribavirin products.

  Simeprevir appears to provide a number of advantages, including improved tolerability and ease of administration in comparison to the currently approved HCV protease inhibitors, boceprevir and telaprevir. Simeprevir is dosed as a single capsule once daily (compared to twice or thrice daily with telaprevir and boceprevir, respectively), and has an improved safety profile in comparison to telaprevir and boceprevir which are both associated with clinically significant anemia, requiring ribavirin dose reductions, and sometimes blood transfusions or use of erythropoiesis stimulating agents (off-label use). In addition, simeprevir has not been associated to date with severe cutaneous skin reactions such as SJS, DRESS and TEN; whereas telaprevir has a Boxed Warning for these events, and a few of these events have been described postmarketing for boceprevir. Additionally, simeprevir is associated with fewer clinically significant drug interactions than boceprevir or telaprevir, and there are no specific contraindications to coadministration of any drugs with simeprevir. Overall the risk-benefit assessment for simeprevir is favorable.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies:** Based on the safety profile of simeprevir, DAVP does not recommend a Risk Evaluation and Management Strategy (REMS) for simeprevir.

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

  Recommended Postmarketing Requirements include:

1. Pediatric studies required under PREA as discussed in section 9 of this review (Pediatrics).
2. Submit 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 will be considered a postmarketing requirement to establish safe 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 such as rash and photosensitivity.
3. Conduct a study to determine the phenotypic susceptibility of TMC435 against:
    - L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K.
    - R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon culture.

Recommended Postmarketing Commitments include:

4. Submit the requisite chemistry and manufacturing data (b) (4) should the results of the above trial deem a lower dose advisable in patients of East Asian ancestry.
5. 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 PegIFNα-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 PegIFNα-2a and ribavirin in the partial and null responder patient populations.

- **Other Postmarketing Commitments discussed:** Because simeprevir should be evaluated in combination with pegylated interferon and ribavirin in patients with chronic hepatitis C (rather than as monotherapy), and because pegylated interferons are contraindicated in patients with moderate and severe hepatic impairment, DAVP does not plan to establish a postmarketing commitment with regard to CHC patients with moderate to severe hepatic impairment, but the Division would like the Applicant to evaluate simeprevir pharmacokinetics and identify an appropriate dose for these patient populations during their ongoing development of simeprevir-containing interferon-free regimens.

- **Recommended Comments to Applicant:** DAVP has no additional comments for the Applicant.

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

/s/

MARY E SINGER
10/30/2013