Antiviral Drugs Advisory Committee Meeting

Briefing Document

Simeprevir (TMC435)
Treatment of Patients with Chronic Hepatitis C

NDA 205123

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

abbreviation	description of abbreviated term
ABC	adenosine triphosphate-binding cassette
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BOC	boceprevir
C_{0h}	predose plasma concentration
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CV	coefficient of variation
CYP	cytochrome P450
DMC	Data Monitoring Committee
$EC_{50/90}$	50%/90% effective concentration
ECG	electrocardiogram
EOT	end of treatment
FC	fold change
FDA	Food and Drug Administration
FSS	Fatigue Severity Score
FU	follow-up
GT	genotype
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV(-1)	human immunodeficiency virus (type 1)
HMG-CoA	3-hydroxy-3-methyl-glutaryl coenzyme A
ICH	International Conference on Harmonisation
IL28B	interleukin-28B
iv	intravenous
K_i	kinetic inhibition constant
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	multidrug resistance-associated protein 2
NDA	New Drug Application
NI	nucleoside inhibitor
NNI	non-nucleoside inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside (nucleotide) reverse transcriptase inhibitor
OATP	organic anion transporting polypeptide
PBO	placebo
PBPK	physiologically-based pharmacokinetic
PegIFN	pegylated interferon
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	PegIFN and RBV
PRO	patient-reported outcome

qd	quaque die; once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBV	ribavirin
RNA	ribonucleic acid
RVR	rapid virologic response
SAE	serious adverse event
SLC	solute carrier family
SLCO	solute carrier organic anion transporter family
SMV	simeprevir
SVR	sustained virologic response
t_{max}	time to reach maximum plasma concentration
TVR	telaprevir
ULN	upper limit of normal
US	United States (of America)
USPI	United States Product Information
USPSTF	US Preventive Services Task Force
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment:Hepatitis C questionnaire

Definition of Terms

The following definitions are used in the **Phase 3 studies** that were conducted and/or are ongoing. In general, similar definitions were used in the Phase 2 studies.

End of treatment (EOT)	**Actual** end of treatment, unless otherwise specified
HCV infection	HCV mono-infection, unless otherwise specified
Treatment-naïve patients	Patients are considered treatment-naïve if they have never received any approved or investigational treatment for chronic hepatitis C infection

The following definitions characterize the response to HCV treatment:

Sustained virologic response *X* (SVR*X*)	Patients are considered to have achieved SVR*X* (with *X* equal to 4, 12, 24) if both conditions below are met: 1) at **EOT** • HCV RNA <25 IU/mL undetectable, **AND** 2) at the **time point of SVR*X*** (ie, *X* weeks after **planned EOT**) • HCV RNA <25 IU/mL detectable or undetectable
Rapid virologic response (RVR)	HCV RNA <25 IU/mL undetectable at Week 4.
Treatment failure	Patients who did not achieve SVR12 or patients who relapsed thereafter
- On-treatment failure	Patients are considered as an on-treatment failure if they have at **EOT** detectable HCV RNA, ie: <25 IU/mL detectable or ≥25 IU/mL
• Viral breakthrough	On-treatment confirmed increase of >1 $\log_{10}$ in HCV RNA from the lowest level reached, or a confirmed HCV RNA >100 IU/mL in patients who previously had HCV RNA <25 IU/mL detectable or undetectable
- Post treatment failure	Patients with undetectable HCV RNA at EOT followed by viral relapse or missing HCV RNA data at the SVR12 time point
• Viral relapse	Patients are considered to have a viral relapse if both conditions below are met: 1) at **EOT**: HCV RNA <25 IU/mL undetectable **AND** 2) during the **follow-up period**: HCV RNA ≥25 IU/mL

The following definitions refer to characterization of response to previous treatment:

Treatment-experienced patients	Patients are considered treatment-experienced if they have failed at least 1 previous course of interferon-based therapy: includes nonresponders and relapsers
- Nonresponders	Nonresponders include (prior) null and partial responders. Patients are considered null responders or partial responders if they have:
• Null responders	On-treatment <2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12

• Partial responders	On-treatment ≥2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at EOT
- Relapsers	Patients are considered relapsers if they have detectable HCV RNA during follow-up after undetectable HCV RNA at the end of the previous treatment

1 EXECUTIVE OVERVIEW

Janssen has developed simeprevir (SMV) in combination with pegylated interferon (PegIFN) alfa and ribavirin (RBV) (PegIFN/RBV [PR]) for the treatment of adult patients with chronic hepatitis C. The currently proposed indication for SMV is for chronic hepatitis C virus (HCV) genotype 1 infection. This comprises patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon (pegylated or non-pegylated) therapy with or without RBV.

In addition, SMV is under development for the treatment of HCV genotype 4 infection and HCV/human immunodeficiency virus type 1 (HIV-1) co-infection (not included in the currently proposed indication) and studies investigating the use of SMV as part of interferon-free regimens have been initiated.

As many as 2 to 4 million persons may be chronically infected with HCV in the United States (US) and an estimated 150,000 new infections occur annually in the US[1-4]. Approximately 78% of persons who test positive for anti-HCV antibodies develop a chronic HCV infection[5]. Chronic HCV infection is one of the main causes of liver disease worldwide and may lead to cirrhosis, liver failure, hepatocellular carcinoma and, eventually, death[4].

To date, HCV infection is largely undiagnosed. Given the burden of HCV infection and the improved clinical outcome in patients treated for HCV, in June 2013 the US Preventive Services Task Force (USPSTF) issued a recommendation to screen for HCV infection in persons at high risk, eg, injection drug users. The USPSTF also recommends offering one-time screening for HCV infection to adults born between 1945 and 1965[5].

Hepatitis C virus is classified in at least 6 distinct genotypes (designated 1-6) with multiple subtypes (designated a, b, c, etc.). In vitro, SMV was most active against HCV genotype 1 and 4 clinical isolates, whereas SMV activity was reduced against HCV genotype 2 and was low against genotype 3 clinical isolates. Hepatitis C virus genotype 1 has a worldwide distribution with subtypes 1a and 1b being the most common; they account for up to 60% of global HCV infections[6]. In North America, approximately 60% to 70% of genotype 1 HCV-infected patients are infected with HCV genotype subtype 1a. Although genotype 4 is mainly found in the Middle East, Egypt and Central Africa, it has recently spread in several Western countries, particularly in Europe (rates of 10% to 24%, especially among immigrants)[7].

Currently, the standard of care for treatment of patients with chronic hepatitis C genotype 1 infection is a protease inhibitor (telaprevir [TVR] or boceprevir [BOC]) + PR. These therapies yield a significantly higher sustained virologic response (SVR) rate (indication of cure), than treatment with PR alone which was the standard of care prior to approval of these two protease inhibitors in 2011. Importantly, these therapies allowed shortening of the overall treatment duration (from 48 to 24 weeks [TVR] or 28 weeks [BOC]) in a number of treatment-naïve and prior relapser patients (overall 65% and 44% of TVR and BOC in treatment-naïve registrational clinical studies)[8-19].

Treatment regimens containing TVR or BOC + PR are however associated with increased rates and severity of adverse events (AEs), including anemia and rash, in comparison to PR administered alone[17,18]. These AEs sometimes require premature treatment discontinuation and additional monitoring and management of AEs compared to PR treatment, including red blood cell transfusions and use of erythropoiesis stimulating agents/close monitoring for skin manifestations, leading to frequent healthcare provider visits, adding to the complexity and costs (direct and indirect) of treatment[20]. Moreover, a significant proportion of HCV-infected treatment-naïve and prior relapser patients and all patients with cirrhosis require 48 weeks of treatment with PR. Since PR treatment is associated with considerable side effects and TVR and BOC increase the side effects compared to PR, there remains a need for HCV therapy which is better tolerated and/or could further increase the number of patients eligible for shorter treatment duration.

Although TVR and BOC represented an important improvement in terms of efficacy, SVR rates with these newer therapies remain low in difficult-to-cure populations such as patients with null response to previous PR therapy, especially when cirrhosis is present[17,18]. In patients with compensated advanced liver fibrosis stages, more effective and safer treatment options resulting in HCV cure could avoid liver decompensation and the need for liver transplantation. Hepatitis C–related end-stage liver disease is the most common indication for liver transplantations among US adults, accounting for more than 30% of cases[5,21]. In addition, hepatitis C virus recurrence post-liver transplantation is influenced by a combination of donor, recipient, viral and immunosuppression factors. Overall, fibrosis progression is accelerated compared with non-immunosuppressed patients, resulting in cirrhosis, graft loss and need for re-transplantation. In these patients, eradication of the HCV virus can result in improvement in liver fibrosis, lower risk of liver decompensation and a lower cumulative mortality post-transplantation[21]. In the setting of post-transplant treatment,

a more favorable drug-drug interaction profile, allowing coadministration with immunosuppressants without the need for intensive pharmacokinetic monitoring and significant dose adjustments of immunosuppressants, is also of great importance. Moreover, the development of interferon-free regimens for the treatment of HCV is important and highly attractive, particularly in patients with decompensated liver disease since interferons are contraindicated in patients with Child-Pugh Score B and C. Simeprevir is currently being investigated as part of several interferon-free regimens and is planned to be studied in post-liver transplant patients.

Telaprevir (in US) and BOC currently require the intake of 6 and 12 pills per day, respectively, divided in three daily doses to be taken with food. A three-times-daily regimen is difficult to comply with and, therefore, could negatively impact treatment adherence[19]. Therapies with a lower pill burden and less frequent dosing may have a positive impact on treatment adherence.

There is an unmet medical need for new agents with improved safety profile, that increase the proportion of patients that can shorten treatment duration, with higher SVR in difficult-to-cure populations (cirrhotics and null-responders), and with a better drug-drug interaction profile. Moreover, a more convenient dosing regimen and a simpler treatment algorithm are desired. Simeprevir has the potential to help addressing these unmet medical needs.

Section 2 (p.24) provides further background information on chronic hepatitis C and current treatment options.

1.1 SIMEPREVIR: BACKGROUND

As TVR and BOC, SMV is a HCV NS3/4A protease inhibitor. Simeprevir structurally belongs to a different class and has a binding mode to the target enzyme which is different (SMV: 14-membered macrocycle; TVR and BOC: α-ketoamid derivatives).

Simeprevir is given as one pill once a day with any type of food. The recommended treatment duration of SMV is:

- 12 weeks in combination with PR for 24 weeks in treatment-naïve and prior relapser patients,
- 12 weeks in combination with PR for 48 weeks in prior nonresponder patients.

Janssen submitted a New Drug Application (NDA No. 205123) for SMV 150 mg capsule to the Food and Drug Administration (FDA) on 28 March 2013 and the FDA has granted priority review for this application.

1.2 SIMEPREVIR DEVELOPMENT PROGRAM

At the time of the NDA submission, data were available from a comprehensive development program including a total of 3,272 persons who received at least one dose of SMV (910 non-HCV infected volunteers [including non-HCV infected patients with hepatic and renal impairment] and 2,362 HCV-infected patients):

- Thirty-eight clinical studies conducted globally (seven Phase 3 studies, two Phase 2b studies, two Phase 2a studies and 27 Phase 1 studies,
- seven studies conducted in Japan (four Phase 3 studies, one Phase 2 study and two Phase 1 studies) with SMV at a 100 mg once daily dosing,
- two interferon-free studies with SMV 150 mg once daily (one Phase 1 and one Phase 2 study).

The safety and efficacy described in this briefing book focus on studies conducted globally supporting the use of SMV 150 mg once daily in genotype 1 infected patients, per the currently proposed indication in the US, and includes data from:

- three double-blind, placebo [PBO]-controlled Phase 3 studies (C208 and C216 in treatment-naïve and HPC3007 in prior relapser patients) investigating SMV 150 mg once daily for 12 weeks in combination with PR for 24 or 48 weeks (based on on-treatment response),
- two double-blind, PBO-controlled Phase 2b studies (C205 in treatment-naïve patients and C206 in treatment-experienced patients, including prior nonresponders) investigating SMV + PR for 24 (treatment-naïve patients only) or 48 weeks at different and durations. Doses investigated were 75 mg and 150 mg in treatment-naïve patients and 100 mg and 150 mg in treatment-experienced patients. Simeprevir was administered for 12 or 24 weeks in treatment-naïve patients and 12, 24 or 48 weeks in treatment-experienced patients.

In these studies, a total of 1,153 HCV genotype 1 infected patients received SMV at the recommended dose of 150 mg once daily for 12 weeks. Information on the dose and SMV treatment duration selection is provided in Section 3.1 (p.32).

In addition, this briefing book contains information on:

- Phase 1 studies, eg, drug-drug interaction studies (Section 4.2.2; p.40), a thorough QT study (Section 4.3; p.44), a photosensitivity study (Section 4.4; p.45), and studies in non-HCV infected patients with impaired renal or liver function (Section 4.2.1; p.38)
- a rollover study for patients who failed treatment with PR in the Phase 2b/3 studies or with short direct acting antiviral containing therapy in Phase 1 studies (C213; N=50; Section 5.1.2.3; p.58),
- an observational long-term virologic follow-up study in HCV genotype 1 infected patients previously treated with SMV + PR in the Phase 2b/Phase 3 studies (HPC3002; Section 5.1.3.2; p.63)

Section 3 (p.27) provides more detail on the planned and ongoing development program of SMV.

1.3 PHARMACOKINETICS

Phase 1 studies with SMV demonstrated a favorable pharmacokinetic profile supporting a convenient dosing regimen with only one pill per day in addition to PR. This SMV regimen decreases the pill burden for patients compared to currently available protease inhibitor-containing therapies and could improve treatment adherence.

Simeprevir is distributed almost exclusively to the target organ, the liver, as a result of transport by organic anion transporting polypeptide (OATP).

Simeprevir is metabolized primarily by cytochrome P450 3A (CYP3A) and therefore is susceptible to drug-drug interactions with moderate and potent inhibitors (such as erythromycin or ritonavir) and inducers of CYP3A (such as efavirenz or rifampin). Clinical drug-drug interaction studies have shown that SMV inhibits the hepatic uptake transporter OATP and the intestinal efflux transporter P-glycoprotein (P-gp).

Simeprevir is a mild inhibitor of CYP3A, with clinically relevant inhibition only of intestinal but not hepatic CYP3A.

Drug-drug interaction studies demonstrated that there was no clinically relevant interaction with the immunosuppressants cyclosporine and tacrolimus nor with the HIV-antiretrovirals tenofovir disoproxil fumarate, rilpivirine and raltegravir.

The pharmacokinetics of SMV are discussed in more detail in Section 4 (p.33).

1.4 EFFICACY

Antiviral Activity

Simeprevir is a potent and selective inhibitor of the HCV NS3/4A protease which is essential for viral replication. In a biochemical assay, SMV inhibits the proteolytic activity of recombinant genotype 1a and 1b HCV protease (median kinetic inhibition constant [K_i] values of 0.5 nM and 1.4 nM, respectively). In addition, in vitro activity of SMV against HCV genotype 1a, 1b and 4 was demonstrated using different cell based replicon assays. (Section 5.1.1; p.46)

In Vitro Virology

Resistance to SMV was characterized in HCV genotype 1a and 1b replicon-containing cells and was evaluated in HCV genotype 1a and 1b replicon assays using site-directed mutants and chimeric replicons carrying NS3 sequences derived from clinical isolates. These analyses showed that some amino acid substitutions at NS3 protease positions F43, Q80, S122, R155, A156, and/or D168 reduced SMV activity. (Section 5.1.3.1; p.62)

Efficacy/Virology in Clinical Studies

Clinical data described in the efficacy section (Section 5.1; p.46) focusses on the Phase 3 studies C208 and C216 in treatment-naïve patients, the Phase 3 study HPC3007 in prior relapser patients and the Phase 2b study C206 in treatment-experienced patients (including prior relapse and nonresponder patients). The primary efficacy endpoint in the Phase 2b (C205 and C206) studies was sustained virologic response 24 weeks after end of treatment (SVR24). In agreement with Health Authorities, the primary endpoint was subsequently modified to SVR12 in the Phase 3 studies.

The primary objective of these Phase 2b/3studies was to demonstrate superiority of SMV + PR over PBO + PR. Both in treatment-naïve and treatment-experienced patients with HCV genotype 1 infection, SVR rates were statistically significantly higher in patients in the SMV group compared to the PBO group (80% versus 50% in treatment-naïve patients [pooled

C208/C216], 79% versus 37% in prior relapsers [HPC3007], 66.7% versus 22.7% in treatment-experienced patients [including prior relapsers, and well characterized prior partial or null responders; C206]; $p<0.001$). In addition, in study C206, analyses were performed to assess the efficacy by response to prior PR treatment (prior partial and null responders and prior relapsers). SVR rates were higher in the SMV 150 mg once daily group compared to PBO group for both the prior null responders and prior partial responders (51% versus 19% in prior null responders and 75% versus 9% in prior partial responders). (Section 5.1.2; p.47)

A key secondary endpoint of the Phase 3 studies was the proportion of patients able to shorten total treatment duration to 24 weeks. In the Phase 3 studies, the total treatment duration in treatment-naïve and prior relapse patients with all degrees of liver fibrosis, including cirrhosis, was based on the on-treatment response at Week 4 and Week 12. Patients required HCV RNA ribonucleic acid (RNA) levels <25 IU/mL detectable or undetectable at Week 4 and undetectable HCV RNA at Week 12 in order to be able to shorten overall treatment to 24 weeks. In the SMV + PR groups, 85% and 91% of the treatment-naïve patients in C208 and C216, respectively, and 93% of the prior relapser patients in HPC3007 were eligible for a shortened total treatment duration with PR from 48 to 24 weeks. In patients meeting these response-guided treatment criteria SVR rates were 91% and 86% in treatment-naïve patients in C208 and C216, respectively, and 83% in prior relapse patients (HPC3007). Prior nonresponder patients received a fixed total treatment duration of 48 weeks. (Section 5.1.2; p.47)

Virology analyses of the SMV Phase 2b/3 studies focused on the prevalence and effect on treatment outcome of HCV NS3 baseline polymorphisms (ie, naturally occurring amino acid substitutions) and characterization of emerging resistance in patients failing SMV + PR therapy. Baseline olymorhpisms that reduce SMV activity were rare (1.3% in SMV Phase 2b/3 studies) with the exception of the low-level resistance Q80K polymorphism. The observed prevalence of Q80K in the Phase 2b/3 studies was 30% in the genotype 1a infected population and varied by region (Europe: 19%; US: 48% of the genotype 1a population). The Q80K polymorphism is only rarely found in HCV genotype 1b infected patients (0.5% in Phase 2b/3 studies). (Section 5.1.3.2; p.63)

Emergence of resistance is expected in patients not achieving SVR with treatments containing potent direct acting antivirals. The resistance profile of SMV has been well characterized and showed that treatment failure was usually associated with the emergence of

high-level SMV resistance associated mutations. A consistent, yet different resistance profile was observed in HCV genotype 1a and 1b infected patients. (Section 5.1.3.2; p.63)

The Phase 3 clinical studies showed that the presence of a genotype 1a Q80K polymorphism resulted in considerably lower SVR rates in the SMV + PR treatment group compared to patients without Q80K polymorphism. This trend was not noted in the PR + PBO group. (Section 5.1.2; p.47)

Subgroup analyses indicated that SVR rates were statistically significantly higher in the SMV + PR group compared to the PBO + PR group for all *IL28B* genotypes and METAVIR fibrosis scores. (Section 5.1.2; p.47)

Recommended SMV + PR Treatment Regimen

Given that the efficacy of SMV + PR was considerably reduced in two out of three Phase 3 studies in patients with HCV genotype 1a with a baseline Q80K polymorphism and the prevalence of the genotype 1a Q80K baseline polymorphism in the US is high, determination of baseline Q80K in HCV genotype 1a infected patients is recommended before initiation of treatment with SMV + PR., determination. (Section 5.1.4.1; p.66)

Given that around 90%-95% of patients without baseline Q80K were eligible for 24 weeks of treatment in the Phase 3 studies and these patients derived high SVR rates while only few patients were assigned to 48 weeks of treatment resulting in modest SVR in this group, it is recommended that all treatment-naïve patients and prior relapser patients be treated with SMV 150 mg once daily for 12 weeks in combination with PR for a total of 24 weeks. Prior nonresponder patients treated with SMV should receive SMV 150 mg once daily for 12 weeks in combination with PR for a total of 48 weeks. (Section 5.1.4.2; p.66).

All treatment should be stopped if a virologic stopping rule at Week 4, 12 or 24 is met, to avoid unnecessary exposure to a failing treatment regimen in patients with low chance of achieving SVR. (Section 5.1.4.3; p.67)

Efficacy is discussed in more detail in Section 5.1 (p. 46).

1.5 SAFETY

Nonclinical Safety

A comprehensive nonclinical toxicology program, including in vitro and in vivo studies using mice, rats, dogs, rabbits and monkeys was performed. The effects of SMV administration

were evaluated for up to 3 months in mice, 6 months in rats and 9 months in dogs via daily administration. There were also evaluations of genotoxic potential, fertility, embryofetal toxicity, pre- and postnatal development and topical tolerability. The comprehensive nonclinical program supports the safe use of SMV in HCV-infected patients at the clinical dose of 150 mg once daily for a duration of 12 weeks. (Section 5.2.1; p.70)

Safety in Clinical Studies

Comprehensive safety data from the Phase 2b and Phase 3 studies were pooled for analysis. The primary pooling consists of the Phase 3 studies C208, C216 and HPC3007. The secondary pooling adds studies C205 and C206 to the primary pooling. In general, data from the secondary pooling did not show a different safety outcome as compared to the primary pooling and, therefore, data from the primary pooling only are described below. (Section 5.2.1; p.70)

Evaluation of the data indicates that the safety profile of SMV + PR is favorable and generally comparable to PR alone in all populations studied, including patients who have failed previous PR treatment (prior relapsers and prior partial and null responders) and patients with cirrhosis (Section 5.2.7; p.89). In general, data from the secondary pooling did not show a different safety outcome as compared to the primary pooling.

The most frequent side effects were fatigue, headache, and influenza-like illness, all of which are common side effects of PR treatment. The incidence of side effects was comparable in patients treated with SMV + PR and those treated with PR alone and were mostly mild in severity. (Section 5.2.2; p.72)

No deaths were reported during the first 12-week treatment phase, but three SMV-treated patients died during the subsequent treatment phase, after completion of SMV/PBO. None of the deaths were considered related to SMV/PBO. In four patients, a SMV/PBO-related serious adverse event [SAE] was reported (three SMV-treated patients and one PBO-treated patient). During the first 12 weeks phase, 1.8% of the SMV-treated patients and 1.3% of the patients on PBO in the primary pooling discontinued SMV/PBO due to an AE. Rash was the most common AE[1] leading to discontinuation of SMV (in 0.6% of SMV-treated patients). Rash was not reported as an AE leading to treatment discontinuation in patients on PBO. Note that the Phase 3 protocols mandated discontinuation of all study drugs in case of a Grade 3 or 4 rash. (Section 5.2.3; p.74)

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[1] Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Based on nonclinical findings for SMV and known toxicity profiles for other protease inhibitors and PR, a number of AEs and laboratory abnormalities were defined to be of interest[2] (ie, bilirubin increased, pruritus, rash [any type], anemia, neutropenia and photosensitivity conditions) and were analyzed in more detail. A higher incidence for rash (includes the term photosensitivity conditions; 23.2% versus 16.9%), pruritus (22.0% versus 14.9%), and photosensitivity conditions (3.3% versus 0.5%) was observed in patients treated with SMV + PR than those treated with PR alone. Also for increased bilirubin, a higher incidence was observed with SMV treatment (7.9% versus 2.8%). In general, these side effects were mild in severity and did not lead to treatment discontinuation. The bilirubin increases were reversible and, in general, not associated with concomitant elevations of hepatic transaminases. The mechanism of bilirubin increases with SMV + PR treatment is understood and is attributed to a decrease in bilirubin elimination related to inhibition of hepatic transporters (OATP and possibly also multidrug resistance-associated protein 2 [MRP2]) by SMV. Furthermore, increased bilirubin production as a consequence of RBV induced hemolysis very likely plays a pathophysiologic role. There was no difference between the treatment groups in mean hemoglobin or neutrophil values over time up to Week 24. (Section 5.2.4; p.76)

Dyspnea was not identified as an AE of interest, however, taking into account the slightly higher incidence in SMV + PR treated patients compared to PBO treated patients (11.8% versus 7.6%) during the first 12 weeks phase, dyspnea (grouped term, see Appendix 5) was further analyzed. (Section 5.2.4; p.76)

Severity of fatigue and functional limitations at work and in daily activities were assessed using patient-reported outcomes (PRO) in studies C208, C216 and HPC3007. Treatment with SMV reduced the duration of fatigue and functional impairments without increasing their severity. The reduced duration is related to the shortened overall treatment duration of PR in the majority of patients in the SMV/PR group as compared to PR alone. (Section 5.2.6; p.86)

In treatment-experienced patients (C206), the safety profile of SMV was similar to that observed in the primary pooling.

Adverse drug reactions for SMV + PR treatment that occurred with at least 3% higher frequency among patients receiving SMV + PR compared to patients receiving PBO + PR

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[2] Events of interest: grouped terms, see Appendix 5.

during the first 12 weeks of treatment in the pooled Phase 3 studies (C208, C216 and HPC3007) include rash (including photosensitivity), pruritus, nausea and dyspnea (grouped terms). (Section 5.2.4; p.76)

Safety is discussed in more detail in Section 5.2 (p. 70).

1.6 BENEFITS/RISKS CONCLUSIONS

The results of the clinical development program indicate that SMV + PR is a well-tolerated and effective therapeutic alternative for HCV-infected patients. Simeprevir 150 mg once daily for 12 weeks + PR is associated with high SVR rates, a good tolerability and drug-drug interaction profile, a simple 24-week regimen in all treatment-naïve and prior relapser patients including cirrhotics, and a convenient single capsule once daily dosing that could reduce treatment burden on patients.

Given the high prevalence of the genotype 1a Q80K baseline polymorphism in the US, determination of baseline Q80K in HCV genotype 1a infected patients is recommended before initiation of treatment with SMV + PR. Alternative therapy should be considered for all genotype 1a patients with the Q80K polymorphism.

Treatment-naïve and prior relapser patients should receive SMV for 12 weeks in combination with PR for 24 weeks while prior nonresponder patients should receive SMV + PR for 12 weeks in combination with PR for 48 weeks rather than a response-guided treatment approach. Stopping rules (HCV RNA is ≥25 IU/mL) are in place at Week 4 and 12 for all patients and Week 24 for prior partial and null responders, are common to all patient subpopulations (treatment-naïve, prior-relapser, partial responder and null responder patients) and do not require additional testing time points beyond the current standard of care.

Adverse reactions for SMV + PR treatment that occurred with at least 3% higher frequency among patients receiving SMV + PR compared to patients receiving PBO + PR during the first 12 weeks of treatment in the pooled Phase 3 studies (C208, C216 and HPC3007) include rash (including photosensitivity), pruritus, nausea and dyspnea (grouped terms[3]). Simeprevir

[3] Grouped term ‘rash’ includes: 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, generalized erythema, dermatitis exfoliative, cutaneous vasculitis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and photodermatosis.

did not cause additional anemia in any of the studied patient populations, including patients with cirrhosis. A recommendation with regard to sun-protective measures will be included in the United States Product Information (USPI). No additional risk evaluation and mitigation strategy is required for SMV related adverse reactions or laboratory abnormalities. Laboratory testing requirements as per the prescribing information for PR treatment, which includes hematology and biochemistry (including hepatic enzymes and bilirubin) testing at baseline, on-treatment and post-treatment, are sufficient to manage the risks of SMV + PR combination treatment.

The benefits-risk overall conclusions for SMV are discussed in more detail in Section 7 (p.94).

Grouped term ‘pruritus’ included the preferred terms pruritus and pruritus generalized.
Grouped term ‘dyspnea’ includes the preferred terms dyspnea and dyspnea exertional

2 BACKGROUND

Janssen has developed simeprevir (SMV) in combination with pegylated interferon (PegIFN) alfa and ribavirin (RBV) (PegIFN/RBV [PR]) for the treatment of adult patients with chronic hepatitis C. The currently proposed indication for SMV is for chronic hepatitis C virus (HCV) genotype 1 infection. This comprises patients with compensated liver disease, including patients with cirrhosis, who are treatment-naïve or who failed prior interferon (pegylated or non-pegylated) therapy with or without RBV.

