FDA ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

OCTOBER 24, 2013

BACKGROUND PACKAGE FOR NDA 205123

SIMEPREVIR (TMC435)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION RESEARCH

OFFICE OF ANTIMICROBIAL PRODUCTS

DIVISION OF ANTIVIRAL PRODUCTS

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought simeprevir to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1.0 REGULATORY BACKGROUND AND INTRODUCTION

The purpose of this document is to provide the Antiviral Products Advisory Committee (AVAC) with a summary of FDA analyses of data submitted by Janssen Research and Development, LLC in support of simeprevir (TMC435) for the treatment of chronic hepatitis C genotype-1 (GT1) infection, in combination with peginterferon-alpha and ribavirin (PR), in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have failed previous interferon-based therapy. During the Advisory Committee meeting to be held on October 24, 2013, the Committee will be asked to consider the safety and efficacy data submitted to support the approval of simeprevir for this indication. The background materials provided represent the findings and opinions of the primary reviewers from different disciplines, based on their reviews of the Applicant's submissions. It must be emphasized that this document represents the review team's preliminary findings, and that no regulatory decision has been made on the status of the application. Indeed, the advice the AVAC provides will be critical in our regulatory decision making.

Simeprevir is a specific inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease. Hepatitis C virus (HCV) protease inhibitors block the NS3/4A protease-dependent cleavage of the HCV polyprotein, thereby inhibiting viral replication in infected host cells. If approved, simeprevir would represent the third HCV protease inhibitor approved in the US. The HCV protease inhibitors, boceprevir (Victrelis®) and telaprevir (Incivek™) were initially approved in 2011.

The current application requests approval for simeprevir in combination with PR for the treatment of chronic HCV in adult patients who are treatment-naïve or who have failed previous interferon-based therapy. The proposed indication is supported by the 60-week safety and efficacy data from the phase 3 trials TMC435-TiDP16-C208, TMC435-TiDP16-C216, and TMC435HPC3007 (hereafter referred to as C208, C216, and HPC3007, respectively in our document) and the completed phase 2b trials TMC435-TiDP16-C205 and TMC435-TiDP16-C206 (hereafter referred to as C205 and C206 in our document). A safety update report was also provided in support of the current application.

2.0 CLINICAL AND NON-CLINICAL DATA

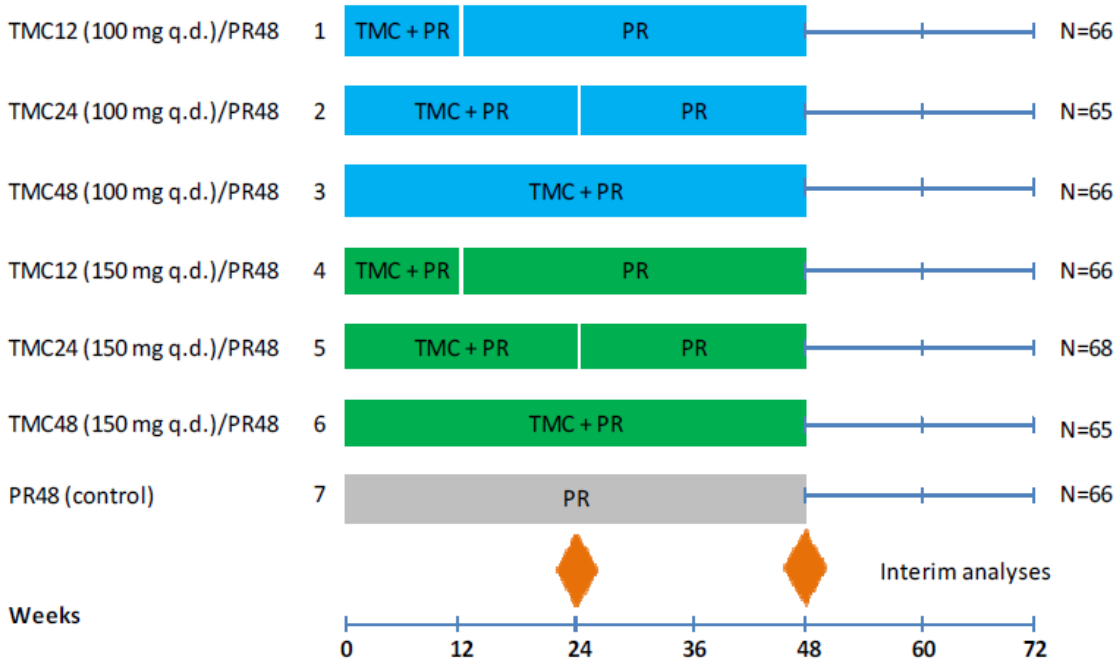
2.1 Study Designs:

The Phase 3 trials C208, C216, and HPC3007 were randomized, double-blind, placebo controlled trials in subjects chronically infected with HCV GT1. These trials assessed the combination of simeprevir (dosed at 150 mg daily for 12 weeks) plus PR for 12 weeks followed by PR alone for either 12 or 36 weeks based on an individual subject's virologic response to therapy (hereafter referred to as response guided therapy or RGT). The Control arm in each of these trials was placebo (for 12 weeks) in combination with PR for a fixed 48 week duration. The primary endpoint for these trials was sustained virologic response 12 weeks after the planned end of treatment (SVR12). SVR12 was defined as an undetectable HCV RNA at the end of treatment and HCV RNA < 25 IU/mL 12 weeks after the planned end of treatment. Stratification factors included HCV genotype/subtype and IL28B status. Trials C208 and C216 were identical in design and enrolled only treatment-naïve subjects. Trial HPC3007 enrolled subjects who had received at least 24 weeks of a pegylated interferon-based therapy and had relapsed within 1 year after the last medication intake (hereafter referred to as "relapsers" in our document).

Data from two Phase 2b trials, C205 and C206, were also provided in support of the proposed indication. Study C205 was a randomized, double-blind, 5-arm, placebo-controlled trial to investigate the safety and efficacy of simeprevir (dosed at 75 and 150 mg daily and given for either 12 or 24 weeks) in combination with PR (for 24 or 48 weeks based on RGT) in treatment-naïve CHC genotype-1 infected subjects. The Control arm was placebo (for 24 weeks) in combination with PR (for 48 weeks). The primary endpoint for this trial was SVR at week 72. This study served as an ancillary source of safety data for our review.