In addition, SMV is under development for the treatment of HCV genotype 4 infection and HCV/human immunodeficiency virus type 1 (HIV-1) co-infection (not included in the currently proposed indication), two populations at high medical need. Moreover studies investigating the use of SMV as part of interferon-free regimens have been initiated. Especially in patients with decompensated liver disease, the need for interferon-free regimens is high since interferons are contraindicated in patients with Child-Pugh Score B and C. An interferon-free study in post-liver transplant patients is planned.

Janssen submitted a New Drug Application (NDA No. 205123) for SMV 150 mg capsule to the Food and Drug Administration (FDA) on 28 March 2013 and the FDA has granted priority review for this application.

Hepatitis C is a widespread global disease with significant public health impact.

Infection with hepatitis C virus is a leading cause of liver disease worldwide. The estimated global prevalence of HCV infection is 3% (up to 170 million people worldwide). As many as 2 to 4 million persons may be chronically infected in the United States (US) and 5 to 10 million in Europe. An estimated 150,000 new infections occur annually in the US and Western Europe[1-5]. Approximately 78% of persons who test positive for anti-HCV antibodies develop a chronic HCV infection[1-5]. This slowly progressive lifelong infection leads to cirrhosis and liver failure in 10% to 20% of chronically infected patients after 10 to 20 years representing one of the main causes for liver transplantation. Chronic hepatitis C infection increases the risk of developing hepatocellular carcinoma and about 5% to 7% of patients may ultimately die of the consequences of the infection[4].

To date, HCV infection is largely undiagnosed. Given the burden of HCV infection and the improved clinical outcome in patients treated for HCV, in June 2013 the US Preventive Services Task Force (USPSTF) issued a recommendation to screen for HCV infection in

persons at high risk, eg, injection drug users. The USPSTF also recommends offering one-time screening for HCV infection to adults born between 1945 and 1965[5].

Hepatitis C virus is classified in at least 6 distinct genotypes (designated 1-6) with multiple subtypes (designated a, b, c, etc.). Genotype 1 has a worldwide distribution and genotype subtype 1a and 1b are the most common accounting for up to 60% of global HCV infections[6]. Genotype 1a is predominantly present in North America (approximately 60% to 70% of HCV genotype 1 infected patients) while in Europe genotype 1b is generally more prevalent (60% to 90% of HCV genotype 1 infected patients). Genotypes 2 and 3 also have a worldwide distribution but genotype 2 is less common than genotype 1 and is found more in Europe than North America. Genotype 3 is endemic in Southeast Asia and variably distributed in different countries. Although genotype 4 is mainly found in the Middle East, Egypt and Central Africa, it has recently spread in several Western countries, particularly in Europe (rates of 10% to 24%, especially among immigrants). Genotype 5 is almost exclusively found in South Africa and genotype 6 is found in Asia[6,7]. Hepatitis C virus genotypes 1, 4, 5, and 6 are considered difficult-to-cure[22].

Rapidly evolving HCV treatment landscape since 2010.

Prior to 2010, standard of care for the treatment of HCV infection was interferon (pegylated and non-pegylated) and RBV. However, this combination had limited efficacy in HCV genotype 1 infection and was associated with considerable side effects. The unmet medical need for HCV treatments has spurred extensive research and discovery efforts which have led to the development of many promising direct acting antivirals belonging to several different pharmacological classes, such as NS3/4A protease inhibitors, nucleoside NS5B polymerase inhibitors, non-nucleoside NS5B polymerase inhibitors, and NS5A inhibitors[19].

In 2011, two protease inhibitor, telaprevir (TVR) and boceprevir (BOC), were approved for the treatment of chronic hepatitis C genotype 1 infection in adults in combination with PR[4]. The approval of these drugs has led to a change in the treatment standard from PR therapy to treatment with a protease inhibitor + PR therapy. Telaprevir and BOC are inhibitors of the HCV encoded NS3/4A protease, which is an essential enzyme for viral replication. In combination with PR, TVR and BOC have demonstrated improved treatment response (SVR) in both treatment-naïve (up to 75%) and treatment-experienced (up to 41% in prior null

[4] Simeprevir Phase 3 studies were initiated before the approval of these agents and, therefore, the SMV Phase 3 studies are placebo-controlled, as agreed upon with the Healthy Authorities.

responders, 59% in prior partial responders and 86% in prior relapsers) patients with HCV genotype 1 infection. In addition, these treatment combinations allowed shortening of the overall treatment duration (from 48 down to 24 or 28 weeks) in a proportion of HCV genotype 1 treatment-naïve and prior relapser patients (response-guided treatment)[8-19]. In the treatment-naïve HCV genotype 1 Phase 3 registrational studies of TVR and BOC, treatment duration could be reduced to 24 weeks in 65% and 28 weeks in 44%, respectively using an algorithm based on on-treatment response[19]. Both treatment-naïve and prior relapser patients are eligible for shortened treatment, however, patients with cirrhosis are recommended to be treated for 48 weeks.

An unmet medical need remains for new, safer and effective treatments for chronic Hepatitis C.

Despite the improvement that TVR and BOC represent in HCV-treatment there continues to be a significant unmet medical need for new HCV treatments:

- Coadministration of TVR or BOC with PR is associated with increased rates and severity of adverse events (AEs), such as anemia and rash, in comparison to PR alone[17,18]. These AEs sometimes require premature treatment discontinuation and additional monitoring and management of AEs compared to PR treatment, including red blood cell transfusions and use of erythropoiesis stimulating agents/close monitoring for skin manifestations, leading to frequent healthcare provider visits, adding to the complexity and costs (direct and indirect) of treatment[20].

- A significant proportion of HCV-infected treatment-naïve and prior relapser patients and all patients with cirrhosis currently treated with TVR or BOC require 48 weeks of treatment with PR. Pegylated interferon + RBV treatment is associated with considerable side effects such as fatigue, influenza-like symptoms, gastrointestinal disturbances, neurologic and psychiatric symptoms, anemia and neutropenia. Therefore, there remains a need for effective HCV therapy which could further increase the proportion of patients eligible for shorter treatment duration.

- Although TVR and BOC represent a considerable improvement in terms of efficacy, SVR rates with these newer therapies remain low in difficult-to-cure populations, such as patients with null response to previous PR therapy (32% with TVR + PR therapy[17] and 41% with BOC + PR therapy[23]) especially when cirrhosis is present

(14% with TVR + PR therapy[17]). Because response rates are low and cirrhosis is associated with significant morbidity and mortality this patient population is at high medical need. In patients with compensated liver disease, more effective and safer treatment options resulting in HCV cure could avoid liver decompensation and the need for liver transplantation. Hepatitis C–related end-stage liver disease is the most common indication for liver transplantations among US adults, accounting for more than 30% of cases[5,21].

- Also, a more favorable drug-drug interaction profile is of great importance for future HCV treatment in certain patient populations, such as liver transplant patients. Hepatitis C virus recurrence post-liver transplantation is influenced by a combination of donor, recipient, viral and immunosuppression factors. Overall, fibrosis progression is accelerated compared with non-immunosuppressed patients, resulting in cirrhosis, graft loss and need for re-transplantation. In these patients, eradication of the HCV virus can result in improvement in liver fibrosis, decreased risk of liver decompensation and cumulative mortality post-transplantation[21]. Pegylated interferon and RBV treatment results in limited SVR rates (26%-48%) and addition of TVR or BOC must be carefully evaluated after liver transplantation due to drug-drug interactions and tolerance. In this setting, a more favorable drug-drug interaction profile, allowing coadministration with immunosuppressants without the need for intensive pharmacokinetic monitoring and large dose adjustments of immunosuppressants, is of great importance[19].

- Telaprevir (in US) and BOC currently require the intake of a total of 6 and 12 pills per day, respectively, divided in three daily doses with food with high fat content. A three-times-daily regimen is difficult to comply with and, therefore, could negatively impact treatment adherence[19]. Therapies with a lower pill burden and less frequent dosing may have a positive impact on treatment adherence.

Simeprevir has the potential to help in addressing these unmet medical needs.

3 SIMEPREVIR CLINICAL DEVELOPMENT

Simeprevir is a HCV NS3/4A protease inhibitor which structurally belongs to a different class than TVR and BOC as it has a different binding mode to the target enzyme (SMV: 14-membered macrocycle; TVR and BOC: α-ketoamid derivatives).

The SMV clinical development program has been designed taking into account the advice from Health Authorities globally, and corresponds with the FDA draft guidance for the development of direct-acting antiviral agents intended for treatment of chronic hepatitis C[24]. At time of the NDA filing, 3,272 non-HCV infected volunteers and HCV-infected patients (910 non-HCV infected volunteers [including non-HCV infected patients with hepatic and renal impairment] and 2,362 HCV-infected patients) had received at least one dose of SMV within this comprehensive development.

The dataset supporting the current application for the use of SMV + PR, for the treatment of treatment-naïve or treatment-experienced (interferon therapy [pegylated or non-pegylated] with or without RBV) chronic HCV genotype 1 infected adults with compensated liver disease (including cirrhosis), consists of data from:

- Twenty-seven completed Phase 1 studies (N=806 SMV-treated non-HCV infected volunteers), including studies in non HCV-infected patients with severe renal impairment and non HCV-infected patients with moderate or severe hepatic impairment and a study investigating the photosensitizing potential of SMV. This Phase 1 program provided a good understanding of the pharmacokinetic characteristics, drug-drug interaction potential, and short-term safety/tolerability of SMV, including the effect of SMV on the QT interval.

- Two completed proof-of-principle, open-label, uncontrolled Phase 2a studies (N=125 SMV-treated patients): (1) C201 evaluating different doses of SMV, ranging from 25 mg to 200 mg once daily in treatment-naïve and treatment-experienced patients and (2) C202 exploring the antiviral activity of SMV 200 mg once daily in treatment-naïve patients infected with HCV genotypes 2, 3, 4, 5, or 6.

- Two completed double-blind PBO-controlled Phase 2b studies (N=705 SMV-treated patients): (1) C205 (PILLAR) which evaluated the safety and efficacy of SMV 75 mg and 150 mg once daily for 12 or 24 weeks in treatment-naïve HCV genotype 1 infected patients and (2) C206 (ASPIRE) which evaluated the safety and efficacy of SMV 100 mg and 150 mg once daily for 12, 24, or 48 weeks in treatment-experienced HCV genotype 1 infected patients (ie, prior relapsers, prior partial and null responders). Both studies investigated SMV + PR.

- Three double-blind, randomized, PBO-controlled Phase 3 studies (N=781 SMV-treated patients) with the primary analysis available, which investigated the safety and efficacy of SMV 150 mg once daily + PR in treatment-naïve patients (C208 [QUEST-1] and C216 [QUEST-2]) and prior relapsers (HPC3007 [PROMISE]). These studies are double-blinded and PBO-controlled.

A total of 1,153 HCV-infected patients received SMV at the recommended dose of 150 mg once daily for 12 weeks. Safety and efficacy data presented in this briefing book focusses primarily on data from the Phase 3 studies (treatment-naïve [C208 and C216] and prior relapser patients [HPC3007]) and the Phase 2b study C206 (prior nonresponder patients).

In addition, data from following currently ongoing Phase 3 studies with SMV + PR are presented:

- An open-label, uncontrolled, rollover study for patients treated with PR in the Phase 2b/3 studies or with short direct acting antiviral containing therapy in Phase 1 studies (C213; N=50 at time of the interim analysis with cut-off date of 15 September 2012),

- An observational long-term virologic follow-up study in HCV genotype 1 infected patients previously treated with SMV + PR in the Phase 2b/Phase 3 studies (HCP3002).

Four additional Phase 3 studies with SMV + PR are ongoing. Data from these studies are not presented in this document since they are not part of the current application and/or data were not available at time of the NDA submission:

- An uncontrolled, open-label study, in HCV genotype 4 infected patients (HPC3011; N=107),

- An uncontrolled, open-label study in HCV genotype 1/HIV-1 co-infected patients (C212; N=106), A double-blinded, active-controlled study in chronic hepatitis C genotype 1 infected patients who were null or partial responders to prior PR therapy to evaluate the efficacy, safety, and tolerability of SMV versus TVR, both + PR is ongoing (HPC3001 [ATTAIN]; N=765). This study is still blinded and no data are currently available.

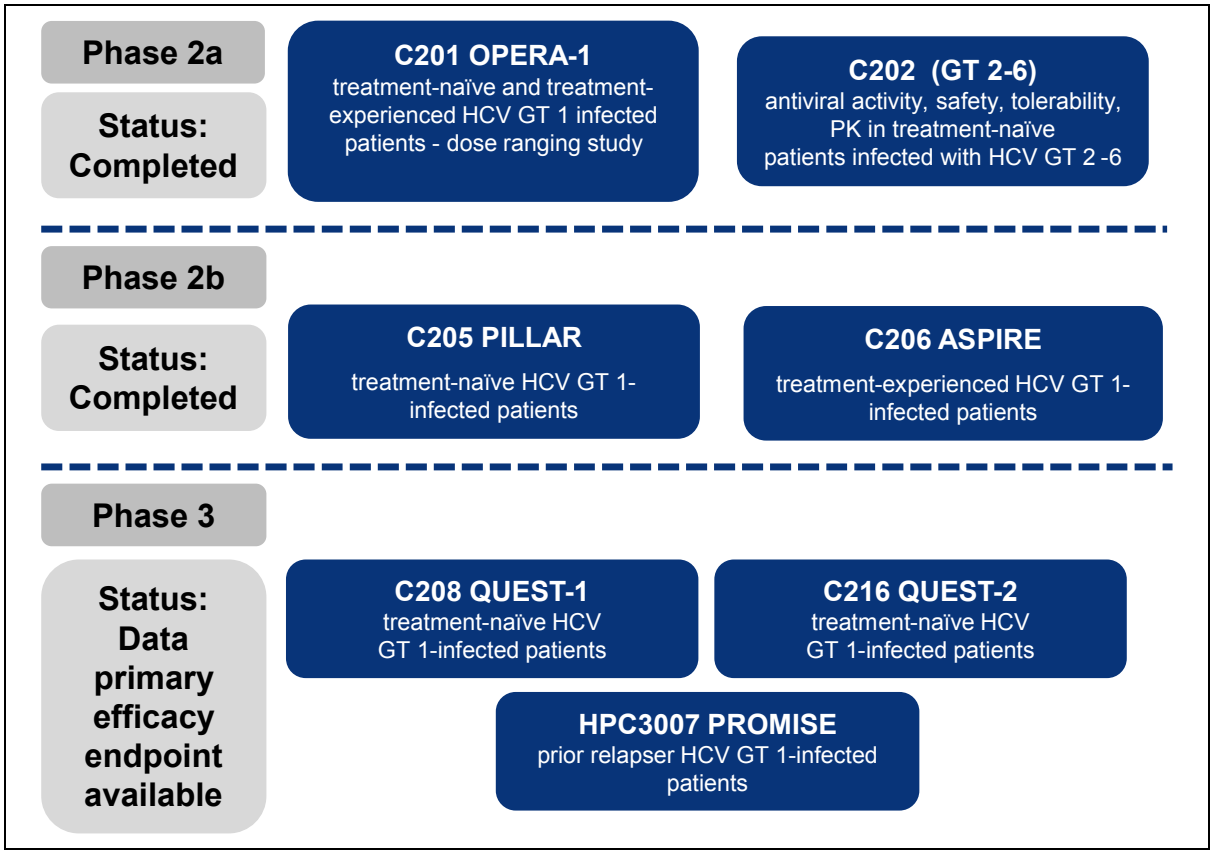
- A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of SMV 100 mg and 150 mg once daily + PR in Chinese and Korean treatment-naïve genotype 1 chronic hepatitis C infected patients in the Asian-Pacific region (HPC3005; N=101). No data for this study are currently available.

Finally, data from one Phase 1 and one Phase 2 (HPC2002 or COSMOS) studies with SMV as part of an interferon-free regimen were available at time of the NDA submission but are not being presented since this study is not part of the current application. Interferon-free studies in pediatric patients and post-transplant patients are planned.

Apart from the development program conducted globally, at time of the NDA data from seven studies conducted in Japan with SMV at a 100 mg once daily dose were available (four Phase 3 studies, one Phase 2 study and two Phase 1 studies). These data are not discussed in this document.

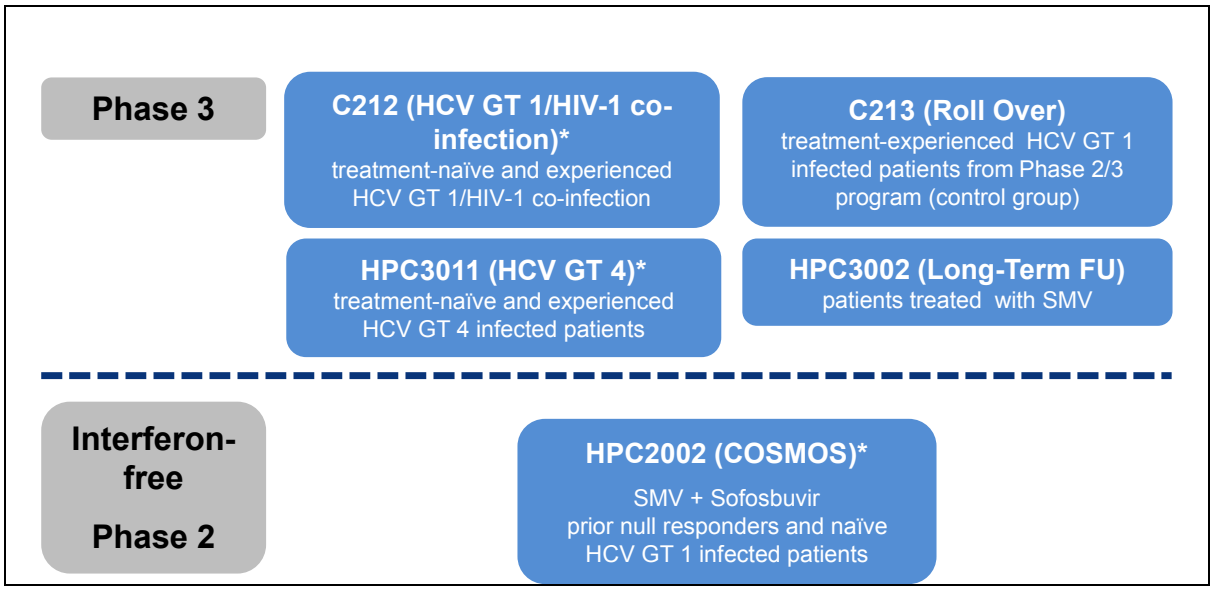
An overview of the Phase 2b/3 studies with primary efficacy data available, which form the focus of this document, is presented in Figure 1. An overview of Phase 2b/3 studies with interim data available is provided in Figure 2. Study designs of each of the key studies are presented in Appendix 1.

Figure 1: Overview of Phase 2/3 Clinical Studies With SMV + PR With Primary Endpoint Data Available



Status: status at time of NDA submission
GT: genotype; PK: pharmacokinetics

Figure 2: Overview of Ongoing Phase 2/3 Clinical Studies With Interim Data Available



* Data not part of this application
GT: genotype; PK: pharmacokinetics; FU: follow-up

The SMV formulation used during the Phase 3 program is a 150 mg capsule, similar to the intended commercial formulation, providing a convenient once-daily dosing regimen. An algorithm based on on-treatment response was used to determine total treatment duration with PR in treatment-naïve and prior relapser patients. Prior nonresponder patients received PR for 48 weeks. According to the response-guided treatment criteria applied in the C208, C216 and HPC3007 studies, PR treatment could be completed at Week 24 in patients with HCV RNA <25 IU/mL (detectable or undetectable) at Week 4 and undetectable HCV RNA at Week 12. Treatment stopping rules were in place in each of the studies to avoid continuation of a failing regimen with the objective of limiting the risk of developing drug resistance to SMV and reducing unnecessary exposure to PR if patients had no or extremely low chance of treatment success (Table 1).

Table 1: Treatment Stopping Rules for Discontinuation of All Study Drugs in Patients With Inadequate On-Treatment Virologic Response – C206, C208, C216 and HPC3007

Study	HCV RNA at Week 4	HCV RNA at Week 12	HCV RNA at Weeks 24 and 36	Additional Stopping Rules
C206	<1 $\log_{10}$ IU/mL reduction from baseline	<2 $\log_{10}$ IU/mL reduction from baseline	Confirmed detectable and ≥25 IU/mL	Viral breakthrough (Day 1 to Week 48)
C208, C216, HPC3007	>1,000 IU/mL*			Not applicable

Note: detectable HCV RNA after previous undetectability had to be confirmed by repeat HCV RNA testing.
* Only SMV/PBO was to be discontinued.

3.1 SIMEPREVIR DOSE AND TREATMENT DURATION RATIONALE

Different doses of SMV, ranging from 25 mg to 200 mg once daily (25 mg, 75 mg and 200 mg in treatment-naïve patients and 75 mg, 150 mg and 200 mg in treatment-experienced patients), were evaluated in the Phase 2a study C201. Results from this study indicated that 25 mg once daily in treatment-naïve and 75 mg once daily in treatment-experienced patients resulted in lower antiviral activity compared to the other doses studied. Similar antiviral activity was observed with SMV 75 mg and 200 mg once daily + PR in treatment-naïve patients and with SMV 150 mg and 200 mg once daily + PR in treatment-experienced patients. The SMV 200 mg dose was not further pursued in development due to an observed dose dependent isolated elevation in plasma bilirubin levels for which the mechanism was not yet understood and given the comparable antiviral activity with lower doses evaluated in study C201. Based on the results of study C201, the following doses were chosen for evaluation in Phase 2b studies:

- Simeprevir 75 mg was selected for the Phase 2b study C205 in treatment-naïve patients and the additional dose of 150 mg was identified for evaluation given its comparable activity with 200 mg in the treatment-experienced population. Simeprevir was administered for a treatment duration of 12 or 24 weeks

- Simeprevir 150 mg was selected for the Phase 2b study C206 in treatment-experienced patients and the additional dose of 100 mg was identified as an appropriate additional dose since it was higher than SMV 75 mg, since 75 mg was shown to have lower antiviral activity in treatment-experienced patients. Simeprevir was administered for a treatment duration of 12, 24, or 48 weeks.

In both the C205 and C206 Phase 2 studies, SVR rates were higher with the 150 mg dose compared to the lower doses in most subgroups, including null and partial responders. All doses tested were well tolerated. Analyses of viral breakthrough (eg, time of viral breakthrough) and viral relapse showed no additional benefit of prolonged SMV duration beyond 12 weeks. These results led to the selection of SMV 150 mg once daily for 12 weeks as the SMV dose and duration to be studied in Phase 3 in all patient populations infected with HCV.

4 OVERVIEW OF CLINICAL PHARMACOLOGY

The clinical pharmacology of SMV has been thoroughly investigated in multiple studies, including 27 studies in non-HCV infected volunteers, containing a study in patients with hepatic impairment and one in patients with renal impairment. Moreover, the pharmacokinetics of SMV in HCV-infected patients has been evaluated in all patient studies to date, including a study in HCV/HIV-1 co-infected patients and a study in HCV genotype 4 infected patients, to assess the effects of patient demographic characteristics and other covariates on SMV pharmacokinetics, and to characterize the exposure-response relationships for efficacy and safety.

Simeprevir has a pharmacokinetic profile that supports once-daily dosing with food. Intake of SMV with food increases the exposure by about 60%, regardless of meal composition.

Simeprevir is distributed almost exclusively to the target organ, the liver, as a result of transport by OATP.

Simeprevir is metabolized primarily by cytochrome P450 3A (CYP3A), and is therefore susceptible to drug-drug interaction with inhibitors (such as ritonavir or erythromycin) or inducers of CYP3A (such as efavirenz or rifampin). Simeprevir is a mild inhibitor of CYP3A, with clinically relevant inhibition only of intestinal but not hepatic CYP3A. Clinical drug-drug interaction studies have shown that SMV inhibits the hepatic uptake transporter organic anion transporting polypeptide (OATP) and the intestinal efflux transporter P-glycoprotein (P-gp). Drug-drug interaction studies demonstrated that there was no clinically relevant interaction with the immunosuppressants cyclosporine and tacrolimus nor with the HIV-antiretrovirals tenofovir disoproxil fumarate, rilpivirine and raltegravir or proton-pump inhibitors.

No dose adjustment of SMV is necessary with regard to age, gender, body-weight and mild, moderate or severe renal impairment. No dose adjustment is necessary in patients with mild hepatic impairment; however, insufficient data are available to provide a dose recommendation for patients with moderate or severe hepatic impairment.

Simeprevir plasma exposures are higher in Asians compared to Caucasians. As available safety and efficacy data are limited, the appropriateness of the 150 mg dose for patients with Asian ancestry cannot unequivocally be established. Exposure of SMV was comparable between Caucasian and Black/African-American HCV-infected patients.

4.1 PHARMACOKINETIC PROFILE OF SIMEPREVIR

4.1.1 Absorption, Distribution, Metabolism, and Excretion of Simeprevir

Absorption

Simeprevir has good oral bioavailability, with the maximum plasma concentration (C_{max}) attained approximately 4 to 6 hours after administration (time to reach C_{max} [t_{max}]). In vitro studies indicated that SMV is a substrate of the intestinal uptake transporter P-gp.

Food delays absorption, increasing time to reach maximum plasma concentration (C_{max}) by 1 to 1.5 hours and increases the exposure of SMV by about 60%, regardless of meal type (normal or high-fat meal). Although SMV was dosed in Phase 3 (C208, C216 and HPC3007) studies without any recommendation with regard to food intake, >80% of the patients had taken SMV with a meal all or most of the time. Therefore, it is recommended that SMV

150 mg once daily is taken with food to achieve optimal exposures comparable with those observed in these Phase 3 studies.

Distribution

Simeprevir is extensively bound to human plasma proteins (>99.9%), mainly albumin and to a lesser extent to alfa-1 acid glycoprotein. Simeprevir and its metabolites are not bound to or distributed to blood cells to any significant extent. In tissue distribution studies in animals, high concentrations of SMV were observed in the liver and the gastrointestinal system. Drug transporter studies in human hepatocytes and physiologically-based pharmacokinetic modeling and simulations indicate that SMV is actively transported into the liver via OATPs.

Metabolism

Metabolic clearance of SMV is low to moderate, based on human liver microsomes and hepatocyte data. Simeprevir is mainly metabolized by CYP3A enzymes. Unchanged drug is the major circulating drug-related moiety in plasma. One minor metabolite was observed in plasma and represented only a small percentage of the parent compound (up to 8% of unchanged drug). The metabolites, identified in feces, demonstrate that SMV is metabolized via 2 main metabolic pathways: 1) oxidation of SMV on the macrocyclic and/or the aromatic moiety, and 2) *O*-demethylation of SMV followed by oxidation. There is no metabolite accumulation after multiple-dose administration of SMV. Based on the metabolic scheme, no reactive intermediates were formed.

Excretion

Simeprevir is predominantly eliminated in the feces via biliary excretion. Following administration of a single oral dose of 200 mg ^{14}C-SMV, 91% of the dose was recovered based upon total radioactivity in feces and urine. Radioactivity was almost exclusively excreted in feces (91% of the dose), with ≤0.14% of radioactivity excreted in urine. Unchanged drug in feces accounted for only 31% of the administered dose, suggesting that the majority of SMV is absorbed and that the majority of the radioactive dose is excreted in the feces as metabolites. Apparent clearance (CL/F) of SMV based on data from Phase 3 studies (Bayesian estimation of pharmacokinetic parameters in studies C208, C216 and HPC3007) was estimated to be 5.07 L/h (with a coefficient of variation [CV] of 69%), indicating a low clearance of SMV.

4.1.2 Pharmacokinetics

After single-dose and multiple-dose administration in healthy volunteers and HCV-infected patients, the exposure of SMV increased more than dose-proportionally at doses above 75 mg once daily. The rate of absorption was not influenced by the dose, the median t_{max} being 4 to 6 hours for all doses. Physiologically-based pharmacokinetic (PBPK) modeling suggested that the nonlinear pharmacokinetics of SMV is mainly driven by saturation of CYP3A-mediated gut and liver metabolism and saturation of hepatic uptake.