The C206 trial was a randomized, double-blind, 7-arm, placebo-controlled trial to compare the safety and efficacy of different regimens of simeprevir (100 or 150 mg daily) plus PR versus PR alone in CHC GT1- infected subjects who had failed to respond during or had relapsed following at least 1 course of PR therapy. Subjects in study C206 were randomized in a 1:1:1:1:1:1:1 fashion over 6 simeprevir dose groups and 1 placebo group (see Figure 1 for details). In treatment groups 1 and 4, subjects received 12 weeks of triple therapy with 100 or 150 mg simeprevir q.d. plus PR, followed by 36 weeks of treatment with PR and simeprevir-matched placebo (identified as the TMC12PR48 100 mg and TMC12PR48 150 mg groups in figure 1 respectively). In treatment groups 2 and 5, subjects received 24 weeks of triple therapy with 100 or 150 mg simeprevir q.d. plus PR (identified as TMC24PR48 100 mg and TMC24PR48 150 mg groups in figure 1 respectively). In treatment groups 3 and 6, subjects received 48 weeks of triple therapy with 100 or 150 mg simeprevir q.d. plus PR (identified as TMC48PR48 100 mg and TMC48PR48 150 mg groups in figure 1

respectively). In treatment group 7, subjects received PR and simeprevir-matched placebo for 48 weeks (Control group).



(P): PegIFN = peginterferon alfa-2a 180 µg/week
(R): Ribavirin 1000 or 1200 mg/day (b.i.d. regimen), depending on body weight (< 75 or ≥ 75 kg)
(TMC): TMC435

Figure 1: Study Schema for Study C206

Data from the C206 trial was provided to support an indication in patients characterized as partial or null responders to previous pegylated interferon therapy. This study served as an ancillary source of safety and efficacy data for our review.

2.2 Demographics:

Phase 2b Trials

In the C205 trial, a total of 386 subjects were enrolled. Eleven percent of subjects were drawn from the Asia-pacific region, 68% from Europe and 21% from North America. In Study C206, a total of 462 subjects were enrolled. Sixty-eight percent of subjects were drawn from Europe, 6% from Australia/New Zealand, and 26% from North America.

Phase 3 Trials

In the C208 trial, a total of 394 patients were randomized from 13 countries. Fourteen percent of subjects were drawn from the Asia-pacific region, 42% from Europe and 44% from North America (with 30% from the United States). In

C216, a total of 391 patients were randomized from 14 countries. Sixty-five percent of subjects were drawn from Europe, 15% from South America and 20% from North America (all from the United States). In HPC3007, a total of 393 patients were randomized from 14 countries. Eight percent of subjects were drawn from the Asia-pacific region, 70% from Europe and 22% from North America (with 18% from the United States).

Demographic characteristics were generally well balanced between the simeprevir arms and Control arms for each of the Phase 3 trials (C208, C216, and HPC3007). The majority of subjects in all arms of the phase 3 trials were Caucasian (range 86-96%) and non-Hispanic/Latino (range 77-95%). Trial C208 had the highest representation of North American subjects at 44%, while rates in C216 (20%) and HPC3007 (22%) were substantially lower. Cirrhotic subjects (Metavir Fibrosis score of F4) comprised from 7 to 15% of subjects across study arms. IL28b CC status ranged from 24-31% across study arms. Both HCV genotype/subtype 1a and 1b subjects were well represented in the Phase 3 trials (range for 1a across arms: 40-57%; range for 1b across arms: 43-59%).

2.3 Clinical Efficacy Results:

Primary Efficacy Endpoint:

As discussed above, the Applicant's proposed indication for the treatment of chronic HCV infection is based primarily on the SVR12 results from the Phase 3 pivotal trials (C208, C216, and HPC3007). As trials C208 and C216 were both performed in a HCV treatment-naïve population and employed a nearly identical study design, efficacy results were pooled for analysis. The pooled SVR12 results from the treatment-naïve studies demonstrated an SVR12 rate of 80% in the simeprevir group and 50% in the Control group. Trial HPC3007 was performed in patients who had relapsed after previous pegylated interferon/ribavirin treatment for chronic hepatitis C infection. In HPC3007, the SVR12 rate in the simeprevir arm was 79% compared to 36% in the Control arm. Please refer to the Table 1 below for details.

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

Studies (Number of Subjects)	C208 & C216 (N=785)		HPC3007 (N=393)	
Treatment Outcome	Pooled TMC435	Pooled PBO	TMC435	PBO
Overall SVR12[a]	419/521 (80%)	133/264 (50%)	206/260 (79%)	48/133 (36%)
On-treatment failure[b]	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.

Secondary Efficacy Endpoints:

SVR24 and SVR72 were included as secondary endpoints in each of the phase 3 pivotal trials. Both SVR24 and SVR72 results correlated well with the primary SVR12 endpoint. However, SVR24 and SVR72 data were incomplete at the time of the Week 60 data cutoff.

Subgroup Analyses:

Table 2 presents SVR12 data by subgroups from the pooled studies in treatment-naïve subjects (C208 and C216) as well as from the trial in subjects who relapsed after prior interferon-based therapy (HPC3007). Subjects in the simeprevir group with genotype 1a (without the Q80K baseline polymorphism) and genotype1b HCV demonstrated similar SVR12 rates.

A number of demographic and baseline characteristics have been shown to predict a lower SVR rate with interferon-based treatment. These include a high viral load at baseline, advanced disease on liver histology (bridging fibrosis and cirrhosis), older age, African American race, and absence of the IL28B CC genetic polymorphism. Each of these factors impacted efficacy results in both the simeprevir and Control groups in the pivotal phase 3 studies, as anticipated.

Most striking in the subgroup analysis was the substantial impact of the Q80K baseline HCV GT1a polymorphism on the efficacy of simeprevir. In subjects with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates was observed when comparing the simeprevir group to the Control group. In the pooled C208 and C216 trials, the SVR12 rate in GT1a subjects with the Q80K polymorphism was 58% in the simeprevir group and 55% in the Control Group. In HPC3007, the SVR12 rate in GT1a subjects with the Q80K polymorphism was 47% in the simeprevir group and 30% in the Control Group. A statistically significant difference was appreciated when comparing the SVR12 rates in simeprevir treated GT1a subjects without the Q80K polymorphism to placebo treated subjects without the Q80K polymorphism in both the pooled treatment-naïve studies and in the relapser study (SVR rates of 84% versus 43% and 78% versus 24%, respectively). In all other subgroup analyses presented in Table 2, SVR12 rates were significantly higher in the simeprevir group compared to the Control group.