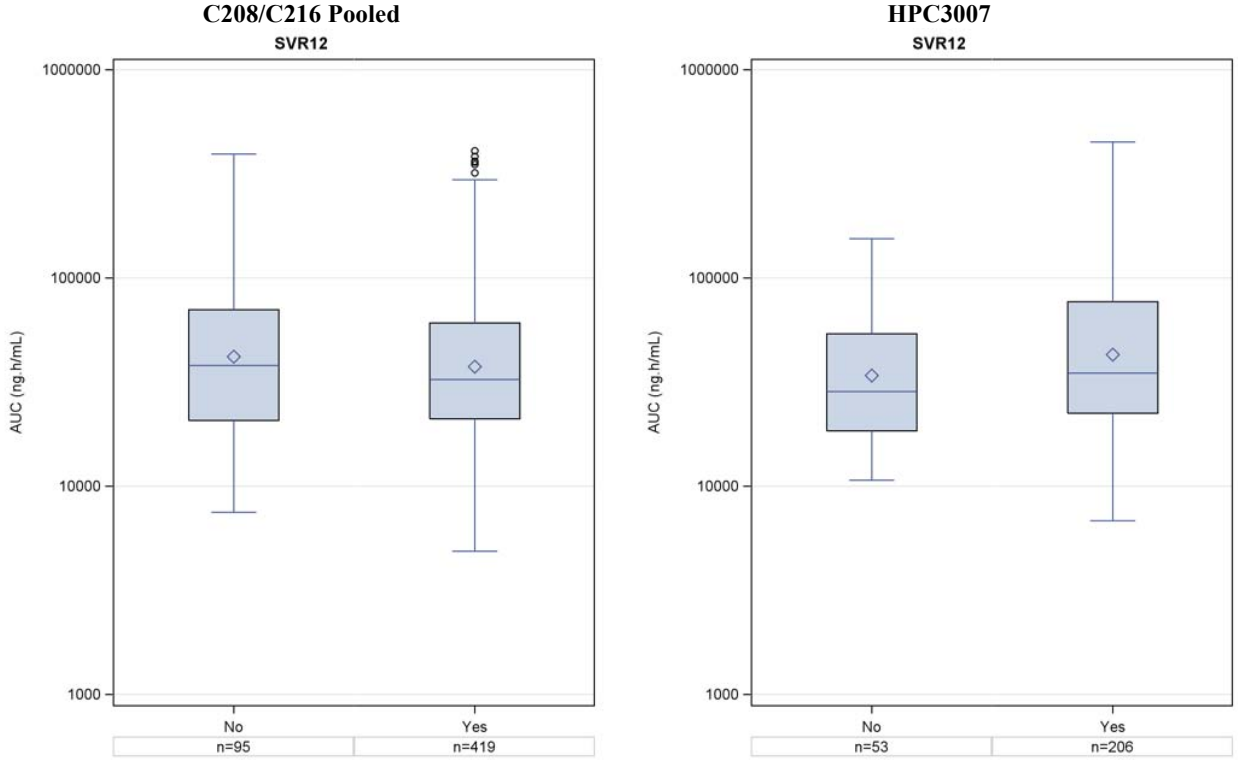
A pooled analysis of Phase 1 studies after 7 days of SMV administration at the 150 mg once daily dose, indicated that the intersubject variability of SMV plasma exposure was high with a CV of 87% for area under the plasma concentration-time curve up to 24 hours postdose (AUC_{24h}; N=221) and 139% for the predose plasma concentration (C_{0h}; N=223). The mean AUC_{24h} was 28,860 ng.h/mL and mean C_{0h} was 602 ng/mL in healthy volunteers. Physiologically-based pharmacokinetic modeling suggests that the large intersubject variability can be attributed to nonlinear drug-disposition in combination with intersubject variability in CYP3A4 and hepatic uptake transporter expression levels.

Irrespective of the dose of SMV administered, the exposure of SMV was generally higher (approximately 2- to 3-fold) in HCV-infected patients compared with healthy volunteers, and the intersubject variability was also high in this population. Population pharmacokinetic analysis of Phase 3 studies (Bayesian estimation of pharmacokinetic parameters in studies C208, C216 and HPC3007) indicated that the mean AUC_{24h} was 57,469 ng.h/mL and C_{0h} was 1,936 ng/mL with CV of 111% and 136% respectively.

In HCV-infected patients, the elimination half-life of SMV was 41 hours after multiple dosing at 200 mg once daily. Steady-state conditions were reached after 7 days of once-daily dosing. Potential factors, identified through PBPK modeling, that may impact the SMV pharmacokinetics in HCV-infected patients relative to healthy volunteers, include differences in number of functional hepatocytes and expression of CYP enzymes.

There was no relationship between SMV exposure and achieving SVR12 in individual analyses of the Phase 3 studies (C208, C216 and HPC3007) nor in the pooled efficacy analysis of the Phase 3 studies in treatment-naïve patients (C208/C216) (Figure 3).

Figure 3: Simeprevir AUC by Virological Response (SVR12) – Pooled C208/C216 and Study HPC3007



Yes: SVR12 was achieved; No: SVR12 was not achieved
AUC: area under the SMV plasma concentration-time curve;
Source: Data on file, Janssen Research and Development

There was a higher incidence of rash and pruritus with increasing SMV plasma exposure, and a trend for a higher incidence of increased bilirubin with increasing SMV plasma exposure (Table 2). No relationship between exposure and treatment discontinuation was identified (Table 2).

Table 2: Number (%) of Patients with Selected Events During the SMV/PBO + PR Phase by Plasma SMV AUC_{24h} Quartiles; All SMV Patients – Pooled C208/C216/HPC3007

	≤Q1 (Q1 = 21238.0)	>Q1 - ≤Median (Median = 33618.0)	>Median - ≤Q3 (Q3 = 65484.0)	>Q3	PBO + PR
Analysis Set: ITT	194	193	193	193	397
Events of special interest					
Increased bilirubin	14 (7.2%)	16 (8.3%)	7 (3.6%)	25 (13.0%)	11 (2.8%)
Events of clinical interest					
Rash (Any Type)	32 (16.5%)	39 (20.2%)	39 (20.2%)	69 (35.8%)	67 (16.9%)
Pruritus	28 (14.4%)	40 (20.7%)	41 (21.2%)	59 (30.6%)	59 (14.9%)
Any AE leading to permanent stop	13 (5.6%)	5 (1.9%)	4 (1.4%)	10 (3.6%)	5 (1.3%)

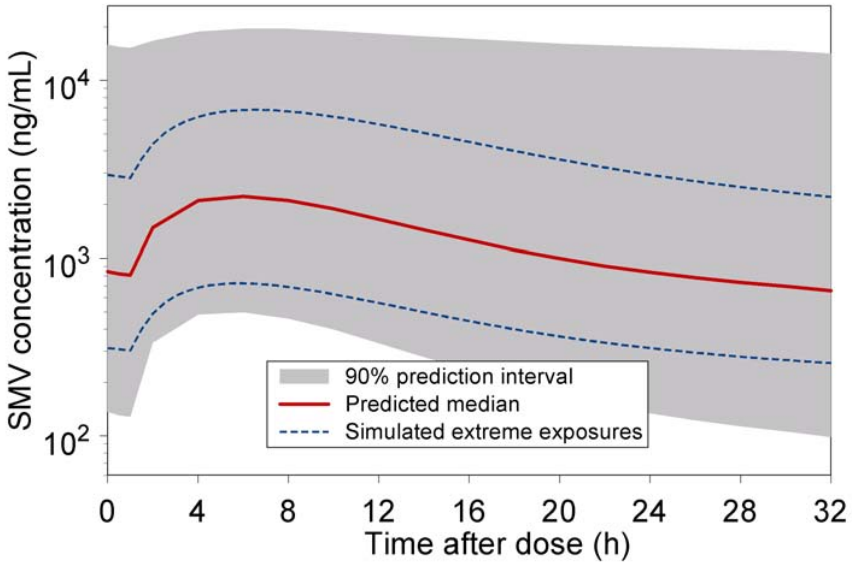
ITT: intent-to-treat; Q: quartile
Patients are counted only once for any given event, regardless of the number of occurring preferred terms (PTs).
Source: Data on file, Janssen Research and Development

4.2 IMPACT OF INTRINSIC AND EXTRINSIC FACTORS ON SIMEPREVIR PHARMACOKINETICS

4.2.1 Intrinsic Factors

- The effect of several intrinsic factors on SMV exposure has been explored using population pharmacokinetic model covariate analysis of the pooled Phase 2b/3 studies (C205, C206, C208, C216, and HPC3007). Part of the variability of SMV pharmacokinetics could be attributed to sex, age, body weight, total bilirubin (baseline), and METAVIR fibrosis score and these covariates were retained in the final population pharmacokinetic model. The clinical relevance of these covariates was further investigated using a simulation approach. The combinations of the extremes of these covariates that produced the greatest and smallest impact on the SMV pharmacokinetic parameters were used to simulate the pharmacokinetic profiles after SMV administration for 12 weeks at 150 mg once daily. The high and low extremes of the simulated pharmacokinetic profiles still fell within the 90% prediction intervals of exposure of the whole study population (Figure 4). Differences in exposure due to sex, body weight, age, total bilirubin at baseline, or METAVIR fibrosis score were smaller than the observed overall variability and are therefore considered not clinically relevant.

Figure 4: Simulated Extreme Exposures of SMV After 12 Weeks of SMV 150 mg Once Daily



h: hour
Extreme covariate combinations: low = young (25 years), heavy (108 kg) male with METAVIR fibrosis score F1 and low total bilirubin at baseline (5 µmol/L); high = old (63 years), light (54.8 kg), female with METAVIR fibrosis score F4 and high total bilirubin at baseline (21 µmol/L).
Source: Data on file, Janssen Research and Development

- Population pharmacokinetic estimates of exposure to SMV showed comparable exposure in Caucasian and Black/African American HCV-infected patients (Table 3). There was large inter-study variability when comparing exposure in Chinese or Japanese versus Caucasians (Table 3), and the number of patients in some of these studies was small. For example, in cross-study comparisons of Phase 1 studies, SMV plasma exposure was 20% lower in Chinese (N=16) than in Caucasians at the 200 mg dose (N=5), and 2.4-fold higher in Japanese (N=8) than in Caucasians at the 100 mg dose (N=4). Two percent of the total study population in the Phase 3 studies (C208, C216 and HPC3007) consisted of Asian patients. The SMV exposure in Asian HCV-infected patients was within the range of exposure observed in Caucasian HCV-infected patients. In the Phase 3 studies, the mean SMV plasma exposure in Asian patients was 3.4-fold higher than in the pooled Phase 3 population. As available safety and efficacy data are limited, the appropriateness of the 150 mg dose for patients with Asian ancestry cannot unequivocally be established.

  Currently a Phase 3, randomized blinded study, HPC3005, studying SMV 100 mg and 150 mg once daily in Chinese and Korean treatment-naïve genotype 1 chronic hepatitis C infected patients is ongoing in the Asian-Pacific region. A Data Monitoring Committee (DMC) has been set up to review the progress of the study and the accumulating data on a

regular basis to detect evidence of safety concerns for the patients while the study is ongoing. At time of the NDA submission no safety issues were identified.

Table 3: Individual Posthoc Population Pharmacokinetic Estimates of Exposure (AUC) of SMV by Race After Administration of SMV at 150 mg Once Daily for 12 Weeks in Patients Infected With HCV Genotype 1 – Pooled C208/C216/HPC3007

	Arithmetic mean (Range)				
Parameter	White	Black	Asian	Other	Pooled
n	703	47	14	7	773*
AUC, ng.h/mL	55,619 (4,868 – 449,185)	47,986 (14,172 – 168,130)	196,750 (22,334 – 408,855)	38,690 (21,573 – 64,794)	57,469 (4,868 – 449,185)

n: maximum number of patients with data; AUC: area under the plasma concentration-time curve
* pooled number contains two patients from which race was missing
Source: Data on file, Janssen Research and Development

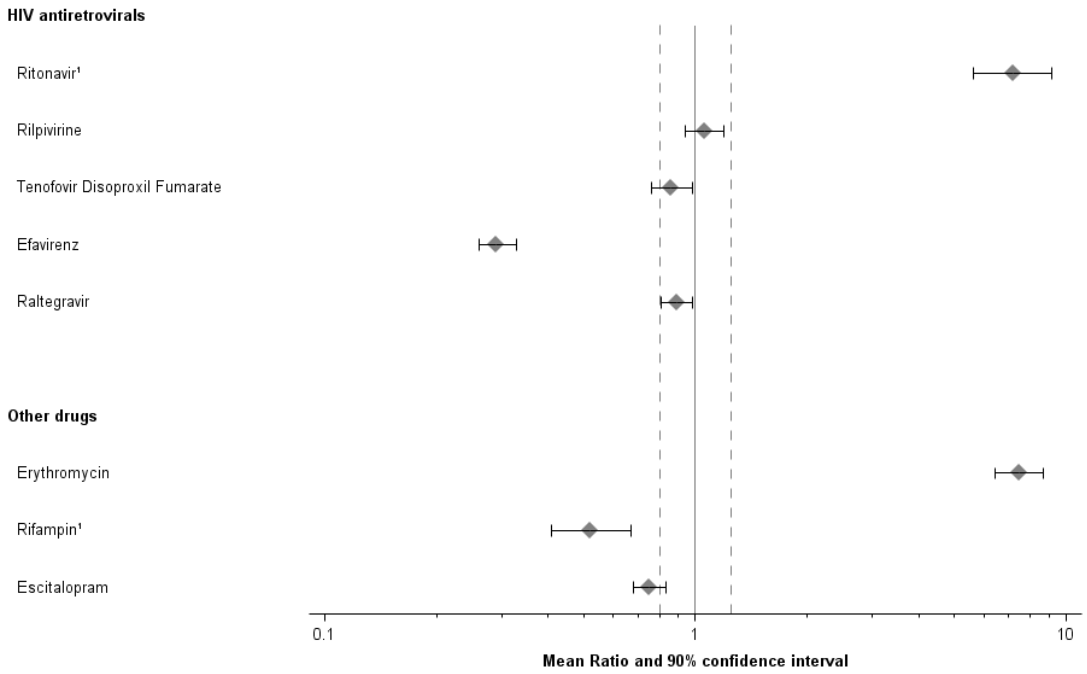
- In a pharmacogenomics analysis, no associations were identified between SMV exposure and any of the single nucleotide variations identified in a set of selected candidate genes that are possibly involved in hepatic disposition of SMV, including genes encoding for CYP enzymes (*CYP3A4*, *CYP3A5*, and *CYP2C19*) and transporters involved in hepatic uptake (solute carrier organic anion transporter family [*SLCO*]*1B1*, *SLCO2B1*, *SLCO1B3*, and solute carrier family 10 [*SLC10*]) and elimination (adenosine triphosphate-binding cassette *[ABC]G2*, *ABCB1*, and *ABCC2*).
- No clinically significant differences in pharmacokinetics were observed in non HCV-infected volunteers with mild, moderate, or severe renal impairment. Creatinine clearance was not identified as a significant covariate of SMV population pharmacokinetics in HCV-infected patients. Therefore, no dose-adjustment of SMV is required in these patients.
- The mean exposure increased 2.4-fold (90% confidence interval [CI] 1.4-4.4-fold) in HCV-negative volunteers with moderate hepatic impairment (Child-Pugh B) and 5.2-fold (90% CI 3.1-8.8-fold) in HCV-negative volunteers with severe hepatic impairment (Child-Pugh C) compared to healthy volunteers. No dose adjustment of SMV is necessary in mild hepatic impairment and no dose recommendation can as yet be given in patients with moderate or severe hepatic impairment. In the context of SMV + PR treatment, it is important to consider that PegIFN is contraindicated in patients with Child-Pugh B or C.

4.2.2 Extrinsic Factors - Drug Interactions

A total of 15 clinical drug-drug interaction studies have been conducted to investigate the interaction between SMV and 23 potentially coadministered drugs. The effect of

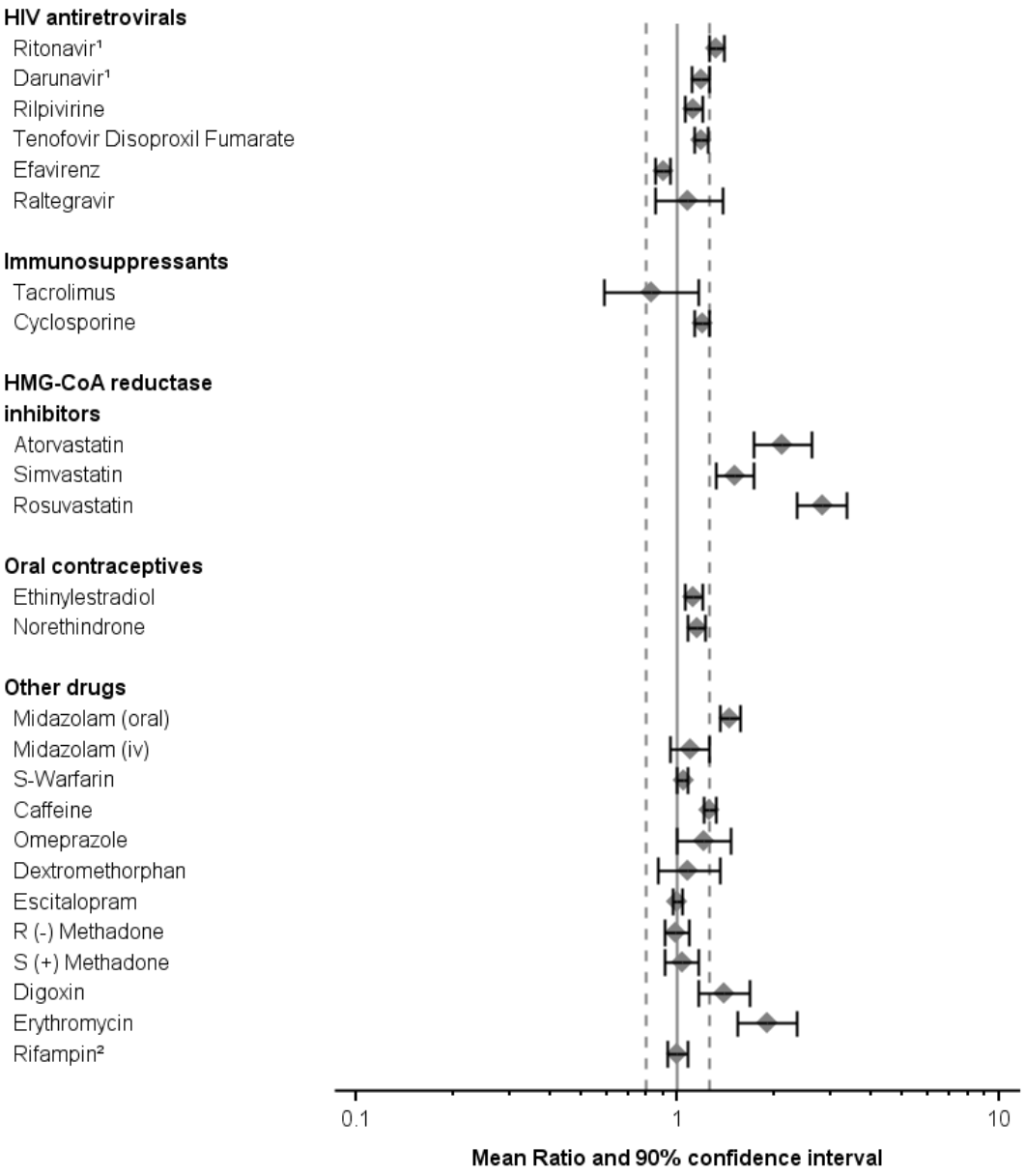
coadministered drugs on SMV exposure is displayed graphically in Figure 5, and the effect of SMV on the exposure of coadministered drugs is displayed graphically in Figure 6. The clinical interactions observed were predictable and could be mechanistically explained on the basis of metabolic or transporter interactions that were also identified in vitro.

Figure 5: Effect of Coadministered Drugs on Exposure of SMV After Administration of SMV at 150 mg Once Daily



rtv: low dose ritonavir. Solid line = no effect; dashed lines = 0.80 to 1.25 bioequivalence limits.
[1] The dose of SMV in the interaction study with ritonavir and rifampin was 200 mg once daily
Source: Data on file, Janssen Research and Development

Figure 6: Effect of SMV Administration at 150 mg Once Daily on Exposure of Coadministered Drugs



HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; iv: intravenous. Solid line = no effect; dashed lines = 0.80 to 1.25 bioequivalence limits.

[1] The dose of SMV in the interaction study with darunavir/ritonavir was 50 mg once daily when coadministered with darunavir/ritonavir and 150 mg once daily when administered alone.

[2] The dose of SMV in the interaction study with ritonavir and rifampin was 200 mg once daily

Source: Data on file, Janssen Research and Development

Simeprevir is mainly metabolized by CYP3A enzymes. Coadministration of SMV with moderate or potent inducers of CYP3A enzymes, such as efavirenz and rifampin, has been shown to decrease SMV plasma concentrations and thereby could potentially reduce its therapeutic effect. Conversely, coadministration of SMV and drugs that are moderate or

potent inhibitors of CYP3A enzymes, such as erythromycin or ritonavir, have been shown to increase SMV plasma concentrations and thereby could potentially increase or prolong its therapeutic and adverse effects. Therefore, coadministration of SMV with substances that are moderate or potent inducers or inhibitors of CYP3A is not recommended.

The clinically relevant impact of SMV on drug metabolizing enzymes is limited to mild inhibition of intestinal (not hepatic) CYP3A and is therefore only considered relevant for drugs with narrow therapeutic index that are solely metabolized via CYP3A. Simeprevir does not induce CYP1A2 or CYP3A. Mild-moderate interactions with the P-gp substrates (eg, digoxin) and OATP substrates (eg, rosuvastatin) have been identified.

The data from drug-drug interaction studies showed that SMV can be administered with several drugs commonly used in patients with HCV infection, such as oral contraceptives, antidepressants, narcotic analgesics, proton pump inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

- **Interactions with HCV drugs**

  The pharmacokinetics of PegIFN and RBV were evaluated in 2 Phase 2 studies (C205 and C206), and plasma concentrations were generally similar in the presence and absence of SMV.

  In addition, potential drug-drug interactions between SMV and sofosbuvir were evaluated as part of a pharmacokinetic substudy in the ongoing Phase 2 study HPC2002. No clinically relevant drug-drug interaction was identified.

- **Interactions with immunosuppressants**

  A drug-drug interaction study in healthy volunteers with the immunosuppressants, cyclosporine and tacrolimus, indicated that these drugs can be coadministered with SMV without *a priori* dose adjustments.

- **Interactions with HIV Antiretrovirals**

  Drug-drug interactions were evaluated between SMV and several HIV antiretrovirals. Simeprevir can be coadministered without dose adjustments with rilpivirine, raltegravir, maraviroc, and all nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs; including tenofovir disoproxil fumarate).

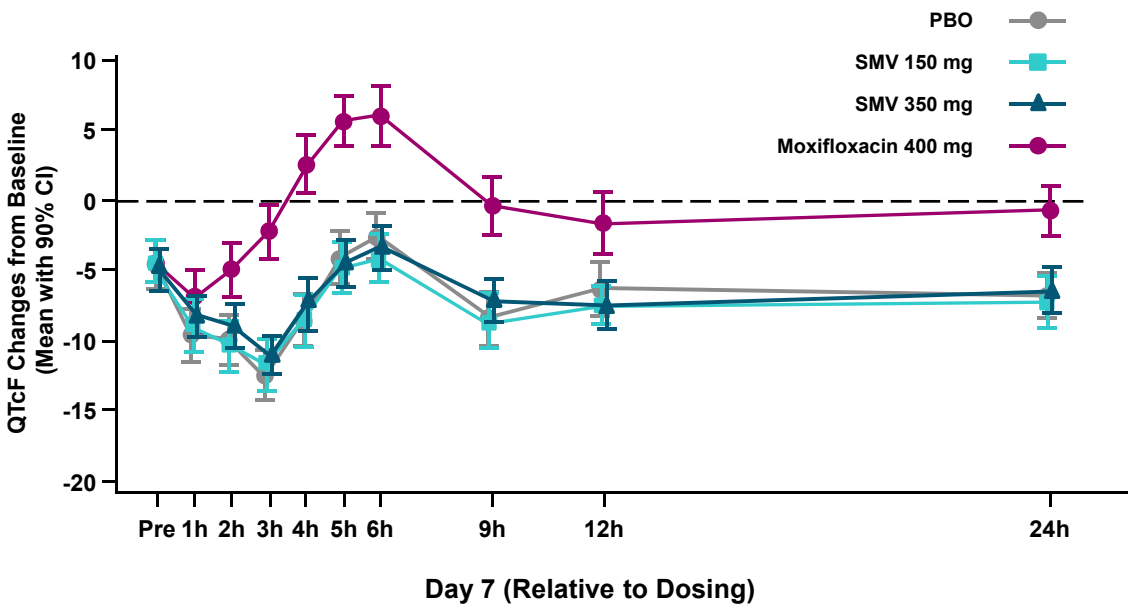
In a drug-drug interaction study, the dose of SMV was lowered to 50 mg in an attempt to enable coadministration with darunavir/ritonavir 800/100 mg once daily. However, decreasing the SMV dose to 50 mg in this combination still resulted in a plasma exposure (AUC) that was 2.6-fold greater than 150 mg once daily SMV administered alone.

It is not recommended to coadminister SMV with ritonavir, boosted or unboosted HIV protease inhibitors, and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine.

4.3 EFFECT OF SIMEPREVIR ON QT INTERVAL

A thorough QT/QT corrected for heart rate (QTc) study in healthy volunteers was performed with SMV at the recommended dose of 150 mg once daily and a supratherapeutic dose of 350 mg once daily (10 times higher exposure compared with 150 mg once daily) for 7 days. Moxifloxacin administered as a single dose of 400 mg was included as a positive control. After administration of SMV at either dose, no relationship was observed between SMV plasma concentrations at steady-state and changes in QTc using Fridericia's formula (QTcF) interval (Figure 7). Study sensitivity was demonstrated with the positive control moxifloxacin, for which the lower limit of the 97.5% CI of the difference between moxifloxacin and PBO in changes from baseline in QTcF was above 5 ms. According to the International Conference on Harmonisation (ICH) E14 guideline[25], the outcome of this thorough QT/QTc study was negative, as the upper limits of all 90% CIs of the time-matched differences in changes from baseline of QTcF between the therapeutic and supratherapeutic dose of SMV and PBO, were below 10 ms.

Figure 7: Mean Changes From Baseline in QTcF on Day 7



Source: Data on file, Janssen Research and Development

In the primary and secondary pooled safety analysis of Phase 2b and 3 studies (for more information on the poolings, refer to Section 5.2.1), mean changes from baseline in electrocardiogram (ECG) parameters were generally small and not considered clinically relevant.

4.4 ASSESSMENT OF PHOTOSENSITIVITY POTENTIAL OF SIMEPREVIR

Simeprevir induced a phototoxic response in BALB/c mouse 3T3 cells exposed to ultraviolet light. Also mild photosensitivity conditions were reported with SMV in early clinical studies. In subsequent studies, patients were therefore recommended to apply sun-protective measures during SMV administration.

A Phase 1 study in healthy volunteers (N=12 per arm) was performed with SMV to further evaluate the cutaneous photosensitizing potential after multiple oral doses of 150 mg. Ciprofloxacin dosed at 500 mg twice daily for 9 days was included as a positive control. In the SMV and PBO groups, mean phototoxicity indices were below the pre-defined limit of 2.0 at all wavebands tested and on a solar simulator covering the clinically relevant spectrum, and were similar between SMV and PBO groups. The mean phototoxicity index in the ciprofloxacin group reached 3.24 and 2.87 at the 335 ± 30 nm and 365 ± 30 nm wavebands, respectively, thus confirming study sensitivity. For SMV, no relationship was observed at any waveband and solar simulator between the phototoxicity index and the AUC_{24h} or C_{max} of

SMV on Day 7, or the SMV plasma concentration at 5 hours postdose on Day 9. For ciprofloxacin, a positive correlation was observed at the 335 ± 30 nm and 365 ± 30 nm wavebands between the phototoxicity index and the AUC_{12h} and C_{max} of ciprofloxacin on Day 7.