Table 2: SVR12 Subgroup Analysis for Treatment-Naive Pooled Studies (C208 and C216) and Relapser Study (HPC3007)

	C208 & C216 (Pooled) (N=785)		HPC3007 (N=393)	
	TMC435 N=521	PBO N=264	TMC435 N=260	PBO N=133
	N (%) of subjects achieving SVR12*		N (%) of subjects achieving SVR12*	
GT1a				
without Q80K	138/165 (84%)	36/83 (43%)	62/79 (78%)	8/34 (24%)
with Q80K	49/84 (58%)	24/44 (55%)	14/30 (47%)	6/20 (30%)
GT1b				
	228/267 (85%)	70/133 (53%)	128/149 (86%)	34/79 (43%)
IL-28B Genotype				
CC	144/152 (95%)	64/79 (81%)	55/62 (89%)	17/34 (50%)
CT	228/292 (78%)	61/147 (41%)	131/167 (78%)	28/83 (34%)
TT	47/77 (61%)	8/38 (21%)	20/31 (65%)	3/16 (19%)
Race				
Black	29/43 (67%)	5/14 (36%)	5/7 (71%)	0/4 (0%)
Caucasian	378/464 (81%)	125/245 (51%)	192/243 (79%)	47/128 (37%)
Sex				
Male	227/288 (79%)	73/151 (48%)	139/179 (78%)	28/79 (35%)
Female	192/233 (82%)	60/113 (53%)	67/81 (83%)	20/54 (37%)
Age				
Age ≤ 45	206/237 (87%)	62/111(56%)	64/78 (82%)	20/35 (57%)
Age > 45	213/284 (75%)	71/153 (46%)	142/182 (78%)	28/98 (29%)
Metavir Fibrosis Score				
F0-F2	317/378 (84%)	107/192(56%)	137/167 (82%)	40/98 (41%)
F3-F4	89/130 (68%)	26/ 72 (36%)	61/83 (73%)	7/34 (21%)
Baseline HCV RNA (IU/mL)				
<=800,000	96/104 (92%)	54/70 (77%)	34/41 (83%)	12/23 (52%)
>800,000	323/417 (77%)	79/194 (41%)	172/219 (79%)	36/110 (33%)

* 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.

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 mechanistic support for the reduced clinical efficacy against Q80K polymorphic variants.

The Q80K polymorphism is a common polymorphism found in GT1a patients in the U.S. population. The Sponsor performed an analysis pooling all subjects from the C205, C206, C208, C216, and HPC3007 trials, and found that of the 298 GT1a subjects in the U.S with sequencing data, 48% had the Q80K polymorphism at baseline. None of the 113 GT1b subjects in the U.S. with sequencing data had the Q80K polymorphism at baseline.

Given the high frequency of the Q80K polymorphism in the U.S. population and its significant impact on rates of SVR12, DAVP is recommending that all GT1a patients be screened for the Q80K polymorphism. Alternative treatment options

should be considered for patients found to be infected with this polymorphic variant. Notably, no Q80K-related reductions in efficacy were observed during the pivotal trials of the currently approved NS3/4A protease inhibitors, telaprevir and boceprevir.

Efficacy in the Partial/Null Responder Population:

The Sponsor has requested an indication for treatment of chronic hepatitis C genotype 1 infection in partial and null responders based on data from the Phase 2b trial, C206. In C206, subjects categorized as partial or null responders received 12, 24, or 48 weeks of simeprevir in combination with PR which was administered for 48 weeks in all treatment arms (refer to Section 2.1 for details on the trial design).

The SVR24 results (the primary endpoint for this study) from the C206 trial by treatment arm and population (including the overall ITT population, prior relapsers, prior partial responders, and prior null responders) are presented in Table 3.

Table 3: SVR24 Rates in Study 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 (%) 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%)

* SVR24 is defined as the proportion of subjects with HCV RNA < 25 IU/mL detectable or undetectable 24 weeks after the actual end of treatment.

DAVP believes it is reasonable to combine the following two study arms for a pooled efficacy analysis: 1) simeprevir 100 mg for 12 weeks with PR for 48 weeks and 2) simeprevir 150 mg for 12 weeks with PR for 48 weeks. For both of these arms the duration of simeprevir was 12 weeks (the Sponsor's proposed duration for approval). Although the doses in the two arms differ (i.e. 100 mg versus 150 mg), there are no data or scientific reasons to anticipate that the 100 mg dose of simeprevir would prove more effective than the 150 mg dose. Therefore, this could be considered a conservative pooling. The SVR24 data from this pooled analysis are presented in Table 4 below.

Table 4: 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 (%) 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%)

* SVR24 is defined as the proportion of subjects with HCV RNA < 25 IU/mL detectable or undetectable 24 weeks after the actual end of treatment.

In partial responders, the difference in SVR24 rates between the pooled simeprevir groups and placebo group reached statistical significance (P-value < 0.0001). 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). The lack of statistical significance in the null responder population may relate 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 the partial and null responder populations may be drawn from an analysis of the more difficult to treat sub-populations found within the Phase 3 treatment-naïve trials, C208 and C216. Specifically, subjects with baseline factors known to impact the effectiveness of HCV treatment, including 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), achieved significantly higher SVR rates with simeprevir/PR versus placebo/PR (refer to Table 5 for details).

Table 5. 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(41%)	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%)

Based on the above analyses, as well as our experience with the approved NS3/4A protease inhibitors, DAVP believes that it is reasonable to extend the indication of simeprevir for the treatment of partial and null responders. Patients in these populations would receive 12 weeks of simeprevir in combination with PR, followed by an additional 36 weeks of PR. DAVP believes screening for the presence of the Q80K polymorphism (as discussed in detail above) will be especially important in these populations in which SVR is already anticipated to be more difficult to achieve. DAVP intends to designate the submission of the final data from the ongoing Phase 3 trial of simeprevir in combination with PR in partial and null responders (HPC3001) a post-marketing commitment.

2.4 Clinical Pharmacology:

Simeprevir is orally bioavailable. It is highly plasma protein-bound (>99.9%) and distributes to the liver. The primary route of simeprevir elimination is hepatobiliary excretion; urinary excretion is negligible. Simeprevir exhibits a greater-than-dose-proportional increase in exposures. 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.

Because it is a CYP3A4 substrate, simeprevir exposures increase in the presence of moderate or strong CYP3A inhibitors (as observed in clinical drug-drug interaction studies with erythromycin and ritonavir) and decrease in the presence of moderate or strong CYP3A inducers (as observed in clinical drug-

drug interaction studies with efavirenz and rifampin); therefore, coadministration of simeprevir with moderate or strong CYP3A inhibitors or inducers is not recommended. Simeprevir inhibits intestinal (but not hepatic) CYP3A, as demonstrated in a drug-drug interaction study with midazolam administered IV or PO. Simeprevir also inhibits OATP1B1/3: exposures of the OATP1B1/3 substrates rosuvastatin and atorvastatin are higher upon coadministration with simeprevir, indicating that a maximum recommended dose for rosuvastatin and atorvastatin is advisable.

Following administration of simeprevir 150 mg QD, mean simeprevir exposures (AUC_{24}) are 2 to 3-fold higher in HCV-infected patients compared to healthy volunteers. This observation appears to be a function of the selected dose (150 mg, at which CYP3A is saturated) as well as lower functional hepatic CYP3A content in patients with chronic HCV infection[1,2,3,4,5], which results in slower simeprevir clearance in patients.

HCV-uninfected subjects with moderate or severe hepatic dysfunction (Child-Pugh B or C, respectively) had mean simeprevir AUC_{24} values that were approximately 2.4- and 5.2-fold higher, respectively, compared to healthy controls. In addition, HCV-infected patients of East Asian ancestry had mean AUC_{24} values that were approximately 3.4-fold higher than the pooled Phase 3 population, which was approximately 91% Caucasian. The higher exposures observed in Chinese and Japanese subjects in Phase 1 studies compared to Caucasian subjects prompted evaluation of lower simeprevir daily doses in the ongoing Phase 3 development programs in Japan, China, and Korea. Similar to the elevated exposures observed in subjects with HCV infection, the increased exposures observed in subjects with moderate hepatic impairment and subjects with East Asian ancestry are likely a consequence of the smaller liver volume and lower amount of functional CYP3A and/or OATP1B1/3 in these subpopulations[6,7] compared to HCV-uninfected and Caucasian subjects, respectively.

Administration of simeprevir 150 mg QD to patients with moderate or severe hepatic impairment or patients with East Asian ancestry may not be advisable for the following reasons:

1. The safety profile of simeprevir exposures anticipated in patients with East Asian ancestry or patients with moderate or severe hepatic impairment following administration of simeprevir 150 mg QD (i.e. average AUC_{24}

[1] Nakai et al. Drug Metab Dispos 2008
[2] Ohnishi et al. J Clin Pharmacol 2005
[3] Lin et al. Hepatogastroenterology 1998
[4] Johnson et al. Clin Pharmacokinet 2010
[5] Barreiro et al. Eur J Clin Pharmacol 2005
[6] Albarmawi A et al. Br J Clin Pharmacol 2013
[7] Tateishi T et al. Clin Pharmacol Ther 2001

values 2 to 5-fold above the Phase 3 mean) has not been well-characterized in the Phase 3 trials;
2. A positive correlation exists between simeprevir exposures and adverse events, including rash and photosensitivity, as indicated by the exposure-response relationships for safety;
3. No additional therapeutic benefit is gained from higher exposures, as indicated in the Phase 3 studies by the flat exposure-response relationship for efficacy at a simeprevir dose of 150 mg QD;
4. With respect to patients with East Asian ancestry, lower doses of simeprevir (in addition to 150 mg, in some countries) are currently being evaluated in Phase 3 trials in East Asian countries; safety data from these ongoing trials have not been evaluated by DAVP.

Based on the above reasons, DAVP recommends that the dose of simeprevir be reduced for patients with moderate or severe hepatic impairment or patients with East Asian ancestry. However, as no reduced dose strengths are currently available, definitive dose recommendations and labeling for these populations will likely need to be accomplished as postmarketing requirements or commitments.

2.5 Non-Clinical Safety:

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).

Simeprevir will be categorized as a Pregnancy Category C in labeling based on reproductive toxicity effects in the pregnant rat and mouse (early mortality and post-implantation loss), the fetus (skeletal variations, adverse body weight decrease) as well as the developing rat offspring (adverse body weight decrease, small size, motor activity decreases). The reproductive effects were seen in the rat at approximately 0.2 to 1 times the mean clinical AUC and in the mouse at 4 times the mean clinical AUC. The potential reproductive toxicity risks will be mitigated by appropriate labeling. Simeprevir is indicated for use in combination with pegylated interferon alfa and ribavirin. Ribavirin has a boxed warning and is contraindicated for use in pregnancy due to potential teratogenic and embryocidal effects. Therefore, the potential risk of simeprevir exposure in pregnant women is low because administration would be avoided during pregnancy due to the indicated use with ribavirin.

2.6 Clinical Safety Results:

Safety Review Strategy:

The primary safety assessment focused on the safety data through Week 60 from the three pivotal Phase 3 trials, C208, C216, and HPC3007. Apart from differences in the patient populations (treatment-naïve versus relapsers), the three trials were virtually identical with respect to their study design (including the primary objective and endpoint, stratification factors, inclusion/exclusion criteria, and study schema). As such, these Phase 3 trials were pooled to facilitate the primary safety assessment. The primary safety pool included 781 subjects in the simeprevir group and 397 subjects in the placebo group. The safety assessment focused largely on the first 12 weeks of the study period (i.e. the period during which simeprevir was administered) to allow for a direct comparison of the safety profile of simeprevir (administered with PR) to that of placebo (administered with PR). In addition to performing the primary safety assessment, selected safety data from the Phase 2b trials (C205 and C206) were reviewed to augment the safety analysis.

Deaths:

Four deaths were reported in subjects receiving simeprevir in the pooled Phase 2b and Phase 3 analysis (including the C205, C206, C208, C216, and HPC3007 trials). The reported causes of death included the following: 1) bacterial meningitis and brain hemorrhage; 2) colon cancer; 3) presumed cardiopulmonary event; 4) bilateral pneumonia and septic shock. No deaths were reported in the Control arms. In each of these cases, the subject's death was judged unrelated to simeprevir by the investigator. The Division concurs with the judgment of the investigators in these cases.

Serious Adverse Events (SAEs):

In the pooled Phase 3 analysis, 2% of subjects in the simeprevir group had SAEs compared to 3% of subjects in the Control group during the first 12 weeks of the trial. No SAE was reported in any MedDRA System Organ Class (SOC) with greater than 1% frequency. Three subjects (0.4%) in the simeprevir group experienced SAEs which were deemed related (i.e. possibly, probably, or definitely related) to simeprevir by study investigator. These included the MedDRA preferred terms (PTs) 'major depression' in one subject and 'photosensitivity reaction' in two subjects. The SAEs related to photosensitivity are discussed in the section below entitled "Specific Safety Assessments."

Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug:

In the pooled phase 3 analysis, 14 subjects (2%) in the simeprevir group and 5 subjects (1%) in the Control group experienced at least 1 AE leading to discontinuation of simeprevir. Adverse events under the System Organ Class of 'Skin and Subcutaneous Tissue Disorders' were responsible for the greatest frequency of AEs leading to discontinuation of simeprevir, accounting for 1% of subjects in the simeprevir group.

Common Adverse Events:

Table 6 presents the AEs by PT and grouped term that occurred ≥3% more frequently in the simeprevir group compared to the Control group during the first 12 weeks of treatment.

Table 6: AEs by PT and Grouped Term that Occurred ≥3% More Frequently in the TMC435 Group Compared to the Control Group during the First 12 Weeks of Treatment.

	TMC435	Control
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Preferred Term or Grouped Term, n (%)		
Rash[1]	218 (28%)	79 (20%)
Influenza like illness	203 (26%)	84 (21%)
Pruritis[2]	168 (22%)	58 (15%)
Nausea	173 (22%)	70 (18%)
Myalgia	126 (16%)	53 (13%)
Dyspnea[3]	92 (12%)	30 (8%)
Increased Bilirubin[4]	61 (8%)	11 (3%)
Photosensitivity[5]	38 (5%)	3 (1%)

1. Grouped term 'Rash' includes the following preferred terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, urticaria, rash generalized, drug eruption, dermatitis allergic, dermatosis, vasculitic rash, toxic skin eruption, exfoliative rash, generalised erythema, dermatitis exfoliative, cutaneous vasculitis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, photodermatosis, and sunburn
2. Grouped term 'Pruritis' includes the following preferred terms: pruritis and pruritis generalized
3. Grouped term 'Dyspnea' includes the following preferred terms: dyspnea and dyspnea exertional
4. Grouped term 'Increased Bilirubin' includes the following preferred terms: hyperbilirubinemia, blood bilirubin increased, jaundice, blood bilirubin unconjugated increased, and bilirubin conjugated increased
5. Grouped term 'Photosensitivity' includes the following preferred terms: photodermatosis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and sunburn

The following section will highlight the AEs of greatest interest that appear on Table 6, including dyspnea, increased bilirubin, and skin and soft tissue AEs (rash, photosensitivity, and pruritis). For each of these AEs of interest, grouped variables were created to facilitate analysis. These grouped terms are defined in the footnote section of Table 6. Grouped variables will be designated by single quotation marks in the discussion that follows.

Specific Safety Assessments:

Cardiopulmonary Safety Assessment:

The most notable finding with respect to the cardiopulmonary assessment was an increased frequency of ‘dyspnea’ in the simeprevir group compared to the Control group. In the pooled Phase 3 studies, ‘dyspnea’ occurred in 12% of subjects in the simeprevir group and 8% of subjects in the Control group during the first 12 weeks of treatment. ‘Dyspnea’ tended to occur early in the simeprevir treatment course, with 61% of cases (57/92 subjects) occurring during the first 4 weeks of treatment. All of these AEs were of mild or moderate severity. There were no grade 3 or 4 AEs, SAEs, or discontinuations due to ‘dyspnea’ during the first 12 weeks of treatment in the simeprevir group. Of the 92 subjects with ‘dyspnea’ reported during the first 12 weeks of the study, 82 subjects (89%) were in the outcome category of “Recovered/Resolved” with respect to this AE and 9 subjects (10%) were in the AE outcome category of "Not Recovered/Not Resolved" based on the available data.

An analysis to ascertain whether the reported ‘dyspnea’ events were associated with the presence of anemia was performed and no association was apparent. The reason for the finding of increased rates of ‘dyspnea’ in the simeprevir group remains unclear.

Hepatobiliary Safety Assessment:

From early in clinical development, hyperbilirubinemia was known to be associated with use of simeprevir and was considered an adverse event of special interest. Both the Sponsor and the Division believe that the higher incidence of bilirubin elevations in simeprevir-treated subjects is primarily attributable to a decrease in bilirubin elimination related to inhibition of the hepatic transporters OATP1B1 and MRP2. The primary focus of our hepatobiliary assessment was to define the time course and magnitude of hyperbilirubinemia and assess for evidence of any hepatic toxicity associated with the anticipated elevation in bilirubin.

The following table includes hepatobiliary AEs (by PT) which occurred in ≥ 2 subjects in the simeprevir group during the first 12 weeks of treatment. Apart from the grouped AE ‘increased bilirubin’ occurring more frequently in the simeprevir group, no other hepatobiliary safety signals were appreciated.

Table 7: Hepatobiliary AEs (by PT) which occurred in ≥ 2 Subjects in the TMC435 Group during the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Increased Bilirubin (Grouped Term)*	61 (8%)	11 (3%)
Alanine aminotransferase increased	8 (1%)	11 (3%)
Amylase increased	7 (1%)	1 (<1%)
Aspartate aminotransferase increased	7 (1%)	8 (2%)
Gamma-glutamyltransferase increased	4 (1%)	6 (2%)
Lipase increased	3 (<1%)	1 (<1%)
Transaminases increased	3 (<1%)	2 (1%)
Hepatic pain	2 (<1%)	1 (<1%)

* Increased Bilirubin Pooled includes the following MedDRA PTs: hyperbilirubinemia, blood bilirubin increased, jaundice, blood bilirubin unconjugated increased, and bilirubin conjugated increased

Grade 3 and 4 AEs under the pooled term 'increased bilirubin' occurred in 2% and < 1% of subjects in the simeprevir group and 1% and 0% of subjects in the Control group, respectively. There were no SAEs and only one discontinuation of simeprevir due to 'increased bilirubin.' That discontinuation involved a 35 year old white male with cirrhosis and both elevated transaminases and hyperbilirubinemia at baseline who developed a Grade 4 increase in bilirubin on study day 15. Notably, this subject experienced normalization of his transaminase values concurrent with his increase in bilirubin values.

Table 8 summarizes the hepatic laboratory abnormalities by severity grade. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test.