As the study concluded that the photosensitizing potential of SMV is similar to PBO, formal recommendations for sun-protective measures were removed from or not included in further SMV study protocols. After analysis of the Phase 3 (C208/C216/HPC3007) studies, in which patients had been dosed with SMV under the formal recommendation for sun-protective measures, photosensitivity conditions were nevertheless identified as adverse reaction of SMV (see Section 5.2.4). Therefore, it was decided to reintroduce the same formal recommendation for sun-protective measures as originally in place in the Phase 3 (C208/C216/HPC3007) studies in SMV studies in which patients are still receiving SMV treatment and planned SMV studies.

For more information on photosensitivity, see Section 5.2.4.2.1.

5 EFFICACY/SAFETY STUDIES SUPPORTING THE CURRENTLY PROPOSED INDICATION

5.1 EFFICACY

5.1.1 Antiviral Activity In Vitro

Simeprevir is a potent and selective inhibitor of the HCV NS3/4A protease which is essential for viral replication. In a biochemical assay, SMV inhibited the proteolytic activity of recombinant genotype 1a and 1b HCV NS3/4A proteases, with median kinetic inhibition constant (Ki) values of 0.5 nM and 1.4 nM, respectively. In addition, in vitro activity of SMV was determined using different cell based replicon assays:

- The median SMV 50% effective concentration (EC_{50}) and EC_{90} values against a HCV genotype 1b replicon were 9.4 nM (7.05 ng/mL) and 19 nM (14.25 ng/mL), respectively. Given the mean minimum plasma concentration (C_{min}) of 150 mg once daily SMV observed in the C205 study (1,579 ng/mL), this results in a C_{min}/EC_{50} and C_{min}/EC_{90} ratio of 224 and 111, respectively.
- The EC_{50} values ranged from 3.7 nM to 25 nM in 3 genotype 1b, and were 23 nM and 28 nM in 2 genotype 1a replicon-containing cells.

- Activity of SMV against a selection of genotype 1a (N=78) and genotype 1b (N=59) chimeric replicons carrying NS3 sequences derived from HCV protease inhibitor-naïve patients resulted in median fold change (FC) in EC_{50} values of 1.4 and 0.4 compared to reference genotype 1b replicon, respectively.
- Genotype 1a (N=33) and 1b (N=2) isolates with a baseline Q80K polymorphism resulted in a median FC in SMV EC_{50} of 11 and 8.4, respectively.
- Median SMV FC values against genotype 2 (N=4), genotype 3 (N=2), and genotype 4 (N=8) baseline isolates tested were 25, 1,014 and 0.3, respectively.
- The presence of 50% human serum reduced SMV replicon activity by 2.4-fold.
- Combination of SMV with interferon, RBV, NS5A or NS5B inhibitors was not antagonistic.

5.1.2 Efficacy in Clinical Studies: HCV Genotype 1 Patient Population

Antiviral activity and clinical efficacy of SMV + PR in HCV-infected patients has been studied in 12 clinical studies (one Phase 1 study, four Phase 2 studies and seven Phase 3 studies). Clinical data described in this efficacy section focusses on two Phase 3 studies in treatment-naïve patients (C208 and C216), one Phase 3 study in prior relapsers (HPC3007), and one Phase 2b study in prior relapsers and prior nonresponders (C206). These studies were conducted globally and all of these studies are double-blinded and PBO-controlled. In agreement with Health Authorities and since neither TVR or BOC were approved at the time the studies were initiated, PBO + PR was used as a control.

In study C206, patients were equally assigned to the different treatment groups. The study was stratified for HCV genotype 1 subtype (1a, 1b, or other) and response to prior PR therapy (null response, partial response, or relapse). The primary efficacy endpoint was SVR24.

In the Phase 3 studies a randomization of 2:1 for SMV:PBO was used and studies were stratified for HCV genotype 1 subtype (1a, 1b, or other), *IL28B* genotype (CC, CT, or TT) and PegIFNα-2a/RBV or PegIFNα-2b/RBV for selected countries (C216 only). In agreement with Health Authorities, the primary endpoint was modified to SVR12 in the Phase 3 studies.

The primary objective of the study C206 and the Phase 3 studies C208, C216 and HPC3007 was to demonstrate superiority of SMV + PR over PBO + PR for SVR12/24. A key secondary objective in Phase 3 treatment-naïve (C208 and C216) and prior relapser

(HPC3007) studies included the proportion of patients able to shorten total treatment duration to 24 weeks (response-guided treatment; HCV RNA levels <25 IU/mL detectable or undetectable at Week 4 and undetectable HCV RNA at Week 12 were required to shorten treatment to 24 weeks).

Treatment stopping rules were in place in each of the studies to avoid continuation of a failing regimen with the objective of limiting the risk of developing drug resistance to SMV and reducing unnecessary exposure to PR if patients had no or extremely low chance of treatment success (Table 1 in Section 3).

In most clinical studies, SMV was evaluated in combination with PegIFNα-2a/RBV (Pegasys® and Copegus®[5]). In the Phase 3 study C216, treatment-naïve patients from selected countries were randomly assigned in a 1:1 fashion to SMV in combination PegIFNα-2a/RBV (PegIntron® and Rebetol®[5]) or with PegIFNα-2b/RBV (Pegasys® and Copegus®[5]), leading to approximately 30% of the overall population randomized to a PegIFNα-2b-containing regimen.

An overview of the study design of the key efficacy studies is provided in Appendix 1.

5.1.2.1 TREATMENT-NAÏVE PATIENT POPULATION (C208 AND C216)

An overview of the most important baseline characteristics of the patient population included in these studies is provided in Table 4.

[5] Note: these are trademarks of other companies

Table 4: Key Demographic and Baseline Disease Characteristics – C208 and C216				
	C208		C216	
	SMV + PR N=264 %	PBO + PR N=136 %	SMV + PR N=257 %	PBO + PR N=134 %
Gender (Female)	44	43	46	43
Race				
Caucasian	87	94	92	92
Black or African American	10	3	6	7
Ethnicity (Hispanic or Latino)	13	11	23	19
Age (years), Median	48	48	46	47
Baseline Q80K Polymorphism				
Geno/subtype 1a/other	56	57	41	40
With Q80K*	41	41	23	26
Without Q80K*	59	59	77	74
Geno/subtype 1b	44**	43	58**	58
IL28B Genotype				
CC	29	28	29	31
CT	57	58	55	53
TT	14	13	16	16
METAVIR fibrosis score				
Score F0-F2	70	69	79	76
Score F3 (bridging fibrosis)	18	18	15	13
Score F4 (cirrhosis)	12	13	7	11

* Denominator: genotype 1a patients with sequencing information
** One genotype 1b HCV-infected patients had a Q80K polymorphism at baseline
Source: Data on file, Janssen Research and Development

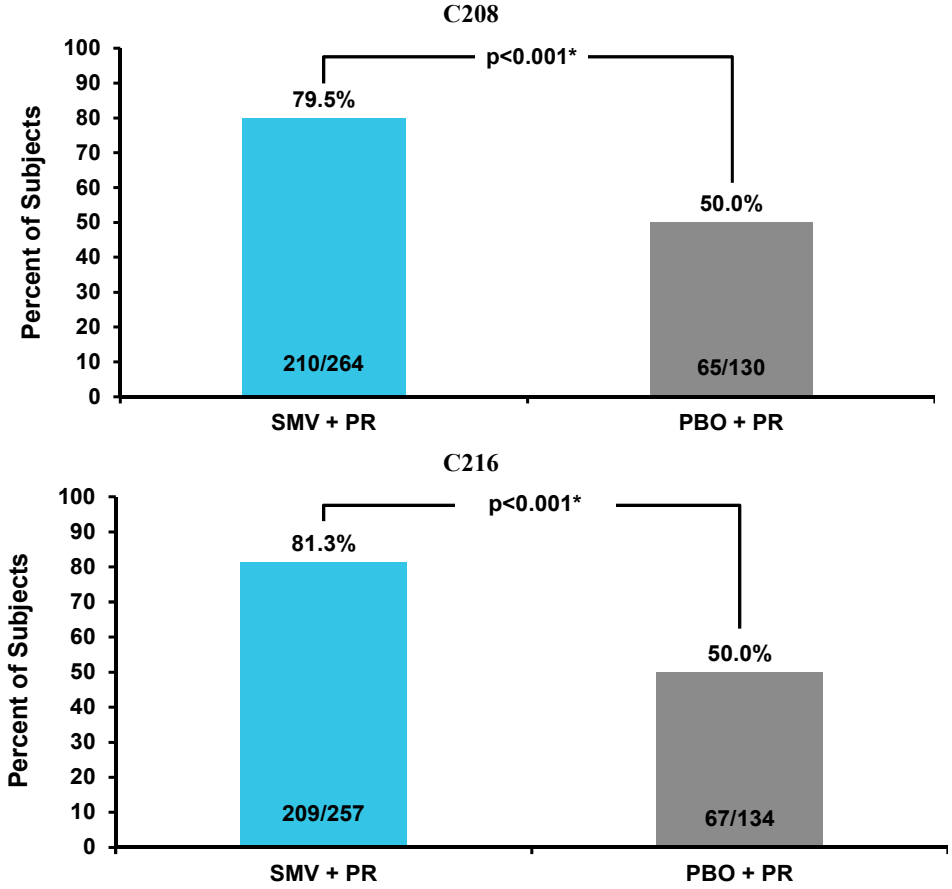
In C208 and C216, 87.5% and 96.1% completed SMV treatment, respectively and 87.1% and 93.8% of the patients respectively were >97% adherent[6] to dosing of SMV.

Following the administration of SMV 150 mg once daily for 12 weeks in combination with PR for 24 or 48 weeks in studies C208/C216 in treatment-naïve patients:

- Simeprevir + PR treatment was statistically significantly superior to PBO + PR (p-value<0.001 for both C208 and C216). Overall SVR12 rates were achieved in 79.5% of the patients in the SMV group in study C208 and 81.3% in study C216, ie, an added benefit over PBO of approximately 30% (SVR12 in PBO + PR group: 50%; see also Figure 8). The high SVR12 rates in the SMV group were maintained through 24 weeks of follow-up (SVR24).

[6] Treatment adherence to SMV was derived from the collected pill count information. Percentage treatment adherence to SMV was calculated as the total dose actually taken (ie, actual dose over actual treatment duration) versus the planned dose (ie, planned dose over the planned treatment duration, ie, 1 capsule a day for 12 weeks).

Figure 8: Proportion of Patients Achieving SVR12 – C208/C216



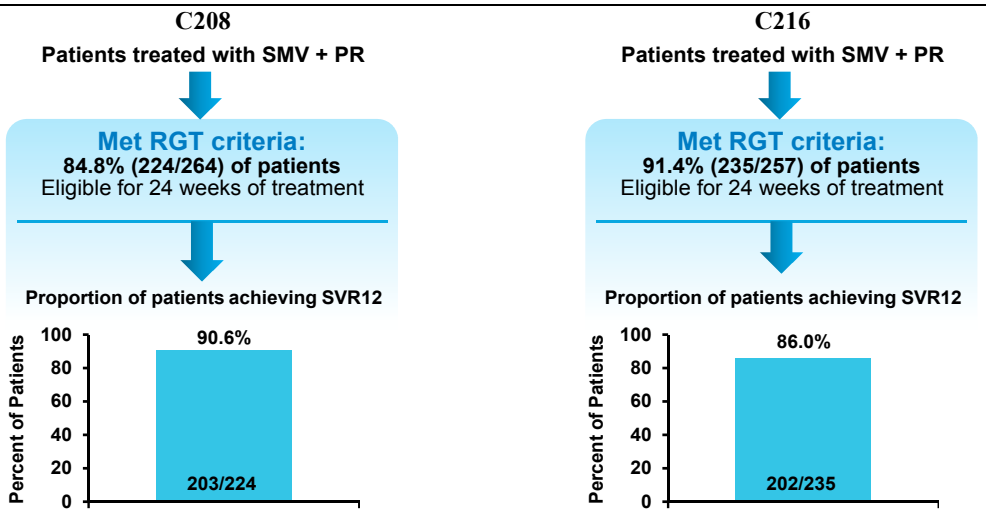
PR: PegIFNα-2a or 2b (C216 only) + RBV; SVR12: sustained virologic response 12 weeks after planned treatment end

* Statistically significant difference between SMV and PBO group

Source: Data on file, Janssen Research and Development

- The proportion of patients in the SMV groups meeting the protocol-defined response-guided treatment criteria, and were thus eligible to shorten the total treatment duration from 48 to 24 weeks, was 84.8% and 91.4% in C208 and C216, respectively. Of the patients in the SMV group who met the protocol-defined response-guided treatment criteria and who accordingly were treated for 24 weeks, 90.6% and 86.0% achieved SVR12, respectively (see also Figure 9).

Figure 9: Response-guided Treatment Duration and Sustained Virologic Response (SVR12) – C208 and C216



PR: PegIFNα-2a or 2b (C216 only) + RBV; RGT: response-guided treatment
Source: Data on file, Janssen Research and Development

- The overall observed on-treatment failure rate was lower in the SMV groups compared to the PBO groups (C208: 9.1% versus 33.8% and C216: 7.0% versus 32.1%).

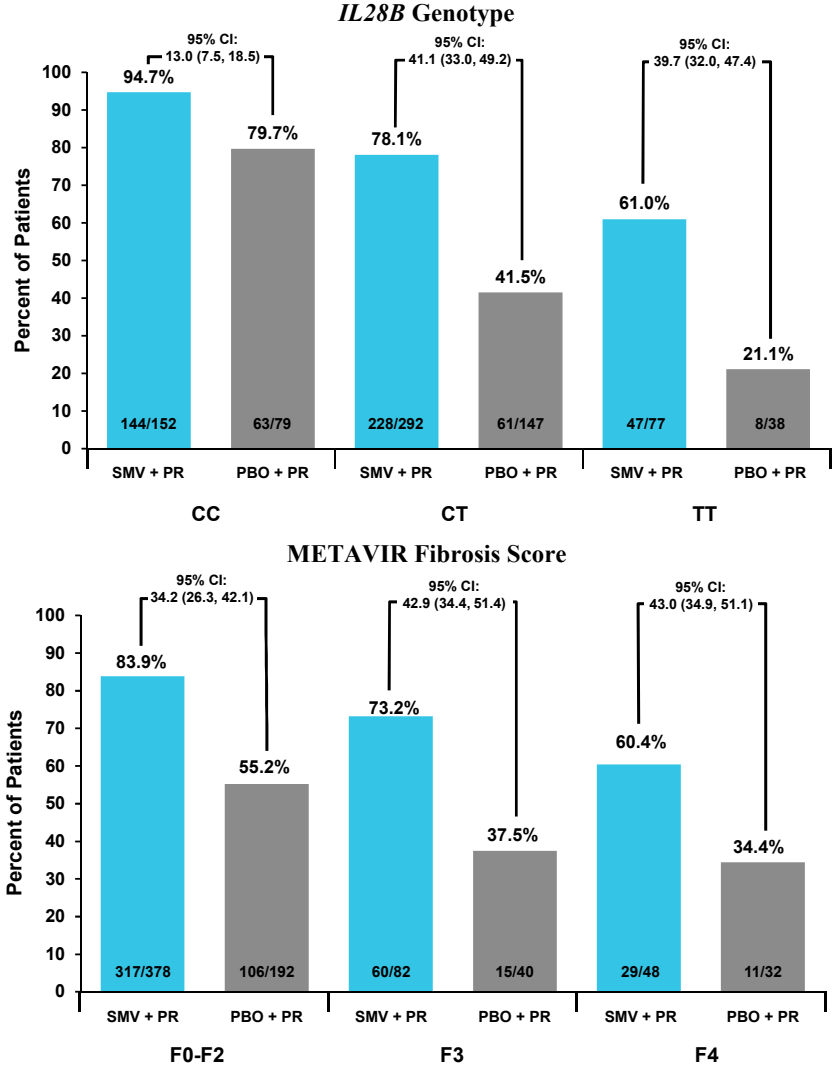
- The overall proportion of patients with viral relapse was lower in the SMV groups than in the PBO groups (C208: 8.0% versus 13.8% and C216:11.7% versus 15.7%). For mutations associated with failure, see Section 5.1.3.2.

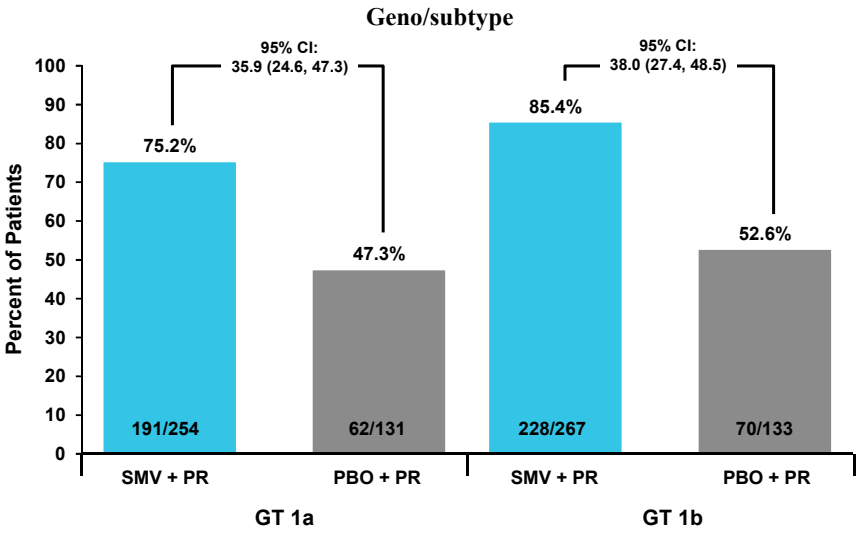
The pooled C208 and C216 data were considered for subgroup analyses to increase sample size and allow for a more meaningful comparison. The overall SVR rate in the pooled C208/C216 analysis was 80.4% in the SMV + PR group compared to 50.0% in the PBO + PR group (difference in proportion [95% CI]: 30.5 [24.1; 36.9]). For each of the subgroups tested, except for presence of genotype 1a Q80K polymorphism, differences in SVR12 rates were statistically significant in favor of SMV + PR, including key subgroups such as but not limited to METAVIR fibrosis score, *IL28B* genotype and HCV genotype subtype, ie, factors known to impact outcome with PR alone (Figure 10 and Figure 33 in Appendix 2).

An additional factor found to have an effect on treatment outcome of SMV + PR, but not with PR alone, was the presence of a genotype 1a NS3 Q80K polymorphism at baseline. A K (lysine) amino acid substitution at amino acid position 80 of NS3, almost exclusively found in genotype 1a, reduces the in vitro activity of SMV, albeit modestly (see Section 5.1.3.1). The presence of a Q80K polymorphism at baseline reduced the SVR rate

considerably in the HCV genotype 1a infected subpopulation compared to patients without this polymorphism (Figure 10). Sustained virologic response rates in SMV-treated genotype 1a patients without Q80K was similar as in genotype 1b patients. The magnitude of the impact of baseline Q80K on SVR12 rates was greater in study C208 compared to C216. In study C208 there was no benefit of SMV treatment over PBO in HCV genotype 1a infected patients with baseline Q80K whereas in study C216 and pooled C208/C216 analysis there was a numerically higher SVR12 rate in SMV + PR treated patients compared to PBO + PR treated patients (Figure 10). The lower SVR12 rate in C208 compared to C216 in SMV-treated genotype 1a patients with Q80K could potentially be explained by a difference in the presence of this polymorphism in combination with other baseline factors known to influence response.

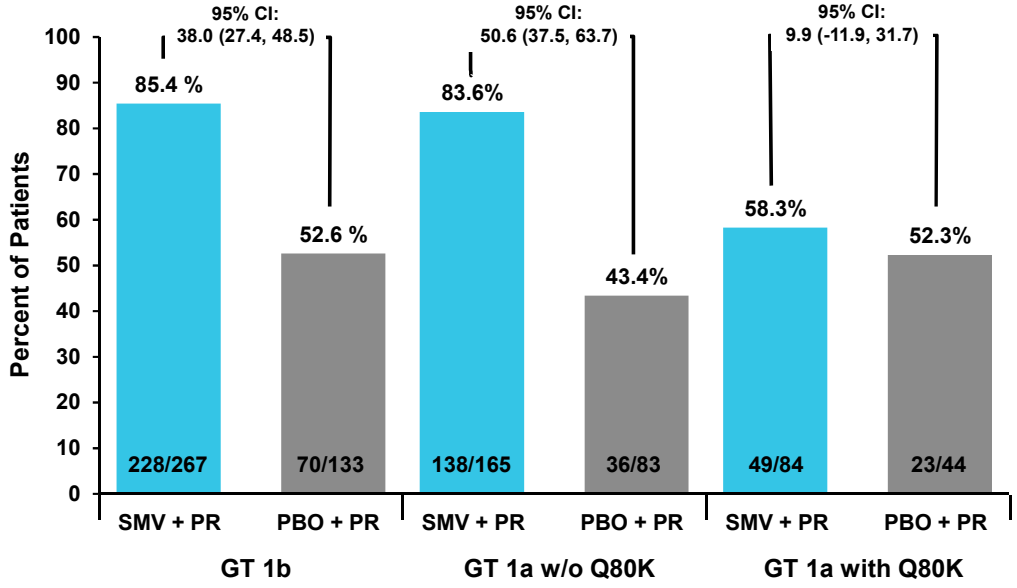
Figure 10: Proportion of Patients With SVR12 by *IL28B* Genotype, HCV Geno/Subtype, METAVIR Fibrosis Score and Baseline Q80K Polymorphism – Pooled C208/C216



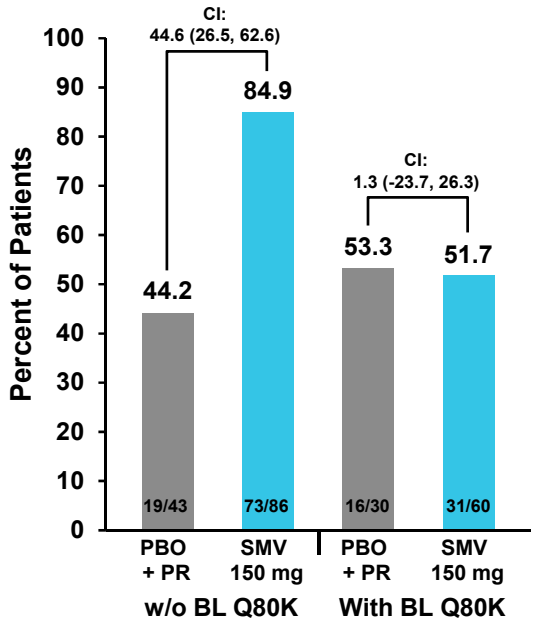


Baseline Q80K Polymorphism

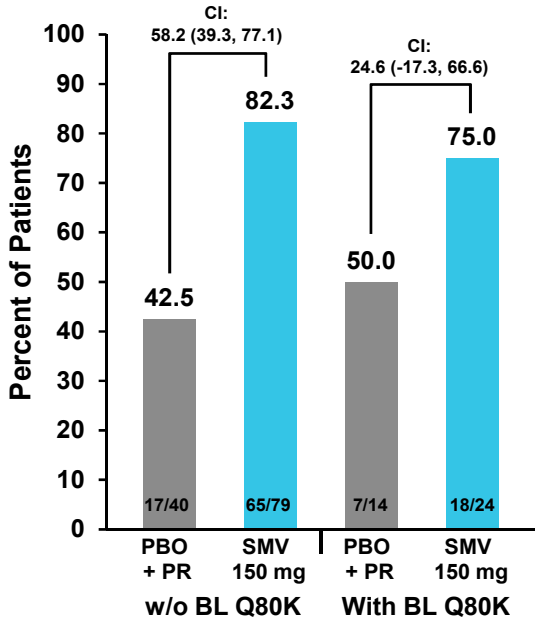
A) Pooled C208/C216



B) C208



C) C216



GT: genotype
The point estimate difference and 95% CI is from logistic regression modelling with stratification factors and type of PegIFN (C216 only) as factors
Source: Data on file, Janssen Research and Development

In study C216, in total, 31.2% of the patients were randomized to receive PegIFNα-2a/RBV and 31.5% to receive PegIFNα-2b/RBV and 37.3% were not randomized and received PegIFNα-2a/RBV. Data demonstrated that SMV + PegIFNα-2a/RBV and SMV + PegIFNα-2b/RBV resulted in statistically significantly higher SVR12 rates compared to PBO + PegIFNα-2a/RBV and PBO + PegIFNα-2b/RBV, respectively, supporting the use of SMV with either type of interferon. SVR12 rates were:

- 88.3% (68/77) with SMV and 62.2% (28/45) with PBO in patients randomized to receive PegIFNα-2a/RBV (p<0.001),
- 77.5% (62/80) with SMV and 41.9% (18/43) with PBO in patients randomized to receive PegIFNα-2b/RBV (p<0.001),
- 79.0% (79/100) with SMV and 45.7% (21/46) with PBO in patients not randomized and thus receiving PegIFNα-2a/RBV (p<0.001).

5.1.2.2 PRIOR RELAPSER PATIENT POPULATION (HPC3007)

An overview of the most important baseline characteristics is provided in Table 5

Table 5: Key Demographic and Baseline Disease Characteristics – HPC3007

	SMV + PR N=264 %	PBO + PR N=136 %
Gender (Female)	31	41
Race		
Caucasian	94	96
Black or African American	3	3
Ethnicity (Hispanic or Latino)	8	5
Age (years), Median	52	52
Baseline Q80K Polymorphism		
Geno/subtype 1a/other	42	41
With Q80K	28	37
Without Q80K	73	63
Geno/subtype 1b	57 [b]	59
IL28B Genotype		
CC	24	26
CT	64	62
TT	12	12
METAVIR fibrosis score[a]		
Score F0-F2	67	74
Score F3	18	11
Score F4	16	14

[a] All but 11 patients had a METAVIR fibrosis score available at baseline
[b] One genotype 1b HCV-infected patients had a Q80K polymorphism at baseline
Source: Data on file, Janssen Research and Development

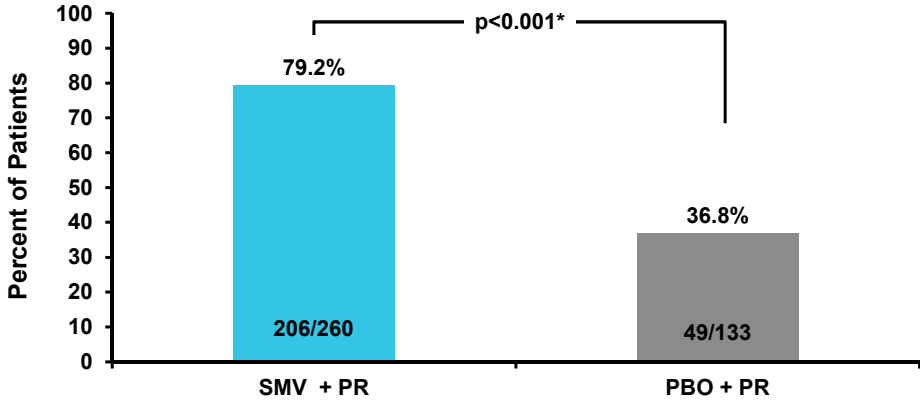
In total, 96.5% completed SMV treatment and 95.8% of the patients was ≥97% adherent[7] to dosing of SMV.

Following the administration of SMV 150 mg once daily for 12 weeks in combination with PR for 24 or 48 weeks in HPC3007:

- Simeprevir + PR treatment was statistically significantly superior to PBO + PR (*p*-value <0.001). The SVR12 rate achieved in the SMV + PR group was 79.2%, an added benefit over PBO + PR of >40% (SVR12 in PBO + PR group: 36.8%; Figure 11). The high SVR12 rates in the SMV group were maintained through 24 weeks of follow-up (SVR24).

[7] Treatment adherence to SMV was derived from the collected pill count information. Percentage treatment adherence to SMV was calculated as the total dose actually taken (ie, actual dose over actual treatment duration) versus the planned dose (ie, planned dose over the planned treatment duration, ie, 1 capsule a day for 12 weeks) and, therefore, took into account dose interruptions.