Table 8: Hepatic Laboratory Abnormalities by Severity Grade during the First 12 Weeks of Treatment

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Maximum toxicity grade, n(%)		
Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	65 (8%)	49 (12%)
Grade 2 (>2.5 to 5 x ULN)	28 (4%)	13 (3%)
Grade 3 (>5 to 10 x ULN)	8 (1%)	5 (1%)
Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	47 (6%)	30 (8%)
Grade 2 (>2.5 to 5 x ULN)	23 (3%)	11 (3%)
Grade 3 (>5 to 10 x ULN)	10 (1%)	8 (2%)
Bilirubin (umol/L)		
Grade 1 (>1 to 1.5 x ULN)	208 (27%)	61 (15%)
Grade 2 (>1.5 to 2.5 x ULN)	143 (18%)	36 (9%)
Grade 3 (>2.5 to 5 x ULN)	32 (4%)	6 (2%)
Grade 4 (>5 x ULN)	3 (<1%)	0 (0%)
Alkaline Phosphatase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	26 (3%)	5 (1%)
Grade 2 (>2.5 to 5 x ULN)	1 (<1%)	0 (0%)
Gamma Glutamyl Transferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	36 (5%)	35 (9%)
Grade 2 (>2.5 to 5 x ULN)	16 (2%)	17 (4%)
Grade 3 (>5 to 10 x ULN)	2 (0%)	5 (1%)
Grade 4 (>10 x ULN)	1 (0%)	2 (1%)

There was no evidence of a concerning trend with respect to graded elevations in AST, ALT, or GGT in the simeprevir group compared to the Control group. As normalization of AST and ALT levels are anticipated early after initiation of HCV treatment, an additional analysis was performed to assess the highest toxicity grade reported following achievement of nadir AST and ALT levels. Again, no concerning trends were noted in this analysis (refer to Table 9 below).

Table 9: Highest Toxicity Grade Reported following Achievement of Nadir AST and ALT Levels

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Maximum toxicity grade, n(%)		
Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	42 (5%)	27 (7%)
Grade 2 (>2.5 to 5 x ULN)	22 (3%)	9 (2%)
Grade 3 (>5 to 10 x ULN)	8 (1%)	3 (1%)
Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	29 (4%)	18 (5%)
Grade 2 (>2.5 to 5 x ULN)	14 (2%)	9 (2%)
Grade 3 (>5 to 10 x ULN)	6 (1%)	5 (1%)

As previously noted, a marked increase in frequency of graded bilirubin elevations in the simeprevir group (49%) compared to the Control group (26%) was present. This difference was primarily driven by grade 1 and 2 laboratory abnormalities. Elevations in bilirubin occurred early after treatment initiation, peaking by Study Week 2. By four weeks following completion of simeprevir treatment (i.e. Week 16), levels were shown to return to near baseline values (see Figure 2 below)

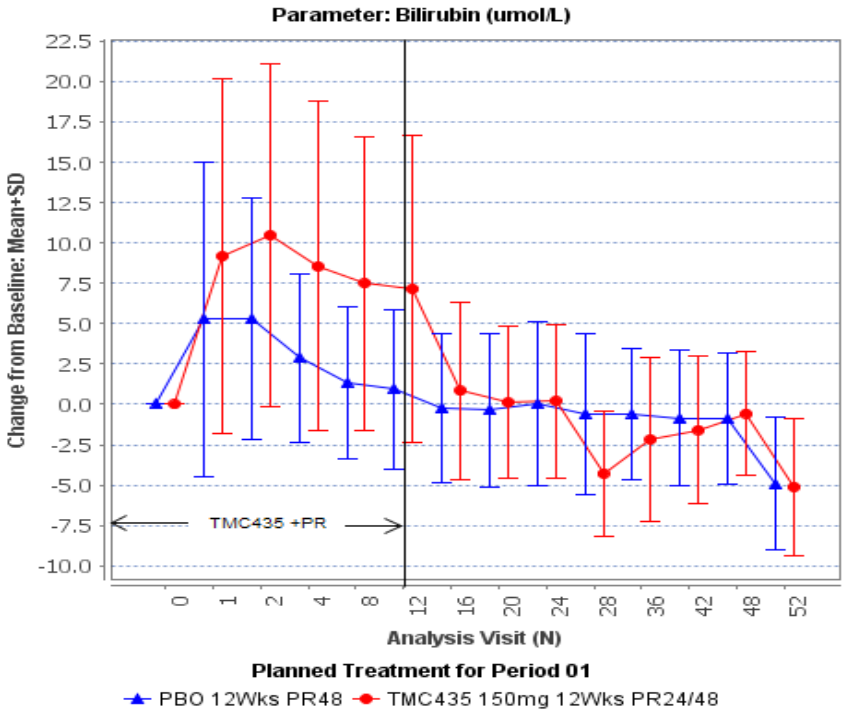


Figure 2: Serum Bilirubin--Change from Baseline over Time (in Weeks)

An increase in grade 1 and 2 elevations in alkaline phosphatase in the simeprevir group (4%) compared to the Control group (1%) was also noted. Elevations in alkaline phosphatase increased steadily upon treatment initiation, peaking at Week 8 and rapidly declining to baseline levels upon completion of simeprevir treatment. Of note, there was no evidence of an increased frequency of biliary AEs (e.g. bile duct obstruction or cholestatic hepatotoxicity) in the simeprevir group compared to the Control group.

Hepatobiliary Safety Summary:

As anticipated, a greater frequency of AEs associated with increased bilirubin (including grade 3 and 4 AEs) were reported in the simeprevir group compared to the Control group. However, little correlation was noted between the development of hyperbilirubinemia and clinical events necessitating discontinuation of study drug or serious adverse events related to study drug use. This lends credence to the Sponsor's view that the increased bilirubin associated with simeprevir use may be largely due to the inhibition of hepatic transporters.

Skin and Soft Tissue Safety Assessment:

In the MedDRA SOC category of skin and subcutaneous tissue disorders, there was a higher frequency of AEs in the simeprevir group (49%) compared to the Control group (38%) during the first 12 weeks of treatment in the pooled Phase 3 studies. Safety analysis led to the identification of three general categories of interest: 'pruritis', 'rash', and 'photosensitivity'. It should be noted, however, that a significant degree of overlap in AE occurrence was noted with respect to these three general categories. In particular, the use of narrow pooling for photosensitivity events may underestimate the actual rate of occurrence of photosensitivity events as some of these events (consistent with photosensitivity) were reported under the more general pooled term of rash.

Pruritis:

'Pruritis' occurred in 22% of subjects in the simeprevir group and 15% of subjects in the Control group during the first 12 weeks of treatment. However, the vast majority of 'pruritis' AEs were of mild or moderate severity, rarely led to discontinuation of simeprevir, and were not the cause of any SAEs over the first 12 weeks of treatment. Additional analyses revealed an association between 'pruritis' and 'rash', but no association was apparent between 'pruritis' and elevated bilirubin levels.