Figure 11: Proportion of Patients Achieving SVR12 – HPC3007

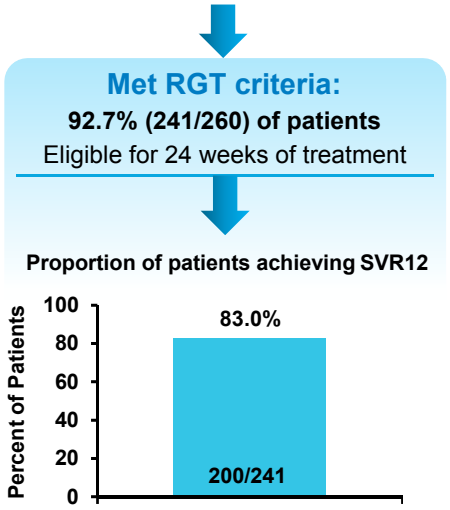


* Controlling for stratification factors
Source: Data on file, Janssen Research and Development

- The proportion of patients in the SMV group meeting the protocol-defined response-guided treatment criteria, were thus eligible to shorten the total treatment duration from 48 to 24 weeks, was 92.7%. Of the patients in the SMV group who met the protocol-defined response-guided treatment criteria who accordingly were treated for 24 weeks, 83.0% achieved SVR12 (Figure 12).

- The SVR rates and the proportion of patients meeting the protocol defined response-guided treatment criteria in the SMV-treated prior relapser patients in HPC3007 were comparable to those in the C208 and C216 studies with treatment-naïve patients.

Figure 12: Response-guided Treatment Duration and Sustained Virologic Response (SVR12) – HPC3007

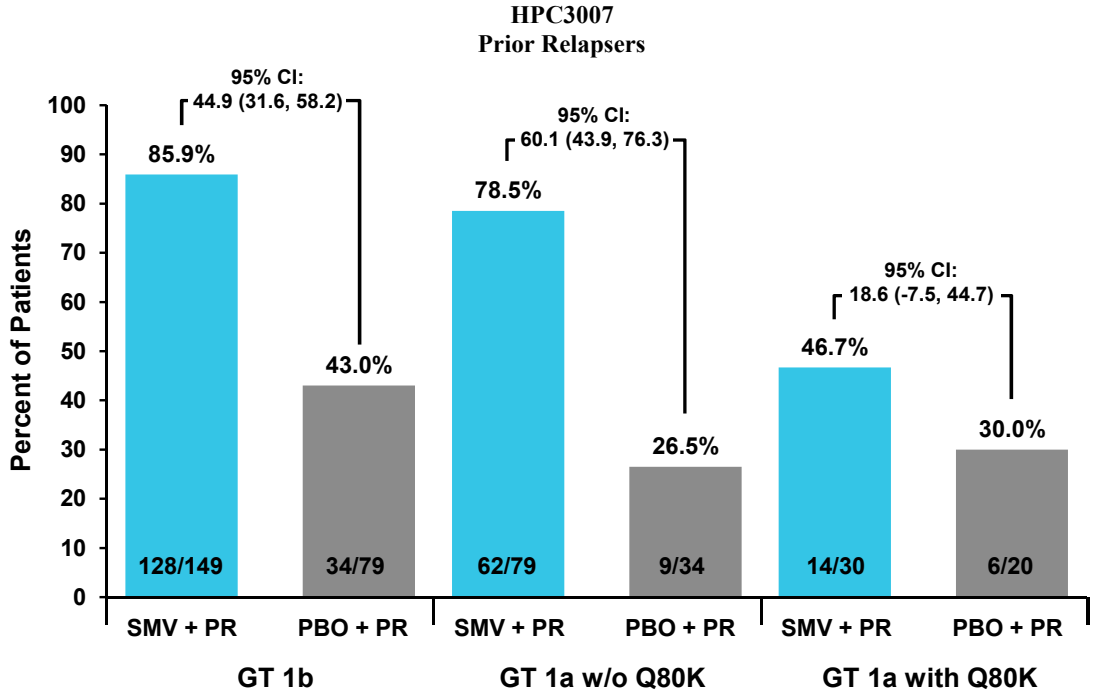


RGT: response-guided therapy
Source: Data on file, Janssen Research and Development

- The observed on-treatment failure was lower in the SMV + PR group compared to the PBO + PR group (3.1% versus 27.1%).
- The proportion of patients with viral relapse was lower in the SMV + PR group than in the PBO + PR group (17.7% versus 33.8%).

Subgroup analyses, including but not limited to SVR12 by *IL28B* genotype, METAVIR fibrosis score, HCV genotype subtype and baseline Q80K polymorphism were performed. The difference in proportion of SVR12 between the SMV + PR and PBO + PR group was statistically significant for all of the tested subgroups (Figure 34 in Appendix 2), except for HCV genotype 1a infected patients with baseline Q80K polymorphism (Figure 13). A numerically, but not statistically significant, higher SVR12 rate was observed in the HCV genotype 1a infected patients with baseline Q80K polymorphism treated with SMV + PR compared to PBO + PR.

Figure 13: Proportion of HCV Genotype 1a Patients With SVR12 by Q80K –HPC3007



GT: genotype
The point estimate difference and 95% CI is from logistic regression modelling.
Source: Data on file, Janssen Research and Development

Data from the HPC3007 study were in line with the data from the prior relapse population from the Phase 2b study C206, where prior relapser patients were treated for a total of 48 weeks.

5.1.2.3 PRIOR NONRESPONDER PATIENT POPULATION (C206, C213)

Study C206

In study C206 including 462 patients, 117 (25.3%) patients were classified as null responder, 160 (34.6%) as partial responder and 185 (40.0%) as relapser to prior PR therapy. Patients were treated with SMV 100 mg or 150 mg (or PBO) for 12, 24 or 48 weeks in combination with PR for 48 weeks.

An overview of the SVR24 rates for each of the treatment groups overall and by subpopulation is provided in Table 6. Although, SVR rates in the SMV 100 mg treatment groups were generally lower compared to the 150 mg groups, SVR rates were statistically significantly higher compared to PBO in all SMV groups ($p<0.001$).

Table 6: SVR24: All Patients – C206

n/N (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66
Overall Population	46/66 (69.7)	43/65 (66.2)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
Relapser	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
Partial Responder	16/23 (69.6)	11/23 (47.8)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
Null Responder	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)

Data in the section below are for the pooled SMV duration groups. It was considered appropriate to pool the data for the SMV treatment duration groups by dose given:

- the observed lack of consistent trends in SVR24 rates across SMV treatment duration groups (Table 6),
- that there was no relevant difference in the frequency of viral breakthrough across SMV treatment durations (Table 17 in Appendix 2),
- the absence of higher viral relapse rate in the SMV 12-week treatment duration groups compared with the groups in which SMV was dosed for longer periods (Table 18 in Appendix 2).

Hereafter, focus of the data is on the prior null and partial responders since data for prior relapsers are available from the Phase 3 HPC3007 study (Section 5.1.2.2). In total, 50 and 51

prior null responders and 68 and 69 prior partial responders were treated with SMV 100 mg and 150 mg, respectively, in study C206.

An overview of the most important baseline characteristics in prior nonresponders for both the SMV 100 mg and 150 mg dose group is provided in Table 7

Table 7: Key Demographic and Baseline Disease Characteristics – C206 Prior Null and Partial Responders

	SMV 100 mg* + PR48	SMV 150 mg* + PR48
Analysis Set: Intent-to-treat	118	120
Gender (Female)	34	33
Race		
Caucasian	91	93
Black or African American	6	7
Ethnicity (Hispanic or Latino)	3	4
Age (years), Median	50	51
Baseline Q80K Polymorphism		
Geno/subtype 1a/other	40	43
With Q80K	35	25
Without Q80K	65	75
Geno/subtype 1b	58	56
IL28B Genotype†	N=80	N=84
CC	10	10
CT	69	65
TT	21	25
METAVIR fibrosis score	N=117	N=119
Score F3	21	15
Score F4	21	20

*Dose groups combined
†*IL28B*, polymorphism on chromosome 19 s12979860 data available for patients who consented to DNA research only
Source: Data on file, Janssen Research and Development

Sustained virologic response 24 weeks after planned end of treatment was significantly higher in both the pooled 100 mg dose group and the pooled SMV 150 mg dose group compared with the PBO group in prior null responders and prior partial responders as well as in the relapser population. The SMV 150 mg dose resulted in higher SVR rates compared to the 100 mg dose group in prior null and partial responders as well as in some subgroups with less favorable baseline characteristics such as patients with advanced fibrosis.

Pooled data for the 150 mg dose (all durations) focusing on the prior null and partial responder patients are provided below.

In **prior null responders**:

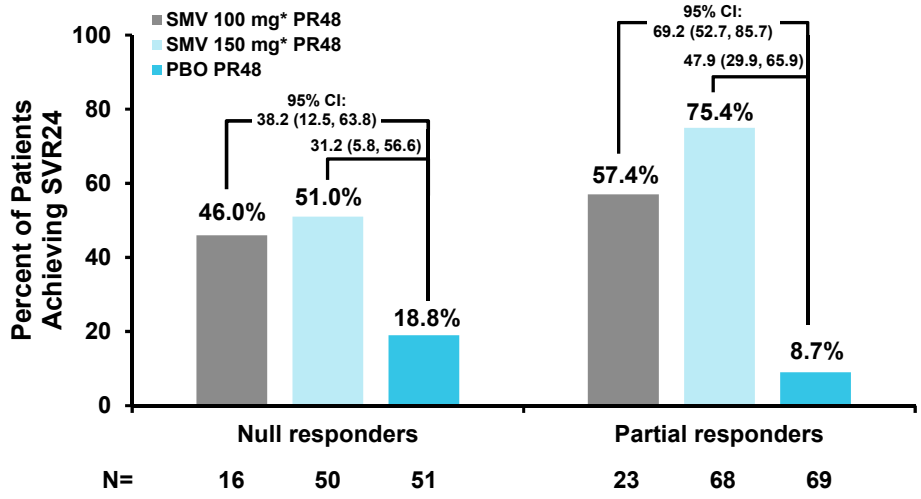
- the SVR24 rate was statistically significantly higher in the SMV 150 mg dose group (51.0%) compared to the PBO group (18.8%; Figure 14).

- on-treatment failure was observed in 29.4% of the patients in the SMV 150 mg dose group and 75.0% of the patients in the PBO group.
- viral relapse occurred in 15.7% of the patients in the SMV 150 mg dose group and 6.3% of the patients in the PBO group.

In **prior partial responders**:

- the SVR24 rate was statistically significantly higher in the SMV 150 mg dose group (75.4%) compared to the PBO group (8.7%, Figure 14).
- on-treatment failure was observed in 15.9% of the patients in the SMV 150 mg dose group and 78.3% of the patients in the PBO group.
- viral relapse occurred in 2.9% of the patients in the SMV 150 mg dose group and 8.7% of the patients in the PBO group.

Figure 14: Proportion of Patients Achieving SVR24 – C206



* pooled SMV treatment duration
The point estimate difference and 95% CI is from logistic regression modelling.
Source: Data on file, Janssen Research and Development

Subgroup analyses, including but not limited to SVR24 by *IL28B* genotype, METAVIR fibrosis score, HCV genotype subtype and baseline Q80K polymorphism were performed. SVR24 rates by HCV genotype subtype, *IL28B* genotype and METAVIR fibrosis score are provided in Table 8 and subgroup analysis by baseline Q80K status is provided in Figure 15.

Higher SVR rates were observed in the SMV 150 mg dose group compared to PBO for each of these subgroups. In study C206, the impact of baseline Q80K on SVR was limited. A

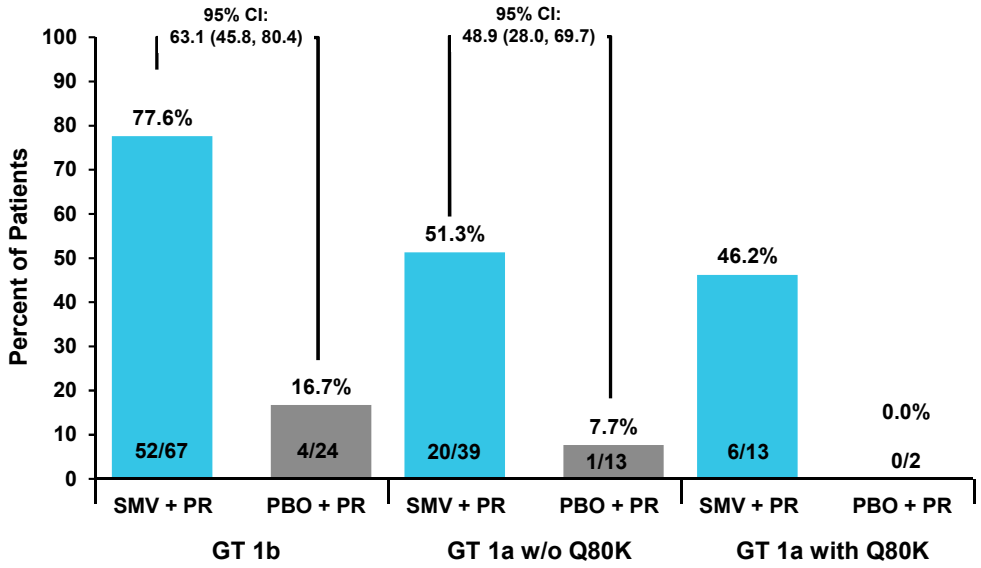
graphical presentation of all performed subgroup analyses is provided in Figure 35 in Appendix 2.

Table 8: Subgroup Analysis – SVR24 by HCV Geno/subtype, *IL28B* Genotype and METAVIR Fibrosis Score: Null and Partial Responders – C206

	Null responders		Partial responders	
	SMV12 150 mg + PR248 N=11	PBO + PR48 N=10	SMV12 + 150 mg PR248 N=13	PBO + PR48 N=17
HCV Geno/subtype				
1a	11/26 (42.3%)	0/7	14/25 (56.0%)	1/8 (12.5%)
1b	14/24 (58.3%)	3/9 (33.3%)	38/43 (88.4%)	1/15 (6.7%)
METAVIR fibrosis score				
F0-F2	19/29 (65.5%)	3/13 (23.1%)	38/48 (79.2%)	1/12 (8.3%)
F3-F4	7/21 (33.3%)	0/3	14/21 (66.7%)	1/10 (10.0%)
F4	4/13 (30.8%)	0/2	9/11 (81.8%)	0/2
IL28B genotype				
CC	1/3 (33.3%)	0/0	5/5 (100.0%)	0/1
CT	12/22 (54.5%)	2/7 (28.6%)	26/33 (78.8%)	1/13 (7.7%)
TT	5/12 (41.7%)	1/3 (33.3%)	7/9 (77.8%)	0/3

Source: Data on file, Janssen Research and Development

Figure 15: Proportion of HCV Genotype 1a Nonresponder Patients With SVR24 Treated with SMV 150 mg Once Daily in Combination with PR by Q80K – C206



GT: genotype

The point estimate difference and 95% CI is from logistic regression modelling. GT 1a with Q80K analysis not available due to the small number of patients
Source: Data on file, Janssen Research and Development

Additional data on nonresponder patients

Preliminary data for prior PR nonresponders are available from study C213: an ongoing, multicenter, open-label, uncontrolled rollover study in which prior nonresponders receive

SMV 150 mg once daily administered for 12 weeks in combination with PR for 48 weeks. The study design is presented in Figure 31 in Appendix 1.

Preliminary results of C213 showed that, overall, of the 10 prior null responders and 5 partial responders with on-treatment data at Week 4, 50.0% and 40.0%, respectively, had rapid virologic response (RVR, ie, HCV RNA <25 IU/mL undetectable at Week 4) and 60.0% and 80.0% had HCV RNA <25 IU/mL at Week 4.

Preliminary results of C213, including the proportion of patients with RVR are in line with the observations in C206.

Taken together, at time of the NDA, a total of 137 HCV genotype 1 infected prior nonresponders (63 prior null-responders and 74 prior partial responders) received SMV at the recommended dose in the completed Phase 2b study C206 and the ongoing Phase 3 study C213. Of those patients, 58 null-responders and 72 partial responders had on-treatment Week 12 data available and 51 and 69 patients had SVR12 data available. Similar efficacy is observed across the two studies indicating a benefit of SMV + PR treatment over PR treatment.

5.1.3 Virology (In Vitro and In Vivo)

5.1.3.1 Resistance - In Vitro

Resistance to SMV was characterized in HCV genotype 1a and 1b replicon-containing cells. Ninety-six percent of SMV-selected genotype 1 replicons carried one or multiple amino acid substitutions at NS3 protease positions 43, 80, 155, 156, and/or 168, with substitutions at NS3 position D168 being most frequently observed (78%). Additionally, resistance to SMV was evaluated in HCV genotype 1a and 1b replicon assays using site-directed mutants and chimeric replicons carrying NS3 sequences derived from clinical isolates. Amino acid substitutions at NS3 positions 43, 80, 122, 155, 156, and 168 reduced SMV activity. Substitutions such as D168V or A, and R155K, were usually associated with SMV treatment failure, and displayed high level resistance to SMV (FC in EC_{50} >50), whereas other substitutions such as Q80K or R, S122R, and D168E displayed low level resistance (FC in EC_{50} between 2 and 50). Other substitutions such as Q80G or L, S122G, N or T did not reduce SMV activity (FC in EC_{50} ≤2). Amino acid substitutions at NS3 positions 80, 122, 155, and/or 168, associated with low level resistance to SMV when occurring alone, generally reduced SMV activity by more than 50-fold when present in combination.

5.1.3.2 CLINICAL VIROLOGY/RESISTANCE IN CLINICAL STUDIES

Clinical virology analyses were performed in SMV clinical studies to i) assess the prevalence and the impact of naturally occurring NS3 baseline polymorphisms on treatment outcome with a SMV + PR regimen and ii) to characterize emerging mutations in patients not achieving SVR. These analyses were performed in each individual study. In addition, emerging mutations were characterized in all patients not achieving SVR with 150 mg once daily of SMV + PR in Phase 2b/3 studies (C205, C206, C208, C216 and HPC3007; N=197 patients without SVR and sequence data available). Prevalence of naturally occurring NS3 baseline polymorphisms was determined using baseline samples from all genotype 1 infected patients participating in the Phase 2b/3 studies (C205, C206, C208, C216 and HPC3007; N=2007 with sequence data).

The focus of the data described in this section is on 6 NS3 amino acid positions: F43, Q80, S122, R155, A156, and D168. Specific amino acid changes at 1 or more of these positions are either known to confer reduced susceptibility to SMV in vitro or to have emerged during in vitro selection experiments. Sequencing data presented here are based on population-based sequencing technology.

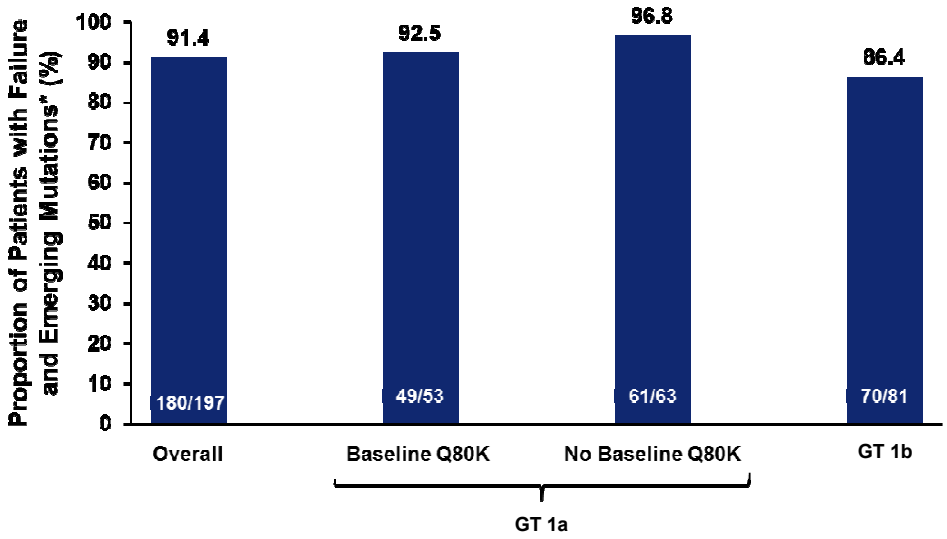
BASELINE POLYMORPHISMS

Naturally occurring baseline polymorphisms at NS3 positions 43, 80, 122, 155, 156, and/or 168, associated with reduced SMV activity in vitro (FC>2) were generally uncommon (1.3%) in patients with HCV genotype 1 infection in the Phase 2b/3 studies (N=2007), with the exception of those carrying the low-level resistance Q80K polymorphism. The observed prevalence of Q80K polymorphism at baseline in the population of the Phase 2b/3 studies was 13.7% (274/2007); 29.5% (269/911) in patients with HCV genotype 1a and 0.5% (5/1096) in patients with HCV genotype 1b. The prevalence of Q80K differed by region (Table 19 in Appendix 3). The overall prevalence in the SMV Phase 2b/3 studies of Q80K in the US was 34.8% and 48.0% in genotype 1a patients. Baseline HCV genotype 1a (N=33) clinical isolates with a Q80K polymorphism exhibited a median fold change in SMV EC_{50} (11 in genotype 1a). Of note, substantial antiviral effect was demonstrated with SMV 75 mg or higher doses in patients with Q80K during short term monotherapy in Phase 1 and Phase 2a studies. No other polymorphisms were identified which impacted the response to SMV + PR treatment.

EMERGING MUTATIONS IN PATIENTS NOT ACHIEVING SUSTAINED VIROLOGIC RESPONSE

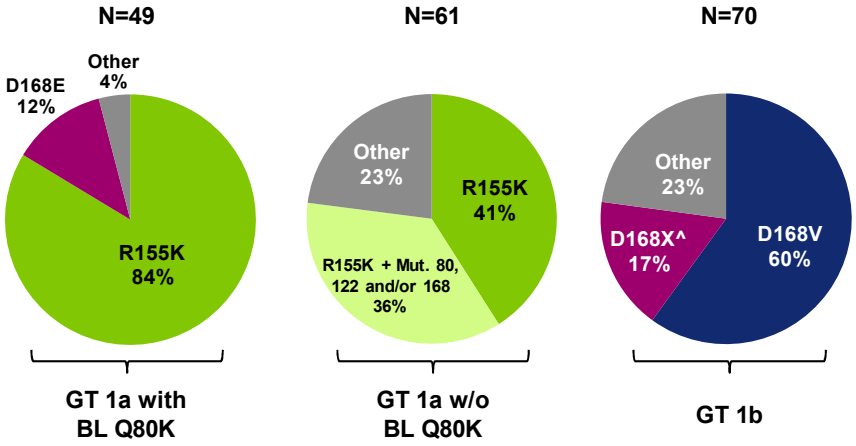
In total, 245 of 1136 (21.6%) treatment-naïve and experienced patients (including prior null and partial responders) treated with 150 mg SMV + PR in the Phase 2b/3 studies (C205, C206, C208, C216 and HPC3007) did not achieve SVR. Out of these 245 treatment failures, 197 patients had sequencing data available. In most SMV-treated patients who did not achieve SVR and had sequencing information available, emerging mutations were detected at one or more of the NS3 positions 80, 122, 155, and/or 168 at time of failure (91.4% overall, 94.8% HCV genotype 1a and 86.4% genotype 1b infected patients; Figure 16). In addition, 2 patients with a Q80K baseline polymorphism had a single emerging I170T mutation at time of failure. Similar mutations were observed in patients with on-treatment failure and in patients with viral relapse. The mutations observed in these patients were consistent with the mutations identified in vitro and generally conferred high level resistance to SMV (FC>50). Differences in type of mutations were observed between HCV genotype 1a and 1b infected patients. In genotype 1a HCV-infected patients without Q80K at baseline, the most frequently emerging mutations were R155K alone or in combination with other mutations at position 80, 122, and/or 168. In genotype 1a patients with Q80K at baseline a single R155K emerged most frequently. Treatment failure in genotype 1b was mostly associated with emerging D168V mutations or other mutations at position 168 (Figure 17).

Figure 16: Proportion of Patients not Achieving SVR With Emerging Mutations – Pooled C205/C206/C208/C216/HPC3007



* Considering mutations at NS3 positions 43, 80, 122, 155, 156 and 168. Pooled analyses from Phase 2b/3 studies. SMV + PR treated patients receiving SMV 150 mg once daily.
Source: Data on file; Janssen Research and Development

Figure 17: Type and Frequency of Emerging Mutations in Patients Not Achieving SVR by Subtype – Pooled C205/C206/C208/C216/HPC3007



* Considering mutations at NS3 positions 43, 80, 122, 155, 156 and 168.
^X: represents amino acids A, E, H, T. Pooled analyses from Phase 2b/3 studies. SMV + PR treated patients receiving SMV 150 mg once daily.
Source: Data on file; Janssen Research and Development

Some of the treatment-emergent NS3 amino acid substitutions detected in SMV-treated patients who did not achieve SVR in clinical studies (such as R155K) have been shown to reduce anti-HCV activity of TVR, BOC, and other HCV NS3/4A protease inhibitors.

RESISTANCE MUTATIONS OVER TIME

The persistence of SMV-resistant NS3 amino acid substitutions was assessed following treatment failure.

In the pooled Phase 2b/3 analysis of patients receiving SMV 150 mg once daily + PR, treatment-emergent SMV-resistance variants were no longer detectable by population sequencing in 90 out of 180 patients (50%) at the end of the studies after a median follow-up of 28.4 weeks (range 0.0-69.9 weeks). Emerging mutation D168V had a shorter median time until mutation became undetectable (17.4 weeks [95% CI, 12.1-20.1 weeks] in HCV genotype 1b) than R155K. Emerging mutation R155K in HCV genotype 1a infected patients with a baseline Q80K polymorphism had a shorter median time until mutation became undetectable (32.1 weeks [95% CI, 30.1-35.9 weeks]) than in genotype 1a patients without a baseline Q80K polymorphism (64.4 weeks [95% CI, 40.1-70.0 weeks]), suggesting a lower fitness of variants carrying both the R155K and Q80K amino acid substitutions.

Data from an ongoing, long-term follow-up study (HPC3002) including, amongst others, patients who did not achieve SVR with a SMV-based regimen in a previous Phase 2b study showed that in 70% (16/23) of these patients emerging mutations were no longer detected

after a median follow-up of 87.9 weeks (range 46.7-147.1 weeks). The long-term clinical impact of the emergence or persistence of SMV-resistance-associated-substitutions is presently unknown.

Simeprevir-resistant variants studied remained susceptible to representative HCV nucleoside and non-nucleoside polymerase inhibitors, and NS5A inhibitors. Of note, recent studies showed SVR rates ranging from 95% to 100% in patients who had failed TVR and BOC based treatment with emerging mutations with an interferon-free regimen consisting of sofosbuvir and a NS5A inhibitor (ledipasvir [N=40] or daclatasvir [N=41]) suggesting that treatment options for patients who have failed HCV protease inhibitor + PR treatment might become available[27,28].

5.1.4 Recommended Treatment Regimens of Simeprevir in Combination with Pegylated Interferon and Ribavirin

The recommended dose of SMV is one 150-mg capsule taken orally once daily with food. Treatment with SMV must be initiated in combination with PR (either PegIFNα-2a or -2b) for a duration of 12 weeks. Total treatment duration with PR is either 24 weeks (treatment-naïve or prior relapser patients) or 48 weeks (prior nonresponders).

5.1.4.1 Impact of Baseline Q80K Polymorphism on Treatment Outcome

As shown in Section 5.1.2 a factor found to have an effect on treatment outcome of SMV + PR but not of PR alone was the presence of a NS3 Q80K polymorphism at baseline. The impact of a baseline Q80K polymorphism varied across studies. Given that the efficacy of SMV + PR was considerably reduced in two out of three Phase 3 studies in patients with HCV genotype 1a with a baseline Q80K polymorphism and the prevalence of the genotype 1a Q80K baseline polymorphism in the US is high, determination of baseline Q80K in HCV genotype 1a infected patients is recommended in genotype 1a patients before initiation of treatment with SMV + PR., determination.

5.1.4.2 Recommended Treatment Duration

In the Phase 3 studies, treatment-naïve and prior relapser patients in the SMV + PR group with HCV RNA <25 IU/mL and with undetectable HCV RNA at Week 12 could stop treatment at Week 24. The majority of the patients (88.1% treatment-naïve patients [pooled C208/C216] and 92.7% of the prior relapser patients [HPC3007]) met the response-guided treatment criteria leading to a very high proportion of patients being eligible for 24 weeks of

treatment. Of these patients, 88.2% and 83.0%, respectively, achieved SVR12. Additional analyses excluding genotype 1a Q80K patients showed that an even slightly higher proportion of patients were eligible for short duration with 91.8% treatment-naïve patients and 94.3% prior relapser patients qualifying for 24 weeks treatment with SVR rates of 85.7% and 89.8%, respectively (Table 9).

Table 9: Proportion of Patients (All and Without Genotype 1a Q80K) Qualifying for 24 Weeks of Treatment and Corresponding SVR Rates – Pooled C208/C216 and HPC3007

	% of patients qualifying for 24 weeks of treatment (all patients)	% of patients qualifying for 24 weeks of treatment (without genotype 1a Q80K)	SVR rates with 24 weeks of treatment (all Patients)	SVR rates with 24 weeks of treatment (without genotype 1a Q80K)
Treatment-Naïve (pooled C208/C216)	88.1%	91.8%	88.2%	85.7%
Prior Relapser (HPC3007)	92.7%%	94.3%	83.0%	89.8%

Source: Data on file; Janssen Research and Development

From the small proportion of treatment-naïve and prior relapser patients without genotype 1a Q80K assigned to 48 weeks of treatment in the Phase 3 studies, only 41.7% and 50.0% completed treatment, resulting in approximately 2% of all SMV-treated patients in the Phase 3 studies receiving this length of PR treatment. Overall SVR rates (completers and non-completers) in patients assigned to 48 weeks of treatment were modest (33.3% and 60.0%, respectively).

Given that around 90%-95% of patients without baseline Q80K were eligible for 24 weeks of treatment in the Phase 3 studies and these patients derived high SVR rates while only few patients were assigned to 48 weeks of treatment resulting in modest SVR rates in this group, it is recommended that all **treatment-naïve patients and prior relapser patients** be treated with SMV 150 mg once daily for 12 weeks in combination with PR for a total of 24 weeks.

Prior nonresponder patients treated with SMV should receive SMV 150 mg once daily for 12 weeks in combination with PR for a total of 48 weeks.

5.1.4.3 TREATMENT STOPPING RULES

Analyses of Phase 2b/3 data correlating on-treatment responses and treatment outcome indicated that patients with HCV RNA <25 IU/mL at Week 4 had a high probability of achieving SVR, whereas patients with HCV RNA ≥25 IU/mL at Week 4 had low chances of achieving SVR (see Table 10).

Table 10: Proportion of Patients (All and Without Genotype 1a Q80K) and SVR by Week 4 HCV RNA Response – Pooled C208/C216, HPC3007, and C206

		Proportion of patients (all patients)	Proportion of patients (without genotype 1a Q80K)	SVR (all patients)	SVR (without genotype 1a Q80K)
C206/C216 (treatment-naïve)	HCV RNA <25IU/mL at Week 4	474/521 (91.0%)	410/437 (93.8 %)	409/474 (86.3%)	362/410 (88.3 %)
	HCV RNA ≥25IU/ml at Week 4	35/521 (6.7 %)	18/437 (4.1 %)	7/35 (20.0 %)	5/18 (27.8 %)
HPC3007 (prior relapse)	HCV RNA <25IU/mL at Week 4	247/260 (95.0%)	222/230 (96.5 %)	201/247 (81.4%)	187/222 (84.2 %)
	HCV RNA ≥25IU/ml at Week 4	12/260 (4.6 %)	8/230 (3.5 %)	5/12 (41.7 %)	5/8 (62.5 %)
C206 (non-responder receiving 150mg SMV)	HCV RNA <25IU/mL at Week 4	97/120 (80.8 %)	92/107 (86.0 %)	76/97 (78.4 %)	72/92 (78.3 %)
	HCV RNA ≥25IU/ml at Week 4	22/120 (18.3 %)	15/107 (14.0%)	2/22 (9.1 %)	0/15 (0%)

Source: Data on file; Janssen Research and Development

Similarly, SVR rates were low in patients with HCV RNA ≥25 IU/mL at Week 12 or 24. Therefore, all treatment should be stopped if HCV RNA is ≥25 IU/mL at Week 4, 12 or 24 (if applicable, Table 11). These stopping rules apply to both treatment-naïve and prior relapse and nonresponder patients.

Table 11: Treatment Stopping Rules in Patients with Inadequate On-Treatment Virologic Response

Stopping Rule	Treatment-Naïve and Prior Relapsers	Prior Nonresponders
Week 4: HCV RNA ≥25IU/mL	Discontinue SMV, PR	Discontinue SMV, PR
Week 12: HCV RNA ≥25 IU/mL	Discontinue PR (treatment with SMV is complete at Week 12)	Discontinue PR (treatment with SMV is complete at Week 12)
Week 24: HCV RNA ≥25 IU/mL	Not applicable	Discontinue PR

5.1.5 Conclusions of Efficacy Profile

Simeprevir + PR treatment showed statistically significantly higher SVR rates over PR alone in genotype 1 chronic hepatitis C infected patients who are treatment-naïve or who have failed previous interferon-based therapy, including patients with cirrhosis and prior null response to PR treatment. The recommended dose regimen is SMV 150 mg once daily for 12 weeks in combination with 24 Weeks of PR (treatment-naïve and prior relapsers) or 48 weeks of PR (prior partial and null responders) as therapy for HCV genotype 1 infected adults with compensated liver disease (including cirrhosis).

Subgroup analyses identified several baseline characteristics that affect SVR rates in patients treated with SMV in combination with PR. Statistically significant differences between the

SMV + PR group compared to PBO + PR were observed for all subgroups, including all *IL28B* genotypes and METAVIR fibrosis scores, except for the presence of a genotype 1a NS3 baseline Q80K polymorphism. Given that the efficacy of SMV + PR was considerably reduced in two out of three Phase 3 studies in patients with HCV genotype 1a with a baseline Q80K polymorphism and the prevalence of the genotype 1a Q80K baseline polymorphism in the US is high, determination of baseline Q80K in HCV genotype 1a infected patients is recommended before initiation of treatment with SMV + PR., determination. Alternative therapy should be considered in genotype 1a patients with the Q80K polymorphism.

At present time in the United States, Q80K determination is available from 2 commercial vendors with an assay meeting the performance requirements for routine clinical practice and which is considered appropriate to guide the use of SMV + PR.

Given that around 90%-95% of patients without baseline Q80K were eligible for 24 weeks of treatment in the Phase 3 studies and these patients derived high SVR rates while only few patients were assigned to 48 weeks of treatment resulting in modest SVR, it is recommended that all treatment-naïve patients and prior relapser patients be treated with SMV 150 mg once daily for 12 weeks in combination with PR for a fixed 24 weeks rather than a response-guided treatment approach.

In treatment-naïve patients, SMV + PR treatment achieved comparable SVR rates as reported in the USPI for TVR and BOC both in combination with PR (approximately 80% for SMV for the overall population and 85% in the population excluding genotype 1a Q80K positive patients, 74% to 79% for TVR, and 63% to 66% for BOC). High SVR rates were also achieved with SMV in combination with PR in prior relapser patients (79% in the overall population and 84% the population excluding genotype 1a Q80K positive patients). A uniform and simplified SMV + PR regimen is proposed for treatment-naïve and prior relapser patients rather than a response-guided treatment duration allowing for a simpler approach to the management of patients. The total treatment duration of 24 weeks is also applicable to treatment-naïve and prior relapser patients with cirrhosis who are recommended to be treated for 48 weeks with TVR and BOC.

Adding a protease inhibitor to PR treatment is a well-accepted approach in the treatment of prior null- and partial responders as it is associated with improved outcome of treatment. Robust efficacy with SMV + PR in the prior nonresponder population have shown that SMV + PR treatment increased SVR rates significantly over PR treatment in both prior null- and

partial responder patients (51% and 75% in prior null and partial responders, respectively, treatment in study C206; up to 38% in prior null responders and 59% in prior partial responders for TVR and BOC + PR). Data available from interim analyses from a roll-over study including prior null and partial responders are in line with the data from C206. Total PR treatment duration for prior partial-responders and -null responders is 48 weeks.

Stopping rules are in place at Week 4 and 12 for all patients and Week 24 for prior partial and null responders, are common to all patient subpopulations (treatment-naïve, prior-relapser, partial responder and null responder patients) and do not require additional testing time points beyond the current standard of care.

5.2 SAFETY

5.2.1 Overview

A comprehensive **nonclinical** toxicology program, including in vitro and in vivo studies using mice, rats, dogs, rabbits and monkeys was performed. The effects of SMV administration were evaluated for up to three months in mice, six months in rats, nine months in dogs and one month in monkeys via daily administration. There were also evaluations of genotoxic potential, fertility, embryofetal toxicity, pre- and postnatal development and topical tolerability.

- Simeprevir safety pharmacology studies did not detect any significant signals that were considered of concern. Simeprevir is considered to have very limited potential for cardiovascular, pulmonary or nervous system effects at the recommended clinical dose.

- Simeprevir induced a multifocal hepatocellular necrosis with associated increases in alanine aminotransferase (ALT), alkaline phosphatase (ALP), and/or bilirubin in dogs. This effect was observed after 6-month dosing at systemic exposures corresponding to 11-fold the clinical exposure and was not confirmed after 9-months of dosing at an exposure corresponding to 4-fold the clinical exposure. Liver necrosis recovered completely after a treatment-free period of one month following daily dosing for one month in dogs.

- Simeprevir has no genotoxic potential. In a rat fertility study, SMV showed no relevant effect on fertility at an exposure comparable to that in humans. Simeprevir

showed no teratogenicity in mice or rats. In a mouse embryofetal study, SMV resulted in early and late in utero losses in pregnant mice at approximately 6-fold the therapeutic exposure. Significantly decreased fetal weights and an increase in fetal skeletal variations were seen at four times human exposure. In a rat embryofetal study, pregnancy parameters were unaffected at an exposure similar to that in the clinic. In a pre- and post-natal study, SMV administration to pregnant rats (1000 mg/kg/day) resulted in early death in maternal animals. This was most probably due to the high viscosity and the irritant nature of the SMV formulation entering the respiratory tract. Significant reduction in body weight gain was seen (500 mg/kg/day) at an exposure of 0.7 times the clinical exposure. The developing rat offspring exhibited significantly decreased body weight, with associated negative effects on physical growth (delay) and development (decreased motor activity) following SMV exposure in utero (via maternal dosing) and during lactation (via maternal milk to nursing pups) at a maternal exposure similar to the therapeutic exposure. Subsequent survival, behavior or reproductive capacity was not affected. The proposed indication for simeprevir is for use in combination with PR. Ribavirin is contraindicated for use in pregnancy due to potential teratogenic and embryocidal effects. Therefore, the potential risk of SMV exposure in pregnant women is low as administration would be avoided during pregnancy due to the indicated use with RBV.

The evaluation of the **clinical** safety profile of SMV + PR is based on 38 studies: seven Phase 3 studies, two Phase 2b studies, two Phase 2a studies, and 27 Phase 1 studies, in which 1,846 HCV-infected patients and 806 healthy volunteers received SMV. A total of 1,153 HCV-infected patients were treated with SMV 150 mg once daily for 12 weeks. This relatively large number of patients exposed to SMV allowed for a good characterization of the SMV clinical safety profile in HCV-infected patients.

Several safety poolings have been performed to increase the likelihood of detecting infrequent events by increasing the number of patients per pooled treatment group as well as to increase the sample size for subgroup analyses.

In this section the safety profile of SMV + PR is described based on the **primary pooling** of studies C208, C216, and HPC3007 in 781 patients with chronic hepatitis C infection who received SMV at the proposed recommended dose regimen (150 mg once daily for 12 weeks). Focus is on the first 12 weeks of SMV + PR treatment. Other safety poolings that

have been performed were **(i)** a secondary pooling of studies C208, C216, HPC3007, C205, and C206 in 924 HCV-infected patients who received SMV 150 mg once daily for 12 weeks + PR, **(ii)** a dose-response pooling by SMV dose (75 mg, 100 mg, and 150 mg once daily) and a treatment duration pooling by SMV treatment duration (12, 24, and 48 weeks), including the same dataset as the secondary pooling, and **(iii)** a multiple-dose pooling and a single-dose pooling for the Phase 1 studies, including 806 non-HCV infected volunteers who received any dose of SMV and 634 volunteers who received SMV 150 mg once daily. In general, data from these poolings did not show a different safety outcome as compared to the primary pooling.

In addition, also more detail is provided on the safety data from study C206 in prior nonresponder patients. Focus is on the overall treatment phase and it is, therefore, important to note that the median duration of the SMV/PBO treatment period was 48.0 weeks in each SMV treatment group (range 1 to 49) and 27.2 weeks in the PBO group (range 1 to 49).

5.2.2 Overall Adverse Event Summary

Five studies (C208, C216, HPC3007, C205 and C206) have been conducted globally. In total, patients from 27 countries were enrolled and treated in these studies. Most patients (62.5%) were enrolled in Europe, whereas 20.5% of those enrolled were in the US. No relevant differences between both treatment groups in the different regions have been observed (Table 12).

Table 12: Patients by Region and Country; Intent-to-treat – Secondary Pooling

	PBO	SMV 150 mg 12 Weeks	All SMV	Total
Analysis Set: Intent-to-treat	540	924	1,486	2,026
Asia-Pacific	38 (7.0%)	70 (7.6%)	119 (8.0%)	157 (7.7%)
Australia	29 (5.4%)	37 (4.0%)	71 (4.8%)	100 (4.9%)
New Zealand	9 (1.7%)	33 (3.6%)	48 (3.2%)	57 (2.8%)
Europe	336 (62.2%)	565 (61.1%)	931 (62.7%)	1267 (62.5%)
North America	147 (27.2%)	248 (26.8%)	395 (26.6%)	542 (26.8%)
Canada	30 (5.6%)	34 (3.7%)	71 (4.8%)	101 (5.0%)
Mexico	8 (1.5%)	13 (1.4%)	13 (0.9%)	21 (1.0%)
Puerto Rico	2 (0.4%)	3 (0.3%)	3 (0.2%)	5 (0.2%)
United States	107 (19.8%)	198 (21.4%)	308 (20.7%)	415 (20.5%)
South America	19 (3.5%)	41 (4.4%)	41 (2.8%)	60 (3.0%)

Source: Data on file, Janssen Research and Development

Overall, in the primary pooling similar results in terms of AE incidence by type and Medical Dictionary for Regulatory Activities (MedDRA) preferred term were observed for SMV-treated patients and patients on PBO during the first 12-week treatment phase in the primary

pooling. The majority of patients reported at least one AE (95.3% in SMV-treated patients and 94.7% in patients on PBO). Most AEs were grade 1 or 2 in severity without relevant differences between both treatment groups. Grade 3 or 4 AEs were reported in 22.9% of SMV-treated patients and in 24.7% of patients on PBO. Simeprevir/PBO-related AEs were reported in 69.4% of SMV-treated patients and in 57.7% of patients on PBO. There were no relevant differences in overall AE profile with respect to METAVIR fibrosis scores, indicating that there was no clinically important liver disease stage-related effect of SMV. More details are provided in Table 13 and in Table 20 in Appendix 4.

Table 13: Summary of AEs; Intent-to-treat – Primary Pooling

	First 12 Weeks Phase	
	PBO	**SMV 150 mg**
Analysis Set: Intent-to-treat	397	781
Any AE	376 (94.7%)	744 (95.3%)
Worst grade 1 or 2 AE	278 (70.0%)	565 (72.3%)
Worst grade 3 or 4 AE	98 (24.7%)	179 (22.9%)
At least possibly related to SMV/PBO	21 (5.3%)	56 (7.2%)
Treatment-related AE	373 (94.0%)	731 (93.6%)
At least possibly related to SMV/PBO	229 (57.7%)	542 (69.4%)
At least possibly related to RBV	280 (70.5%)	596 (76.3%)
At least possibly related to PegIFN	370 (93.2%)	707 (90.5%)
Any AE with fatal outcome	0	0
Any SAE[a]	10 (2.5%)	16 (2.0%)
At least possibly related to SMV/PBO	1 (0.3%)	3 (0.4%)
AE leading to permanent stop[b]	18 (4.5%)	20 (2.6%)
SMV/PBO[c]	5 (1.3%)	14 (1.8%)
PegIFN and/or RBV	13 (3.3%)	8 (1.0%)

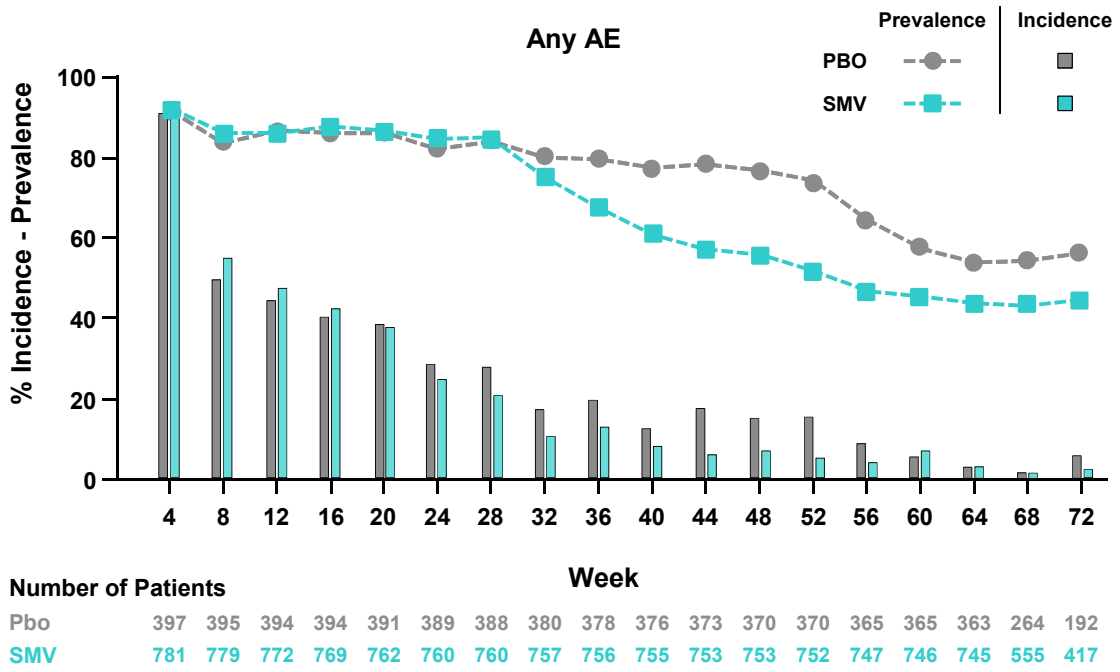
[a] Including fatal AEs.
[b] Permanent stop of at least one drug.
[c] Without regard to PR
Source: Data on file, Janssen Research and Development

The most frequent AEs (in >25% of SMV-treated patients) by MedDRA preferred term, were fatigue (35.6%), headache (33.2%), and influenza-like illness (26.0%). All of these events are common adverse reactions of PR treatment. The incidence of these AEs was similar in SMV-treated patients and in patients on PBO. Pruritus by preferred term was the only AE with >5% higher incidence in SMV-treated patients than in patients on PBO (20.6% versus 13.6%). More details are provided in Table 21 in Appendix 4.

The incidence (ie, onset of new events) of AEs was the highest during the first 4 weeks of treatment. Incidence was slightly higher in SMV-treated patients when compared to patients on PBO in the next 4 weeks (54.7% versus 49.1%). As of Week 12 the incidence became similar for both treatment groups until Week 24, and was relatively higher in the patients on

PBO thereafter. Up to Week 28, the prevalence (ie, number of ongoing events) was similar between SMV-treated patients and patients on PBO. After completion of PR treatment in the majority of SMV-treated patients (ie, at Week 24), a pronounced decrease in the prevalence of AEs was observed (Figure 18).

Figure 18: Incidence and Prevalence of AEs Over Time, 72-Week Study Period; Intent-to-treat – Primary Pooling



Line plots: prevalence
Bars: incidence during the preceding 4 weeks
Source: Data on file, Janssen Research and Development

5.2.3 Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation of Study Drug

Deaths

In the primary pooling, no deaths were reported during the first 12-week treatment phase in the primary pooling, but 3 SMV-treated patients died during the subsequent treatment phase, after completion of SMV/PBO:

- A 49-year old white female with METAVIR fibrosis score F3 at baseline completed 12 weeks of treatment with SMV and continued with PR. On study day 168 she was hospitalized because of colon cancer, and discontinued PR on the same day. On study

day 194, the patient died due to colon cancer. The investigator assessed the relationship between the colon cancer and all study drugs as not related.

- A 62-year old American Indian or Alaska native female with METAVIR fibrosis score F4 at baseline completed 12 weeks of treatment with SMV + PR and was eligible for shorter treatment duration based on response-guided treatment criteria. On study day 112, she discontinued PR due to grade 2 diarrhea. On study day 116, the patient died due to an unknown cause (in the opinion of the investigator most likely pulmonary embolism or sudden cardiac death). The investigator assessed the relationship between the sudden death and all study drugs as not related.

- A 57-year old white female with METAVIR fibrosis score F4 at baseline and a medical history including chronic obstructive pulmonary disease and opiate addiction, discontinued PegIFN, RBV and SMV on study days 76, 79 and 82, respectively. The patient was hospitalized with confusional state, dyspnea, pancytopenia, pneumonia, pyrexia, respiratory acidosis, and septic shock on study day 87. On study day 88, grade 4 bradycardia was reported and the patient died the same day (in the opinion of the investigator due to bilateral pneumonia and septic shock). The investigator assessed all events as not related to SMV/PBO and RBV, and not or doubtfully related to PegIFN.

In C206, also no deaths were reported during the SMV+ PR treatment phase. One death was reported more than 4 months after completion if SMV treatment, during the PR only phase:

- A 47-year old white male with METAVIR fibrosis score F2 at baseline started treatment with SMV 150 mg once daily + PR on 22 January 2010. The patient completed 12 weeks of SMV and continued with PR. He was hospitalized with brain injury and bacterial meningitis on study day 224, and cerebral hemorrhage was reported on study day 233. He died on study day 239 due to bacterial meningitis and brain injury. The investigator assessed bacterial meningitis and brain injury as not related to SMV and RBV and probably related to PegIFNα-2a; cerebral hemorrhage was assessed as not related to any study drug.

Serious adverse events

In the primary pooling, a SMV/PBO-related SAE was reported (by the investigator) in four patients: major depression (one SMV-treated patient, very likely related to PegIFN,

doubtfully related to RBV), photosensitivity reaction (two SMV-treated patients; one possibly related to PR, one not related to PR), and anemia (one patient on PBO, not related to PegIFN, very likely related to RBV).

In C206, seven and three SAEs that were considered possibly related to SMV/PBO were reported in five SMV-treated patients and one PBO patient, respectively. Of these, one SMV-treated patient experienced three SAEs (one case of diarrhea and two cases of vomiting) that were considered very likely related to SMV.

Adverse events leading to discontinuation of study drug

In the primary pooling, the proportion of patients who discontinued SMV/PBO early was 6.7% in SMV-treated patients and 66.5% in patients on PBO, mainly due to meeting the treatment stopping rule at Week 4. During the first 12 weeks phase, 1.8% of the SMV-treated patients and 1.3% of the patients on PBO in the primary pooling discontinued SMV/PBO due to an AE (Table 22 in Appendix 4).

Rash was the most common MedDRA preferred term reported as AE leading to discontinuation of SMV (in 0.6% of SMV-treated patients). Rash was not reported as an AE leading to treatment discontinuation in patients on PBO.

In C206, 7.8% of the SMV-treated patients and 4.5% of the patients on PBO discontinued SMV/PBO + PR due to an AE during the overall treatment period. Hyperbilirubinemia and rash were the most common MedDRA preferred terms reported as AE leading to discontinuation of SMV (in 1.0% and 0.8% of SMV-treated patients, respectively). These AEs were not reported as an AE leading to treatment discontinuation in patients on PBO.

Note that the protocols mandated discontinuation of SMV for certain AEs.

5.2.4 Events of Interest

Based on nonclinical findings for SMV and known toxicity profiles for other protease inhibitors, PegIFN and RBV, a number of AEs were predefined to be of interest in the Phase 3 studies (ie, increased bilirubin, rash [any type], pruritus, anemia, neutropenia, and photosensitivity conditions). Increased bilirubin is considered of specific interest for its potential as a signal for liver toxicity. The events of interest represent grouped terms; for an overview of the MedDRA terms included, refer to Appendix 5.

In the SMV clinical studies, anemia, neutropenia and increased bilirubin were assessed by analysis of two parameters:

- Changes in laboratory abnormalities (increases or decreases) as reported by the central laboratory and classified according to the World Health Organization (WHO) laboratory abnormality grading scale.
- Adverse events by preferred term as reported by the investigator in case the laboratory abnormality was considered clinically significant.

Dyspnea was not identified as an AE of interest, however, taking into account the slightly higher incidence in SMV + PR treated patients compared to PBO treated patients during the first 12 weeks phase, dyspnea (grouped term, see Appendix 5) was further analyzed.

Dyspnea was retained as an event where a possibility of association to SMV+PR treatment could not be ruled out. Therefore, dyspnea in addition to, rash (including photosensitivity), pruritus, nausea and dyspnea (grouped terms[8]) are listed in the proposed USPI as adverse reaction for SMV + PR treatment that occurred with at least 3% higher frequency among patients receiving SMV + PR compared to patients receiving PBO + PR during the first 12 weeks of treatment in the primary pooling.

5.2.4.1 INCREASED BILIRUBIN

In early SMV studies, increases in bilirubin levels (both indirect and direct) with increasing SMV plasma exposure were observed. These were asymptomatic and in general not associated with transaminase (AST and ALT) increases, were partially reversible during SMV treatment and completely reversible after completion of SMV intake. Inhibition by SMV of the hepatic transporter OATP, which has a role in the hepatic uptake of bilirubin, and to a limited extent possibly also inhibition of MRP2, which has a role in excretion of conjugated bilirubin into bile, may explain these increases. Furthermore, increased bilirubin production as a consequence of RBV induced hemolysis very likely plays a pathophysiologic role.

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[8] Grouped term 'rash' includes: 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, generalized erythema, dermatitis exfoliative, cutaneous vasculitis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and photodermatosis.
Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.
Grouped term 'dyspnea' includes the preferred terms dyspnea and dyspnea exertional

In the primary pooling:

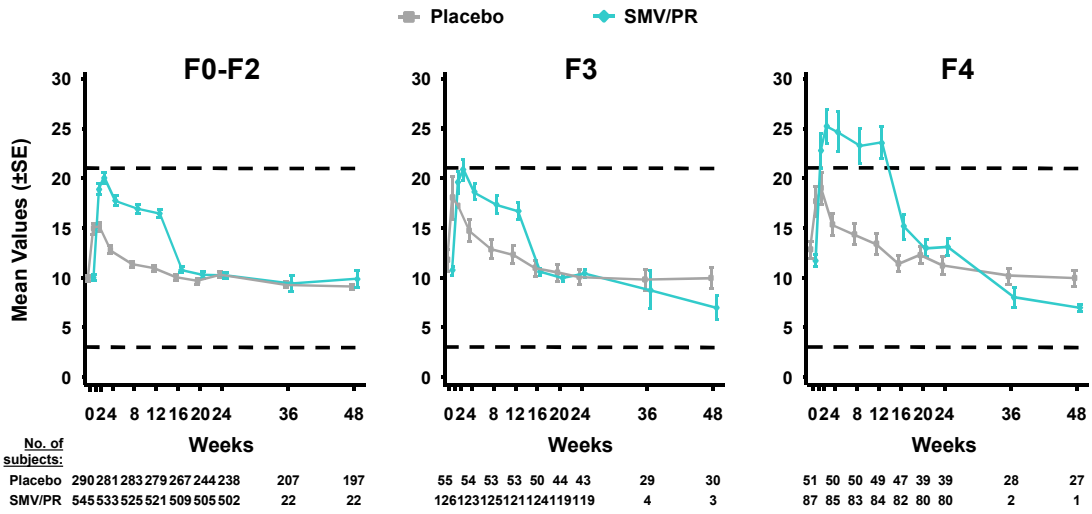
- The incidence of increased bilirubin reported as AE was higher in SMV-treated patients than in patients on PBO (7.9% versus 2.8%). In 1.8% of SMV-treated patients and 0.5% of patients on PBO grade 3 events were reported. Grade 4 events were reported in 2 (0.3%) SMV-treated patients. None were reported as SAE. Only one patient (0.1%) discontinued SMV due to blood bilirubin increased (grade 4) as required by a protocol-defined toxicity management guideline.