Photosensitivity:

In vitro studies revealed that simeprevir was phototoxic after UVA exposure and photosensitivity reactions were reported with initial clinical experience.

Therefore, as a precaution, subjects were asked to adhere to sun-protection measures during simeprevir administration in the Phase 2b (C205 & C206) and Phase 3 trials (C208, C216, and HPC3007).

Of note, a dedicated photosensitivity study (C125) was performed in healthy subjects. This study revealed evidence of immediate photosensitivity in 33% of subjects in the simeprevir group and in no subjects in the ciprofloxacin (positive control) or placebo groups. There was a positive association in this study between higher exposures to simeprevir and the development of immediate photosensitivity reactions. It should be noted that Study C125 was performed in healthy subjects and that the anticipated AUC for simeprevir is 2 to 3-fold lower in a healthy population than a population with chronic hepatitis C infection.

With respect to the Phase 3 trials, during the first 12 weeks of treatment, 'photosensitivity' was reported in 38 subjects (5%) in the simeprevir group compared to 3 subjects (1%) in the Control group. One 'photosensitivity' event in the simeprevir group met grade 3 criteria; there were no grade 4 AEs reported in either the simeprevir or Control group. Two 'photosensitivity'-related SAEs occurred in the simeprevir group during the first 12 weeks of treatment; while no SAEs occurred in the Control group. Both of these events led to hospitalization and one of these events involved the use of systemic steroids for treatment.

Rash:

'Rash' (excluding the photosensitivity events described above) occurred in 25% of subjects in the simeprevir group and 19% of subjects in the Control group during the first 12 weeks of treatment. 'Rash' occurred at a disproportionately higher rate early after initiation of simeprevir. In the Phase 3 trials, 56% of the 'rash' cases in the simeprevir group occurred during the first 4 weeks of treatment with simeprevir, with 42% of cases occurring in the first 2 weeks.

Of the seven AEs in the SOC category of 'Skin and Subcutaneous Tissue Disorders' leading to discontinuation of simeprevir, 6 were subsumed under the category of 'rash'. The following table summarizes both SAEs and AEs leading to discontinuation of study drug (simeprevir or placebo) under the MedDRA SOC category of 'Skin and Subcutaneous Tissue Disorders' during the first 12 weeks of treatment. An increase in both frequency (1% versus <1% respectively) and severity of 'rash'-related AEs leading to discontinuation of simeprevir compared to the Control group was noted. Several of the subjects who discontinued study drug in the simeprevir group developed mucosal findings in close temporal proximity to the onset of their rash events (refer to table 10). In several of these cases the possibility of erythema multiforme major could not be excluded. There were no reported cases of Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS) in the Phase 3 trials. There were no life-threatening AEs or deaths related to 'rash' (including photosensitivity events) in the Phase 3 trials.

Table 10: Summary of Subjects in the Pooled Phase 3 Trials with AEs Leading to Discontinuation of TMC435 or SAEs under the MedDRA SOC 'Skin and Subcutaneous Tissue Disorders' During the First 12 Weeks of Treatment

Subject Number	Age Race/ Sex	MedDRA PT	SD (Onset/ Resolution)	Worst Toxicity Grade	Associated Laboratory Findings*/ SD	Associated Mucosal Findings	Systemic Steroids Admin.
TMC435 TREATMENT GROUP							
1	48 W/F	Rash	31/49	3	No	No	No
2	56 W/M	Rash	54/194	2	Grade 1 ALT/ SD86	No	No
3	59 W/F	Rash	61/129	3	No	No	No
4	59 W/M	Rash	67/~240	2	↑Eos (0.73 x 10^9)/ SD86	Apthous Stomatitis/ SD75	Yes
5	46 W/M	Psoriasis	14/ Ongoing	3	No	No	No
6	49 W/F	Rash	52/93	2	No	Mouth Ulceration/ SD57	No
7	40 W/M	Maculo-Papular Rash	32/61	3	No	Conjunctivitis/ SD23 Apthous Stomatitis/ SD42	No
8	35 W/M	Photo-sensitivity†	69/86	2	No	No	Yes
9	44 W/M	Photo-sensitivity†	41/114	3	No	No	No
CONTROL GROUP							
10	38 W/F	Maculo-Papular Rash	44/71	2	↑Eos (0.71 x 10^9)/ SD62	No	No

SD= Study Day
*Specifically blood eosinophilia and/or presence of transaminitis
† These AEs were SAEs but did not lead to discontinuation of TMC435; for Subject 9, the failure to discontinue simeprevir + PR was deemed a protocol violation.

Additional Skin and Soft Tissue Safety Analyses Using Pooled Phase 2b Data:

Additional analyses were also conducted by pooling data from Phase 2b trials (C205 and C206) to better define the skin and soft tissue safety profile of simeprevir. These studies included simeprevir doses ranging from 75 mg to 150 mg and simeprevir durations ranging from 12 weeks to 48 weeks.

The grouped variable 'pruritis' occurred in 33 subjects (23%) in the Control arm and in 204 subjects (29%) in the pooled simeprevir arms in the pooled C205 and C206 trials during the first 12 weeks of treatment. The pooled variable 'photosensitivity' occurred in 1 subject (1%) in the Control arm and in 11 subjects

(2%) in the pooled simeprevir arms in pooled C205 and C206 trials during the first 12 weeks. The grouped variable 'rash' (excluding the pooled photosensitivity events) occurred in 27 subjects (19%) in the pooled Control group and in 165 subjects (23%) in the simeprevir group during the first 12 weeks of treatment.

A total of 8 subjects (1%) in the simeprevir group discontinued study drug versus 1 subject (1%) in the Control group during the period of simeprevir/placebo +PR administration. Two of the discontinuations in the simeprevir group were classified as SAEs. These were the only SAEs in the simeprevir group reported under the SOC 'skin and subcutaneous tissue disorders' during the period of simeprevir administration; no SAEs were reported in the placebo group. Table 11 provides a summary of the characteristics of the subjects who discontinued simeprevir due to an AE under the category of 'skin and subcutaneous tissue disorders' during the period of simeprevir administration in C205 and C206. Consistent with the Phase 3 trials, an increase in severity of 'rash'-related AEs leading to discontinuation of simeprevir compared to the Control group was noted. There were no reported cases of SJS, TEN, or DRESS in the Phase 2b trials.