- In both treatment groups, mean total bilirubin increased from baseline during the first two weeks of treatment. The mean increase from baseline was larger in SMV-treated patients than in patients on PBO. A subgroup analysis of mean total bilirubin over time by METAVIR fibrosis score showed a similar pattern; however, mean values were higher and converted more slowly to baseline values (by Week 20 rather than by Week 16) in SMV-treated patients with METAVIR fibrosis score F4. Mean values were also higher in patients on PBO with METAVIR fibrosis score F4 (Figure 19). Bilirubin elevations were in general not associated with transaminase increases, were partially reversible during SMV treatment, in most cases completely reversible after completion of SMV intake, and occasionally only reversible after completion of treatment with PR.

- A higher incidence of the laboratory abnormality hyperbilirubinemia was observed in SMV-treated patients (49.5%) than in patients on PBO (26.1%). Grade 3 or 4 hyperbilirubinemia was infrequent (<5% of patients) in both treatment groups and tended to occur more often in patients with METAVIR fibrosis score F4. No cases of drug induced concomitant increases in ALT/AST >three times the upper limit of normal (ULN) and total bilirubin >two times ULN concomitant or 30 days subsequent ('Hy's law' constellation, named after Hyman Zimmerman) were identified.

More details are provided in Table 23 in Appendix 4.

Figure 19: **Mean (+/- SE) Values for Total Bilirubin Over Time for On-Treatment Patients by METAVIR Fibrosis Score; Intent-to-treat – Primary Pooling**



Restricted to on-treatment patients.
Dotted lines represent the normal ranges. In case of multiple normal ranges the highest and lowest normal range are shown.
Y-axis: total bilirubin (µmol/L)
Source: Data on file, Janssen Research and Development

In C206, a benign, isolated and reversible increase in plasma bilirubin levels was observed in SMV-treated patients, but these bilirubin elevations were not associated with elevation of liver enzymes. Hepatobiliary events (mainly of hyperbilirubinemia type) were reported at a frequency of 7.3% in SMV-treated patients versus 4.5% in the PBO group. These findings are in line with the observations from the Phase 3 studies.

5.2.4.2 SKIN EVENTS

5.2.4.2.1 Rash

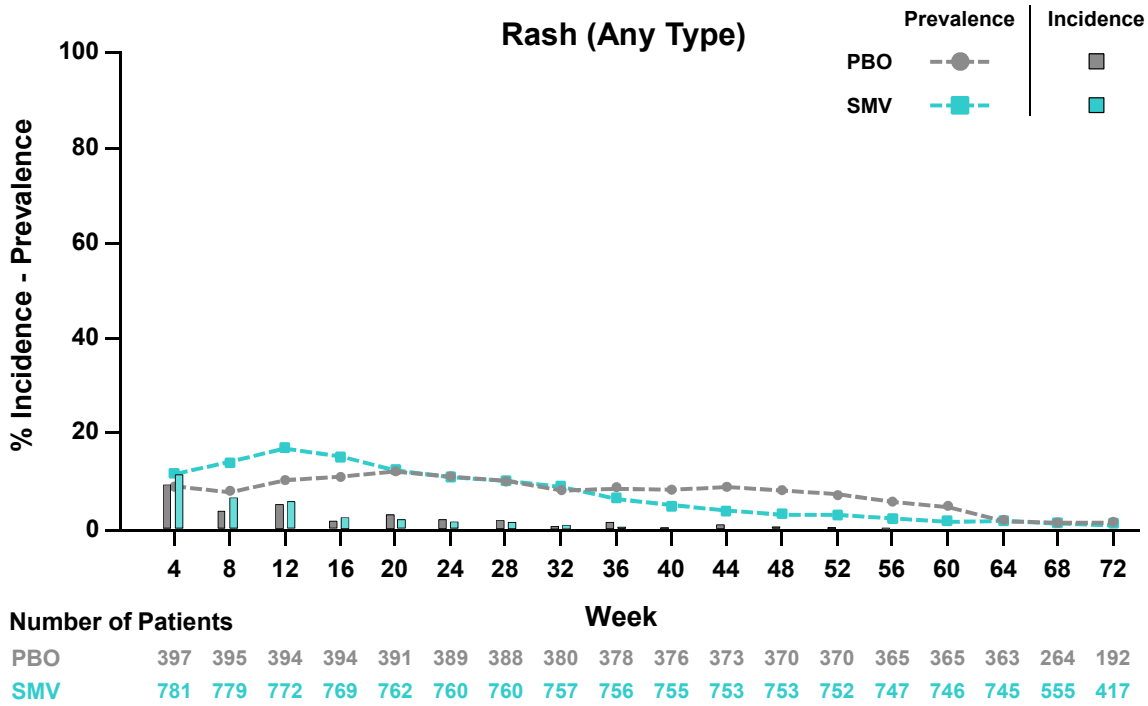
Rash (any type) is an adverse reaction of PegIFN and RBV. The protocol-defined toxicity management guideline mandated discontinuation of all study drugs in case of a grade 3 or 4 rash. Photosensitivity is also considered an event of interest and is discussed within this section.

Overall, the incidence of rash was low. In the primary pooling, the incidence of rash was higher in the SMV group compared to the PBO group (any type: 23.2% versus 16.9%). Most AEs were grade 1 or 2 in severity. Grade 3 events were reported in 5 (0.6%) SMV-treated patients. No fatal events and no grade 4 AEs such as Stevens Johnson syndrome and toxic epidermal necrolysis were reported, and 0.5% patients discontinued treatment due to rash

(four patients). No difference between SMV-treated patients and patients on PBO was observed for rash in patients from North America (22.6% versus 26.9%).

The incidence of rash (any type) continuously decreased after the first four weeks of treatment in both treatment groups. The prevalence in patients on PBO was relatively stable throughout the study. The prevalence in SMV-treated patients was higher during the first 16 weeks of treatment and became lower after 36 weeks than that in patients on PBO (Figure 20).

Figure 20: Incidence and Prevalence of Rash (Any Type) Over Time - 72-Week Study Period; Intent-to-treat – Primary Pooling



Line plots: prevalence
Bars: incidence during the preceding 4 weeks
Source: Data on file, Janssen Research and Development

Photosensitivity was identified as an event of interest based on results from nonclinical and clinical studies. More information on the photosensitivity potential of SMV is presented in Section 4.4.

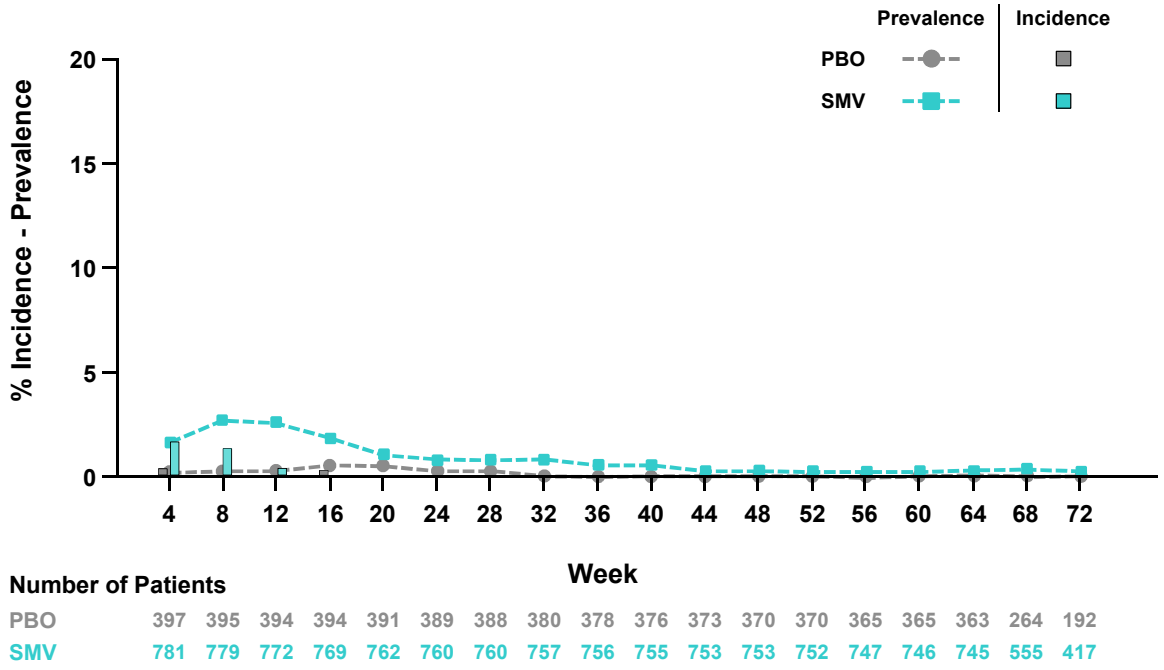
In the primary pooling, the incidence of photosensitivity conditions was low in both treatment groups during the first 12-week treatment phase but was higher in SMV-treated patients (3.3%) versus patients on PBO (0.5%). All photosensitivity conditions were grade 1 or 2 in

severity, apart from one patient with a grade 3 photosensitivity condition. There were no events leading to discontinuation. Two (0.3%) SMV-treated patients had SMV-related events reported as SAEs (one grade 3 and one grade 2 photosensitivity reaction); the seriousness criterion for both cases was hospital admission. Both SAEs resolved.

In addition, an analysis was performed when the preferred term 'Sunburn' was grouped with the defined photosensitivity conditions to address the concerns of the potential underestimation of the photosensitivity. The corresponding incidence in the primary pooling was 4.9% in SMV-treated patients versus 0.8% in PBO-treated patients.

The majority of photosensitivity conditions were reported in the SMV-treated patients during the first 12 weeks of treatment. No clear pattern regarding the incidence and prevalence of photosensitivity conditions over time could be established (Table 19).

Figure 21: Incidence and Prevalence of Photosensitivity Conditions Over Time; Intent-to-treat – Primary Pooling



Line plots: prevalence
Bars: incidence
Source: Data on file, Janssen Research and Development

More details are provided in Table 24, Table 25 and Table 26 in Appendix 4.

In C206, a higher incidence for rash and photosensitivity was observed in patients treated with SMV + PR than those treated with PBO + PR (26.5% versus 18.2% for rash and 3.5% versus 1.5% for photosensitivity) during the overall treatment phase.

5.2.4.2.2 Pruritus

Pruritus is an adverse reaction of TVR, PegIFN and RBV.

A higher incidence was observed in the SMV group compared to the PBO group for pruritus in the primary pooling (22.0% versus 14.9%), but the severity of pruritus with SMV was in general mild. A grade 3 event was reported in one (0.1%) SMV-treated patient. There were no grade 4 events and none were reported as SAE. One (0.1%) SMV-treated patient discontinued all study drugs due to grade 2 pruritus.

No correlations were seen between pruritus or rash and increases in ALP or bilirubin parameters.

More details are provided in Table 27 in Appendix 4.

In C206, a higher incidence for pruritus was observed in patients treated with SMV + PR than those treated with PBO + PR (34.1% versus 16.7%) during the overall treatment.

5.2.4.3 ANEMIA

Anemia is an adverse reaction of other HCV protease inhibitors. Also both PegIFN and RBV are associated with decreased hemoglobin levels and anemia.

Adding SMV to treatment with PegIFN and RBV did not increase the incidence of anemia or worsen its severity.

In the primary pooling:

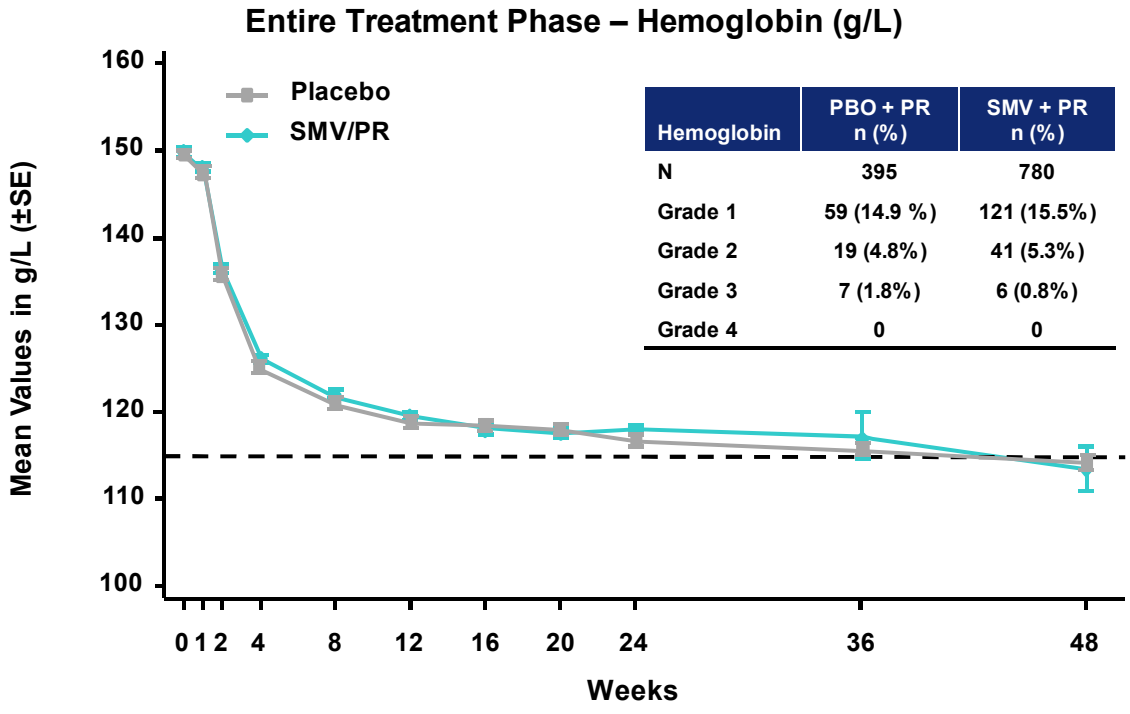
- There was no difference between the treatment groups in mean hemoglobin values over time (Figure 22).
- The incidence of decreased hemoglobin as laboratory abnormality (any grade) was 21.5% in both treatment groups during the first 12-week treatment phase. Grade 3 decreased hemoglobin was observed in 0.8% of SMV-treated patients and in 1.8% of patients on PBO. No grade 4 decreased hemoglobin was observed.

- In cirrhotic patients, there was neither a difference in mean hemoglobin changes over time nor in graded hemoglobin abnormalities between the SMV and PBO group (Figure 23).

- The incidence of anemia reported as AE in SMV-treated patients and patients on PBO was similar: 13.4% versus 10.8%. Most anemia events were of mild or moderate severity (grade 1 or 2); 1.0% of SMV-treated patients and 1.8% of patients on PBO experienced grade 3 anemia. One (0.3%) patient on PBO had a grade 4 event, which was SMV/PBO-related and reported as SAE (anemia). There were no events leading to discontinuation of SMV/PBO.

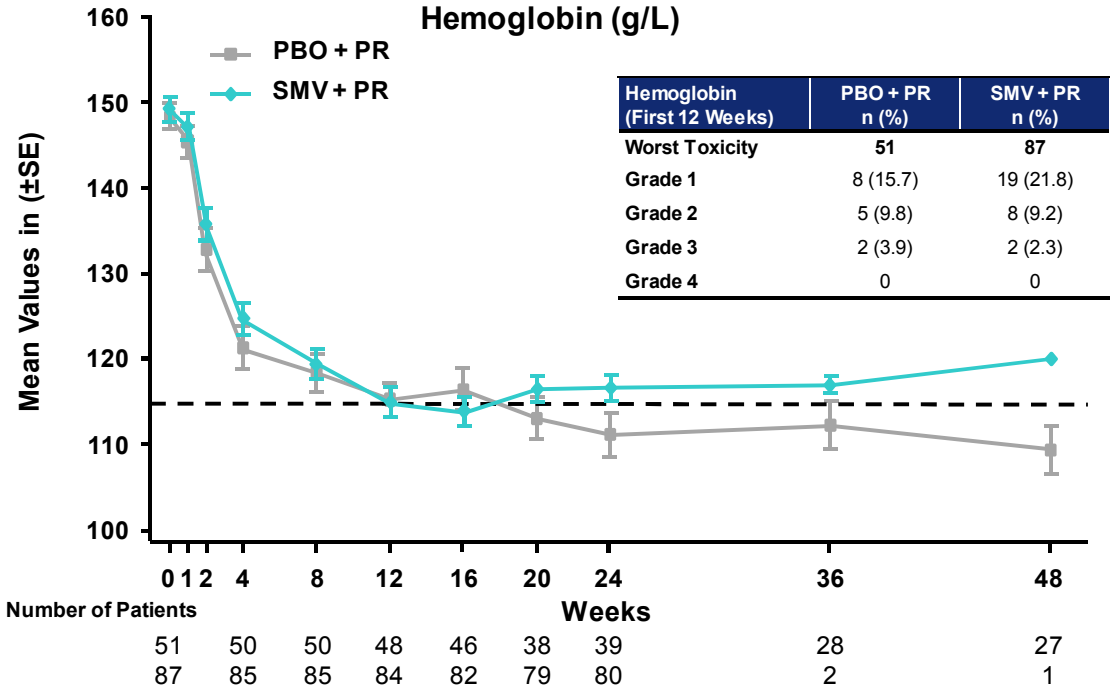
During treatment with marketed HCV protease inhibitors, the use of erythropoiesis-stimulating agents and blood transfusions is commonly required. Note that in the studies with SMV, the use of an erythropoiesis-stimulating agent was not allowed per protocol (except in France) and only very few patients used this medication for a short period of time.

Figure 22: Mean (+/- SE) Values for Hemoglobin Over Time for On-Treatment Patients; Intent-to-treat – Primary Pooling



On-treatment patients.
Dotted lines represent the normal ranges. In case of multiple normal ranges the highest and lowest normal range are shown.
Source: Data on file, Janssen Research and Development

Figure 23: Mean (+/- SE) Values for Hemoglobin Over Time for On-Treatment Patients With Cirrhosis; Intent-to-treat – Primary Pooling



Hemoglobin (First 12 Weeks)	PBO + PR n (%)	SMV + PR n (%)
Worst Toxicity	51	87
Grade 1	8 (15.7)	19 (21.8)
Grade 2	5 (9.8)	8 (9.2)
Grade 3	2 (3.9)	2 (2.3)
Grade 4	0	0

Source: Data on file, Janssen Research and Development

In C206, adding SMV to treatment with PR did not increase the incidence of anemia (grouped term). Anemia AEs were reported in 19.4% of the SMV-treated subjects and in 19.7% of the subjects in the PBO group.

5.2.4.4 NEUTROPENIA

In C206, neutropenia AEs (reported as preferred terms 'neutropenia' and 'neutrophil count decreased' combined) were reported more frequently in the SMV-treated patients (28.0% versus 18.2%), however no difference was observed when objective laboratory neutrophil count shifts from baseline were compared across groups. It is possible that the difference in overall treatment exposure between SMV and the PBO group (median duration of 48.0 weeks versus 27.3 weeks) influenced the frequency with which some AEs known to occur with PR were reported during the overall treatment period.

In the primary pooling adding SMV to treatment with PR did not increase the incidence of neutropenia or worsen its severity:

- There was no difference between treatment groups in mean neutrophil values over time until Week 24. After completion of PR treatment (ie, at Week 24 in the majority

of SMV-treated patients and at Week 48 in most patients on PBO), mean values increased towards baseline.

- The incidence of decreased neutrophils (any grade) was similar in SMV-treated patients and patients on PBO during the first 12-week treatment phase: 75.9% versus 77.2%. Grade 3 decreased neutrophils was observed in 12.3% of SMV-treated patients and in 13.2% of patients on PBO. Grade 4 decreased neutrophils was observed in 2.9% and 2.8%, respectively.

- The incidence of neutropenia reported as AE in SMV-treated patients and patients on PBO was similar during the first 12-week treatment phase: 16.5% versus 15.1%. Grade 3 events were reported in 7.9% of SMV-treated patients and 8.3% of patients on PBO. Grade 4 events were reported in 2.4% of SMV-treated patients and in 1.5% of patients on PBO. None were reported as a SAE. One (0.3%) patient on PBO discontinued treatment only due to neutropenia.

5.2.4.5 DYSPNEA

During the first 12 weeks phase, the incidence of dyspnea was higher in SMV-treated patients than in patients on PBO: 11.8% versus 7.6%. By preferred term, the most frequent event was dyspnea (7.7% of SMV-treated patients and 5.5% of patients on PBO), while dyspnea exertional was reported in <5% of patients in either treatment group.

The incidence of SMV/PBO-related events was 4.9% in SMV-treated patients and 2.5% in patients on PBO. All events were grade 1 or 2. No events were reported as SAE. One patient on PBO discontinued PR due to dyspnea.

Of the SMV-treated patients who did experience dyspnea, 23.9% (22 out of 92) experienced anemia as well.

5.2.5 Clinical Laboratory Evaluations

An overview of selected laboratory parameters (ie at least grade 3 in at least 1 patient) is presented in Table 28 in Appendix 4. There were no differences in hemoglobin, neutrophils or platelets between both treatment groups.

Apart from increased bilirubin, a slight difference between the SMV and PBO group was seen for mean ALP although remaining well within the normal range at all time points. Alkaline phosphatase laboratory abnormalities occurred in <5% of patients, were almost

exclusively grade 1 and in general reversed quickly after completion of SMV treatment. Increases in ALP showed a correlation with increases in direct bilirubin, suggesting a link to hepatic transporter inhibition.

Creatinine did not meet this criterion and is therefore not shown in Table 28. A grade 1 laboratory abnormality was noted in 2.4% of the SMV-treated patients and in 3.0% of patients on PBO. A grade 2 laboratory abnormality was noted only in one SMV-treated patient and in three patients on PBO (0.8%). Only grade 1 laboratory abnormalities were noted for blood urea nitrogen (1.3% of the SMV-treated patients versus 2.5% of patients on PBO). This confirms that SMV did not affect kidney function.

In C206, apart from bilirubin-related abnormalities (hyperbilirubinemia, direct and indirect bilirubin above normal limits), which were more commonly seen in the SMV treatment groups than in the PBO group, there were no substantial differences between treatment groups for any of the laboratory abnormalities. Overall, incidences of grade 3 or 4 laboratory abnormalities and laboratory-related AEs were low.

Changes over time in the clinical laboratory parameters, if any, returned to baseline values after end of treatment in both the primary pooling and study C206.

5.2.6 Patient Reported Fatigue and Functional Limitations

Severity of fatigue and functional limitations at work and in daily activities were assessed using patient-reported outcomes (PRO) in studies C208, C216 and HPC3007. The individual studies as well as the pooled analysis of the three studies showed that addition of SMV did not increase tolerability problems commonly associated with PR. There was no evidence of increased severity of patient reported fatigue or functional limitations (impairments in work and daily activities) in the SMV group compared to PBO. No differences between treatments were observed in time missed from work for those patients in the labor force at baseline.

Additionally, SMV-treated patients had significantly reduced time (weeks) with fatigue and impairment in work and daily activity, which is related to a shortened overall treatment duration with PR in the majority of patients as compared to PR alone. Similar increases in symptoms and functional limitations (worsening of PRO scores) were observed at Weeks 4 through 24 in both treatment groups. Mean PRO scores returned to levels at or significantly below baseline sooner for SMV-treated patients (after Week 24) than for the PBO group (after Week 48). The statistically significantly better AUC_{60} and statistically significantly

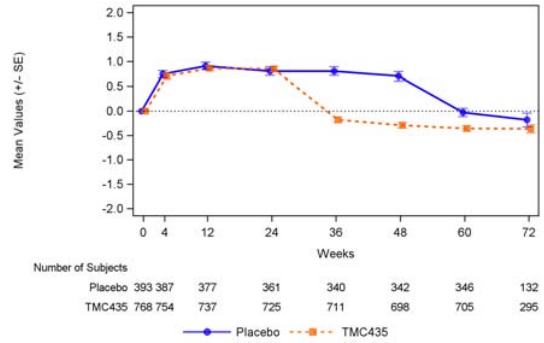
shorter duration of clinically important worsening in symptoms or functional impairments in the SMV group are consistent with the similar incidence and severity of AEs in both treatment groups and with response-guided PR treatment duration, enabling the majority of SMV-treated patients to have a shorter PR treatment duration than patients on PBO.

The PRO pooled analysis linking PRO and AE data confirms validity of the PRO measures as sensitive assessments of what is important to patients with chronic hepatitis C infection.

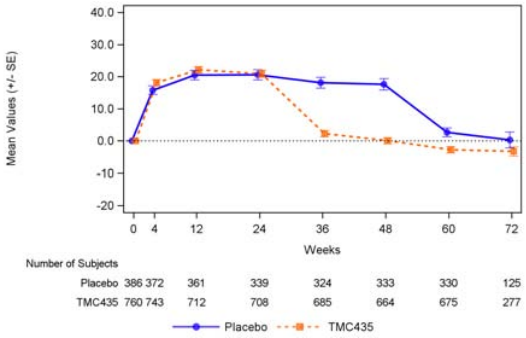
Figure 24 presents the mean change from baseline in fatigue, productivity impairment, activity impairment and absenteeism from the primary pooling. Table 29 in Appendix 4 provides the results of statistical analysis of the four PRO endpoints from the individual studies and the pooled analysis confirming consistency of the findings.

Figure 24: Mean (+/-SE) Changes over Time in the Fatigue Severity Score Total Score, Work Productivity and Activity Impairment Scores and Absenteeism - 72-Week Study Period; Intent-to-treat – Primary Pooling

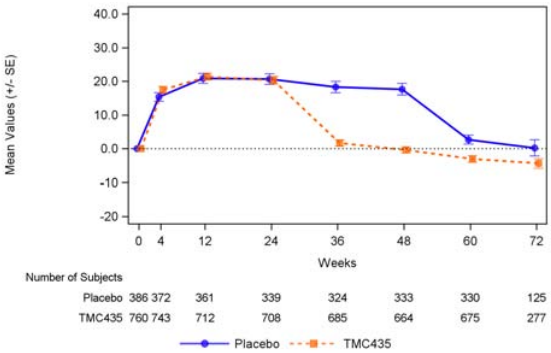
Fatigue Severity Score*



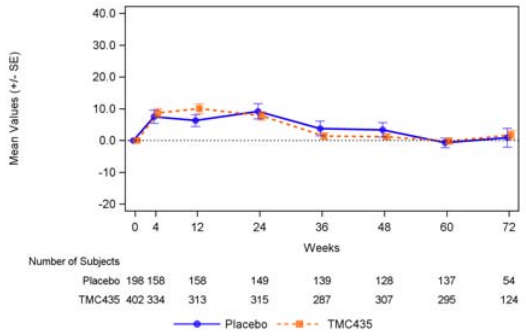
WPAI Productivity Impairment Score**



WPAI Activity Impairment Score***



WPAI Absenteeism Score****



* The fatigue severity score (FSS) total score ranges from 1 to 7, with higher scores indicating worse outcome.

** Work Productivity and Activity Impairment (WPAI) productivity scores range from 0 to 100, with higher scores indicating more impairment in work and/or daily activities; WPAI Productivity score is available for all patients who completed the questionnaire; for patients who were not employed during the study, the score is based only on individual Question 6 (multiplied by 10).

*** WPAI Activity Impairment score is based on WPAI Question 6: "During the past 7 days, how much did HCV affect your ability to do your regular daily activities"; scores range from 0 (no effect on activities) to 10 (completely prevented me from doing my daily activities); for the purpose of the analysis, the score was multiplied by 10; this score is available for all patients who completed the questionnaire.