Table 11: Summary of Subjects in the Pooled Phase 2b Trials with AEs Leading to Discontinuation of Study Drug Under the MedDRA SOC 'Skin and Subcutaneous Tissue Disorders' During the TMC435/Placebo + PR Period of Administration

Subject Number	Age Race/ Sex	MedDRA PT	SD (Onset/ Resolution)	Worst Toxicity Grade	Associated Laboratory Findings*/ SD	Associated Mucosal Findings	Systemic Steroids Admin.
TMC435 TREATMENT GROUP							
11	56 W/F	Dermatitis Exfoliative	68/ Ongoing	3	↑Eos 13%/ SD84	No	Yes
12	44 W/F	Rash	43/141	2	↑Eos 8%/ SD50	No	No
13	33 W/F	Rash	13/ Ongoing	2	No	No	No
14	46 W/F	Cutaneous Vasculitis†	63/ Ongoing	2	No	No	Yes
15	55 W/F	Rash	22/ Ongoing	3	No	No	No
16	44 W/F	Rash	173/254	2	No	No	No
17	27 W/M	Drug Eruption†	29/86	3	↑Eos 13% (0.7×10^9)/ SD56	No	No
18	65 W/M	Rash	7/168	1	No	Oral herpes/SD7	No
CONTROL GROUP							
19	21 WM	Rash	81/169	2	↑Eos 14%/ SD140	No	No

SD= Study Day
† These AEs were SAEs and also led to discontinuation of simeprevir

Skin and Soft Tissue Safety Summary:

A safety signal was noted with respect to rash and photosensitivity events in the Phase 2b (C205 & C206) and pivotal Phase 3 trials (C208, C216, and HPC3007). This included an increased frequency and severity of rash and photosensitivity adverse events and serious adverse events, as well as an increase in rates of discontinuation of simeprevir due to rash and photosensitivity- related adverse events. A significant degree of overlap was noted between adverse events strictly categorized as rash, and those AEs strictly categorized as photosensitivity. The use of narrow pooling for photosensitivity events may lead to an underestimation of the actual rate of occurrence of photosensitivity events as some of these events which were consistent with photosensitivity were reported under the more general pooled term of rash. DAVP intends to include a warning related to photosensitivity in the prescribing information including a recommendation for sun protection measures for all patients receiving simeprevir consistent with the measures which were in place in the Phase 2b and Phase 3 trials.

2.7 General Summary:

In the pivotal Phase 3 trials, C208, C216, and HPC3007, simeprevir in combination with PR was demonstrated to be superior to placebo (in combination with PR) in achieving a sustained virologic response in both HCV treatment-naïve subjects and subjects who relapsed after prior pegylated interferon-ribavirin therapy. In the subgroup of subjects with the Q80K baseline polymorphism, a substantial impact on the efficacy of simeprevir was observed. Given the high frequency of the Q80K polymorphism in the U.S. population and its significant impact on rates of SVR12, DAVP is recommending that all GT1a patients undergo screening for this baseline polymorphism prior to treatment with simeprevir and that alternative treatment options be considered for patients found to be infected with this polymorphic variant. DAVP believes that it is reasonable (in the setting of a Q80K screening recommendation) to extend the indication of simeprevir for the treatment of partial and null responders based on the available data, including the results of trial C206, a Phase 2b trial which included these patient populations.

Subjects with moderate or severe hepatic impairment and subjects of East Asian ancestry had substantial increases in mean simeprevir exposures compared to healthy subjects and compared to the pooled Phase 3 population, respectively. Based on 1) the paucity of safety data in a subjects having mean simeprevir exposures 2- to 5-fold higher than the mean observed in Phase 3 trials; and 2) the positive relationship between simeprevir exposures and the incidence of adverse events including rash and photosensitivity, DAVP recommends a reduced simeprevir dose for patients with moderate or severe hepatic impairment or patients of East Asian ancestry. However, as no reduced dose strengths are currently available, definitive dose recommendations and labeling for these

populations will likely need to be accomplished as postmarketing requirements or commitments.

The nonclinical safety package for simeprevir was deemed adequate with the liver and GI system identified as the major target organs across animal species. Simeprevir will be categorized as a Pregnancy Category C in labeling based on reproductive toxicities in the rat and mouse that indicate potential adverse effects in the pregnant animal, the fetus, and the developing offspring.

The safety profile of simeprevir was generally acceptable. An increased frequency and severity of hyperbilirubinemia was associated with simeprevir use, however no association between the bilirubin elevation and clinically relevant hepatototoxicty was appreciated. The major safety signal identified in the review involved rash and/or photosensitivity events. This included an increased frequency and severity of rash/photosensitivity adverse events and serious adverse events, as well as an increase in rates of discontinuation of simeprevir due to rash/photosensitivity related adverse events. DAVP intends to include a warning related to photosensitivity in the prescribing information including a recommendation for sun protection measures for all patients receiving simeprevir.

3.0 PRELIMINARY TOPICS FOR THE ADVISORY COMMITTEE

The Division is convening this meeting to solicit the committee's comments on the following topics. Please note, however, that these are preliminary topics and are still subject to change.

1. Please comment on the safety profile of simeprevir focusing on rash and photosensitivity events reported during the clinical trials.

    a. Does the committee agree that a discussion of the photosensitivity events should be included in the Warnings and Precautions section of the simeprevir prescribing information?

    b. Based on the available data, does the committee agree that sun-protection measures should be recommended for all patients receiving simeprevir?

    c. Does the committee believe it appropriate and/or necessary to include a discussion of rash events (separate from that for photosensitivity) in the Warnings and Precautions section of the prescribing information?

2. 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 infection?

a. DAVP intends to recommend screening all subjects with GT1a infection for the Q80K 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?

3. At the proposed dose of simeprevir 150 mg once daily, mean exposures were approximately 3.4-fold higher in individuals of East Asian ancestry compared to the pooled Phase 3 population. Similarly, simeprevir 150 mg once daily provided 2.4- and 5.2-fold higher exposures in subjects with moderate or severe hepatic impairment, respectively, compared to healthy controls. Considering the lack of safety data in patients with mean exposures that are 2- to 5-fold higher compared to those observed in the Phase 3 population, as well as the positive relationship between simeprevir exposures and the incidence of adverse events (including rash, photosensitivity, pruritus, dyspnea, and increased bilirubin), should the dose strength of simeprevir be reduced in the following patient subgroups:

   a. Patients of East Asian ancestry
   b. Patients with moderate or severe hepatic insufficiency

4. Are there post marketing studies that should be conducted to further define risks or to optimize use of simeprevir?