**** WPAI Absenteeism score is the number of hours missed from work because of HCV divided by the total number of hours supposed to work, and expressed as a percentage and is based on Question 2: "In the last 7 days, how many hours were you absent from your job because of problems that are related to your HCV?" WPAI Absenteeism score is only provided for patients who were in the labor force at baseline.

In study C206, the addition of SMV to PR treatment did not impact fatigue negatively. After the end of therapy, fatigue returned to baseline values in all treatment groups.

5.2.7 Subgroup Analyses

Subgroup analysis by age, sex, region, body mass index (BMI) and METAVIR fibrosis score of AEs in general and of interest, indicated that overall, the safety and tolerability profile of SMV was similar, regardless of demographic and baseline disease characteristics.

There were no relevant differences in overall AEs between METAVIR fibrosis scores, indicating that there was no liver disease stage-related effect of SMV. Increased bilirubin and anemia were reported at a higher incidence in patients with METAVIR fibrosis score F4 (cirrhosis). However, a more pronounced difference between SMV-treated patients and patients on PBO was seen only for the laboratory abnormality hyperbilirubinemia in patients with METAVIR fibrosis score F4 and not for hemoglobin. More details are provided in Table 20 and Table 30 in Appendix 4.

5.2.8 Conclusions on Safety

The safety profile of SMV + PR has been established based on the large double-blind PBO-controlled data set.

Simeprevir + PR treatment has a comparable safety profile to PR alone and requires no additional on-treatment monitoring of safety parameters compared to PR given alone. A similar incidence of hemoglobin abnormalities in SMV-treated patients and patients on PBO was noted.

Increases in bilirubin were noted more frequently with SMV treatment, but were not treatment-limiting and reversed to baseline values after end of treatment.

Treatment with SMV reduced the duration of fatigue and functional impairments by reducing the overall treatment length with PR in many patients, without increasing their severity.

Adverse reactions for SMV + PR treatment that occurred with at least 3% higher frequency among patients receiving SMV + PR compared to patients receiving PBO + PR during the first 12 weeks of treatment in the pooled Phase 3 studies (C208, C216 and HPC3007) include rash (including photosensitivity), pruritus, nausea and dyspnea (grouped terms). Simeprevir did not cause additional anemia in any of the studied patient populations, including patients with cirrhosis. No additional risk evaluation and mitigation strategy is required for SMV related adverse reactions or laboratory abnormalities. Laboratory testing requirements as per the prescribing information for PR treatment, which includes hematology and biochemistry

(including hepatic enzymes and bilirubin) testing at baseline, on-treatment and post-treatment, are sufficient to manage the risks of SMV + PR combination treatment.

After the availability of the Phase 3 data on photosensitivity it was decided to reintroduce formal recommendation for sun-protective measures as originally in place in the Phase 3 (C208/C216/HPC3007) studies in SMV studies in which patients are still receiving SMV treatment and planned SMV studies. Sun-protective measures will also be recommended in the USPI.

6 OTHER ONGOING AND PLANNED STUDIES

6.1 HCV GENOTYPE 1/HIV-1 CO-INFECTED PATIENT POPULATION

The efficacy and safety of SMV 150 mg once daily for 12 weeks in combination with PR in HCV genotype 1/HIV-1 co-infected patients is being investigated in the ongoing Phase 3 study C212. This study is conducted globally, including 7 countries in Europe and North America. Patients could be enrolled regardless of whether they were on highly active antiretroviral therapy (HAART, ie, a combination of at least 3 antiretroviral agents) or not. Response-guided 24- or 48-week total treatment for PR is being evaluated in treatment-naïve patients and prior relapsers without cirrhosis. In prior nonresponders and patients with cirrhosis (regardless of treatment experience), the total treatment duration with PR is 48 weeks. A total of 106 HCV treatment-naïve and treatment-experienced patients who were co-infected with HCV genotype 1 and HIV-1 were treated, of which 93 patients were on HAART and 13 were not. The antiretroviral therapy allowed in this study included NRTIs (lamivudine, emtricitabine, tenofovir or abacavir), rilpivirine, enfuvirtide, raltegravir or maraviroc. In the Week 24 interim analysis (cut-off 18 September 2012, when all patients reached Week 24 or discontinued early), 90.6% patients had completed SMV treatment. The study is continuing as planned.

A summary of the baseline characteristics is provided in Table 14.

Table 14: Key Demographic and Baseline Disease Characteristics – C212	
	SMV/PR N=106 %
Gender (Female)	15
Race	
Caucasian	82
Black or African American	14
Ethnicity (Hispanic or Latino)	6
Age (years), Median	48
HCV geno/subtype	
1a	82
1b	17
IL28B Genotype	
CC	27
CT	56
TT	17
Cirrhosis	12

Source: Data on file, Janssen Research and Development

6.2 HCV GENOTYPE 4 PATIENT POPULATION

The safety and efficacy of SMV 150 mg once daily for 12 weeks in combination with PR in treatment-naïve and treatment-experienced HCV genotype 4 infected patients are being investigated in the ongoing Phase 3 study HPC3011. This study is conducted in France and Belgium. Response-guided 24- or 48-week total treatment for PR is evaluated in treatment-naïve patients and prior relapsers. For prior nonresponders, the total treatment duration with PR is 48 weeks.

At time of the interim analysis with cut-off date 17 January 2013, 107 patients had received at least one dose of SMV 150 mg once daily in combination with PR. All 107 patients are still in the study. Eighty-six (80.4%) patients completed SMV treatment. The study is continuing as planned.

A summary of the baseline characteristics is provided in Table 15.

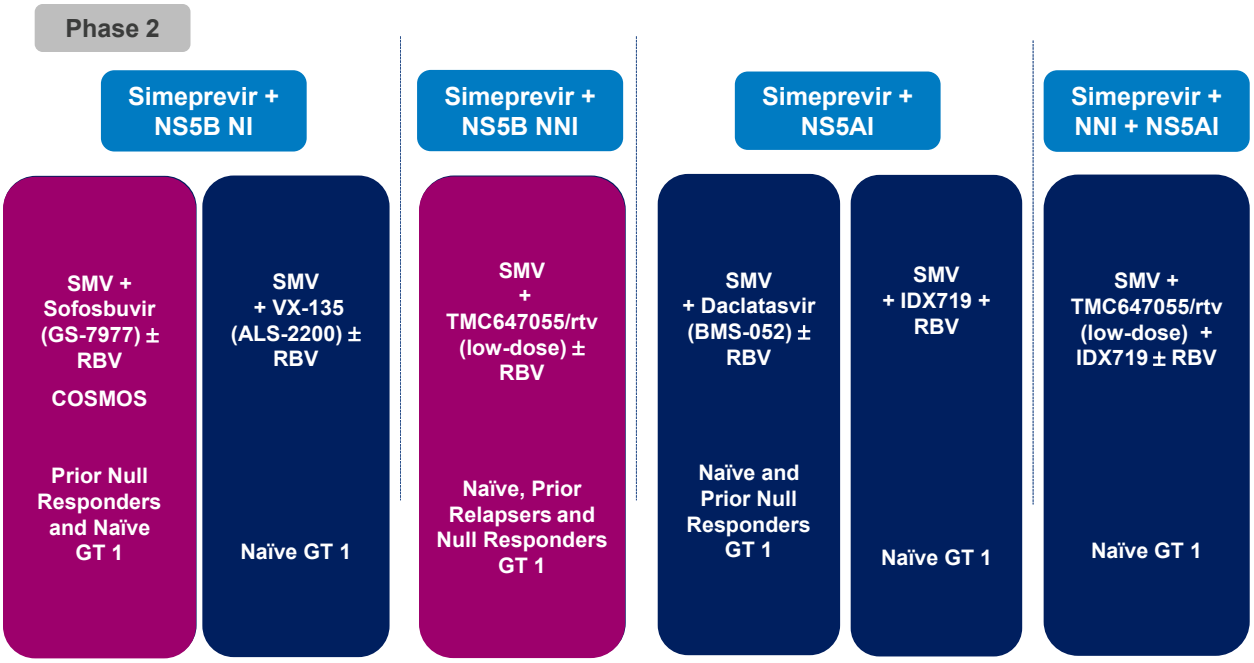
Table 15: Key Demographic and Baseline Disease Characteristics – HPC3011	
	SMV/PR N=107 %
Gender (Female)	21
Race	
Caucasian	72
Black or African American	28
Ethnicity (Hispanic or Latino)	7
Age (years), Median	49
HCV geno/subtype*	
4a	42
4d	24
4r	8
IL28B Genotype	
CC	8
CT	58
TT	35
METAVIR F4	29

Other genotype subtypes included 4c, e, f, h, k, o, and q, all present in <5% of the patients
Source: Data on file, Janssen Research and Development

6.3 SIMEPREVIR AS PART OF AN INTERFERON-FREE REGIMEN

Simeprevir is being investigated in combination with other direct acting antivirals as part of an interferon-free regimen in the presence or absence of RBV. An overview of the combinations currently under investigation in Phase 2 is provided in Figure 25.

Figure 25: Simeprevir Containing Interferon-Free Regimens Under Investigation in Phase 2



GT: genotype; rtv: ritonavir; NI: nucleoside inhibitor; NNI: non-nucleoside inhibitor

Preliminary results from the ongoing HPC2002 study (COSMOS) are available. In this randomized, open-label study conducted in the US, SMV 150 mg once daily is administered for 12 or 24 weeks in combination with the HCV polymerase inhibitor sofosbuvir (GS-7977) 400 mg once daily with and without RBV (Copegus® 1,000 to 1,200 mg/day). For the study design, see Figure 32 in Appendix 1.

Interim data of Cohort 1 including data obtained up to the data cut-off date of 18 January 2013 (when all patients in the 12-week treatment groups had reached 4 weeks after planned end of treatment) are available. As of this cut-off date, 80 prior null responders without advanced hepatic fibrosis (METAVIR fibrosis score F0-F2) were randomized and treated. Fifty-seven (71.3%) patients had completed all study treatment and 18 (22.5%) were still on treatment.

A summary of the baseline characteristics is provided in Table 16. Patients were primarily male (61.3%) and Caucasian (71.3%). In total, 62 patients (77.5%) had HCV genotype 1a and 18 patients (22.5%) had HCV genotype 1b. A Q80K polymorphism was present at baseline in 37.2% (29 of 78) of the overall population with sequence data; all patients with Q80K had HCV genotype 1a (29 of 60; 48.3%).

Data on *IL28B* genotype were available for 78 patients. Of these, 5 (6.4%) had genotype CC, 54 (69.2%) had genotype CT, and 19 (24.4%) had genotype TT.

Table 16: Key Demographic and Baseline Disease Characteristics – HPC2002

	SMV/PR N=80 %
Gender (Female)	39
Race	
Caucasian	71
Black or African American	29
Ethnicity (Hispanic or Latino)	25
Age (years), Median	56
HCV geno/subtype	
1a	78
1b	23
IL28B Genotype	
CC	6
CT	70
TT	24

Source: Data on file, Janssen Research and Development

Twenty four and 27 patients received SMV/sofosbuvir with RBV for 24 and 12 weeks, respectively, and 15 and 14 patients received SMV/sofosbuvir without RBV for 24 and 12 weeks, respectively.

Preliminary safety data indicate that mean bilirubin levels are only increased in the subgroups of patients who received RBV together with SMV/sofosbuvir, supporting the hypothesis that the hyperbilirubinemia observed with SMV + PR is caused by hepatic transporter inhibition (OATP) by SMV in the presence of an increased bilirubin load due to RBV induced hemolysis. The study is continuing as planned.

In addition to the SMV containing interferon-free studies listed in Figure 25, Janssen is planning to study a SMV containing interferon-free regimen in post-transplant and in pediatric patients.

6.4 OTHER ONGOING PHASE 3 STUDIES

Two additional Phase 3 studies are still ongoing without data available:

- A double-blind, PBO-controlled, Phase 3 study (HPC3001) in HCV genotype 1 infected patients with prior null or partial response to PR therapy, evaluating SMV versus TVR, is ongoing. No data for this globally conducted study are currently available.
- A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of SMV 100 mg and 150 mg once daily + PR in Chinese and Korean treatment-naïve genotype 1 chronic hepatitis C infected patients in the Asian-Pacific region (HPC3005). No data for this study are currently available.

7 BENEFITS-RISKS/OVERALL CONCLUSIONS

The results of the clinical development program indicate that SMV + PR is a well-tolerated and effective therapeutic alternative for HCV-infected patients. Simeprevir 150 mg once daily for 12 weeks + PR is associated with high SVR rates, a good tolerability and drug-drug interaction profile, a simple 24-week regimen in all treatment-naïve and prior relapser patients including cirrhotics, and a convenient single capsule once daily dosing that could reduce treatment burden on patients.

Simeprevir + PR has consistently demonstrated substantial improvements in SVR rates across many patient populations studied compared to treatment with PR alone, including difficult-to-cure HCV genotype 1 infected patients (eg, prior null responders and patients with cirrhosis). The increased SVR rates with SMV are both statistically significant and clinically meaningful. Simeprevir has shown an efficacy rate at least similar to TVR and BOC.

Subgroup analyses identified several baseline characteristics that affect SVR rates in patients treated with SMV in combination with PR. Statistically significant differences between the SMV + PR group compared to PBO + PR were observed for all subgroups, including all *IL28B* genotypes and METAVIR fibrosis scores, except for the presence of a genotype 1a NS3 baseline Q80K polymorphism. Given that the efficacy of SMV + PR was considerably reduced in two out of three Phase 3 studies in patients with HCV genotype 1a with a baseline Q80K polymorphism and the prevalence of the genotype 1a Q80K baseline polymorphism in the US is high, determination of baseline Q80K in HCV genotype 1a infected patients is recommended before initiation of treatment with SMV + PR. Alternative therapy should be considered for all genotype 1a patients with the Q80K polymorphism.

At present time in the United States, Q80K determination is available from 2 commercial vendors with an assay meeting the performance requirements for routine clinical practice and which is considered appropriate to guide the use of SMV + PR.

Treatment-naïve and prior relapser patients should receive SMV 150 mg once daily for 12 weeks in combination with PR for 24 weeks while prior nonresponder patients should receive SMV + PR for 12 weeks in combination with PR for 48 weeks, rather than a response-guided treatment approach. Stopping rules (HCV RNA is ≥25 IU/mL) are in place at Week 4 and 12 for all patients and Week 24 for prior partial and null responders, are common to all patient subpopulations (treatment-naïve, prior-relapser, partial responder and null responder patients) and do not require additional testing time points beyond the current standard of care.

Adverse reactions for SMV + PR treatment that occurred with at least 3% higher frequency among patients receiving SMV + PR compared to patients receiving PBO + PR during the first 12 weeks of treatment in the pooled Phase 3 studies (C208, C216 and HPC3007) include rash

(including photosensitivity), pruritus, nausea and dyspnea (grouped terms[9]). Simeprevir did not cause additional anemia in any of the studied patient populations, including patients with cirrhosis. A recommendation with regard to sun-protective measures will be included in the United States Product Information (USPI). No additional risk evaluation and mitigation strategy is required for SMV related adverse reactions or laboratory abnormalities. Laboratory testing requirements as per the prescribing information for PR treatment, which includes hematology and biochemistry (including hepatic enzymes and bilirubin) testing at baseline, on-treatment and post-treatment, are sufficient to manage the risks of SMV + PR combination treatment.

Furthermore, the once-daily dosing of SMV with one capsule per day is likely to be beneficial for adherence compared to currently approved direct acting antivirals requiring three times daily intake. Simeprevir is metabolized primarily by CYP3A and therefore is susceptible to drug-drug interactions with moderate and potent inhibitors and inducers of CYP3A. The overall drug interaction profile of SMV is, however, well established and generally favorable, allowing it to be coadministered with a variety of commonly used drugs in HCV-infected patients.

These features show that SMV can address unmet medical needs that are present with the drugs currently marketed for HCV treatment.

Taken together, the results of the clinical development program indicate that SMV 150 mg once daily for 12 weeks in combination with PR for 24 or 48 weeks as therapy for HCV genotype 1 infected adults with compensated liver disease (including cirrhosis), who are treatment-naïve or have failed previous interferon (pegylated or non-pegylated) therapy with or without RBV is a promising therapeutic alternative to those available today for HCV-infected patients. The good tolerability profile and convenient dosing regimen will reduce the treatment burden on patients.

Simeprevir is also being investigated in patients co-infected with HCV genotype 1/HIV-1, patients infected with HCV genotype 4 and interferon-free and PR-free regimens in a wide range

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[9] Grouped term ‘rash’ includes: 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, generalized erythema, dermatitis exfoliative, cutaneous vasculitis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and photodermatosis.
Grouped term ‘pruritus’ included the preferred terms pruritus and pruritus generalized.
Grouped term ‘dyspnea’ includes the preferred terms dyspnea and dyspnea exertional

of HCV genotype 1 infected patients. Interferon-free studies in pediatric patients and post-transplant patients are planned.

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APPENDICES

Appendix 1: Overview of the Study Designs

Figure 26: Study Design Phase 2b Study in Treatment-Naïve HCV Genotype 1 Infected Patients – C205

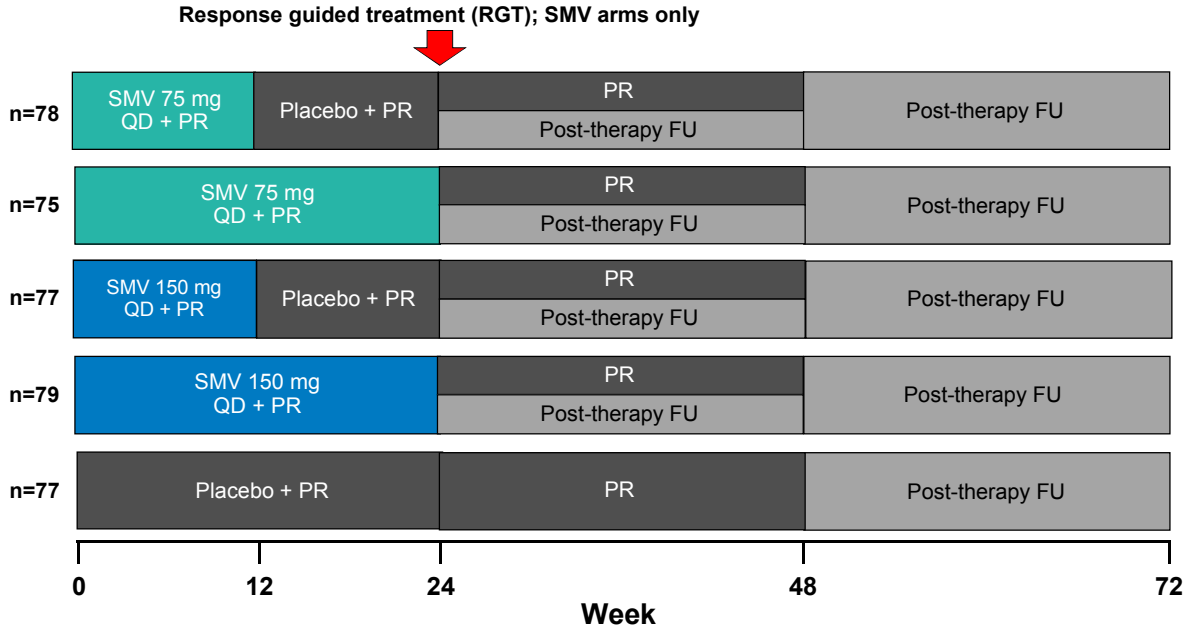


Figure 27: Study Design Phase 2b Study in Treatment-Experienced HCV Genotype 1 Infected Patients – C206

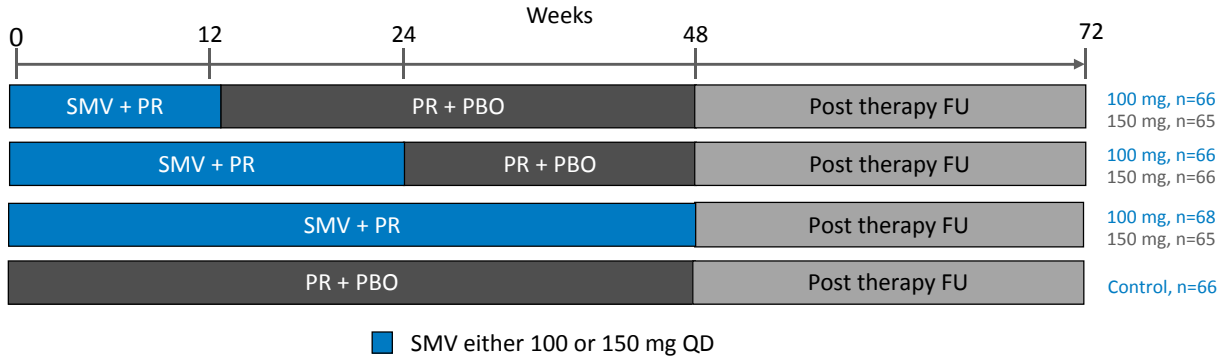


Figure 28: Study Design Phase 3 Studies in Treatment-Naïve HCV Genotype 1 Infected Patients – C208 and C216 and Phase 3 Study in Prior Relapser HCV Genotype 1 Infected Patients – HPC3007

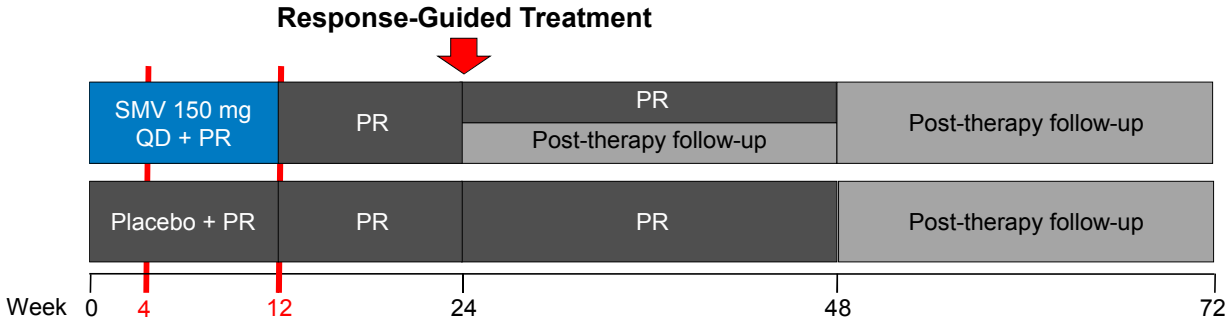
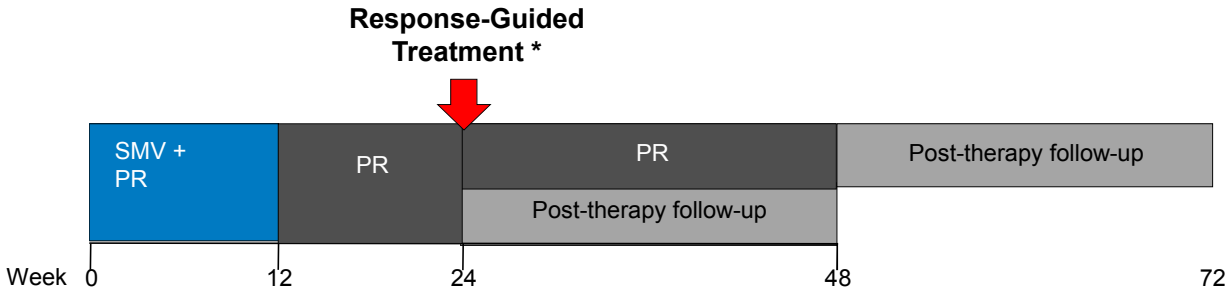
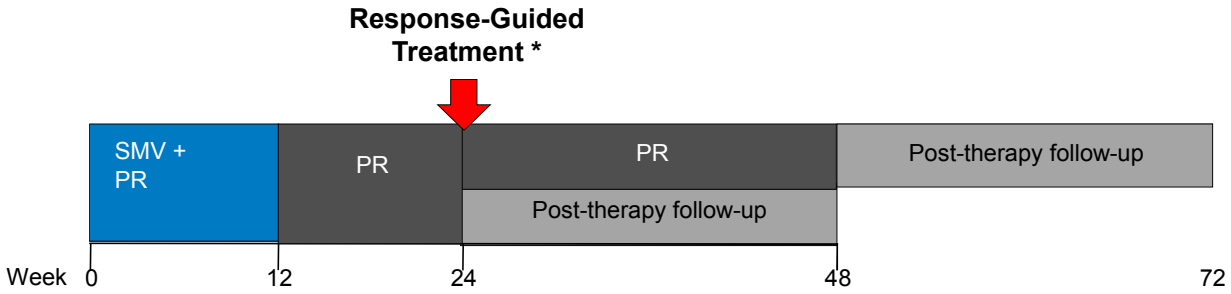


Figure 29: Study Design Phase 3 Study in HCV genotype 1/HIV-1 Co-infected Patients – C212



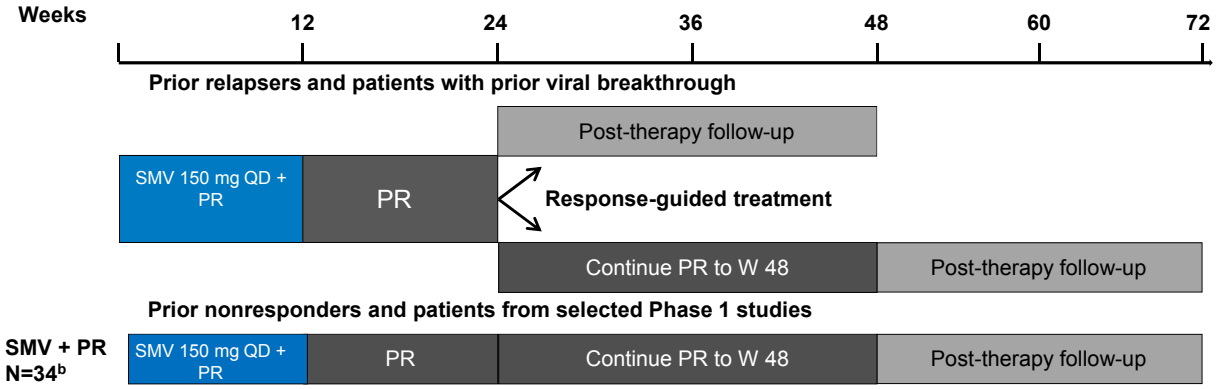
* HCV treatment-naïve patients and prior HCV relapsers without cirrhosis where eligible for shortened treatment duration. Prior nonresponder patients and all cirrhotic patients regardless of treatment history received a fixed total of 48 weeks of therapy

Figure 30: Study Design – Phase 3 Study in HCV Genotype 4 Infected Patients - HPC3011



* Response-guided treatment duration (for HCV treatment-naïve patients and previous HCV relapsers only). Non-responders will receive 48 weeks of treatment.

Figure 31: Study Design – C213

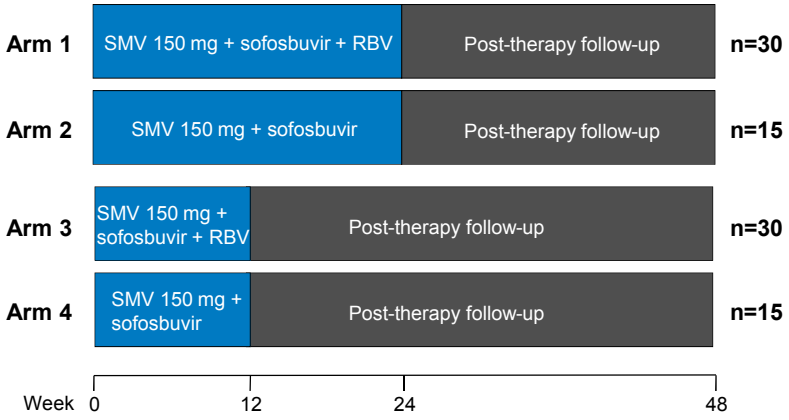


N: number of subjects enrolled and treated (ie, received at least 1 dose of study drug) at the time of data cut-off (15 September 2012); PR: PegIFNα-2a + RBV; TMC: TMC435

[a] Including 12 patients with prior relapse and 4 patients with prior viral breakthrough.

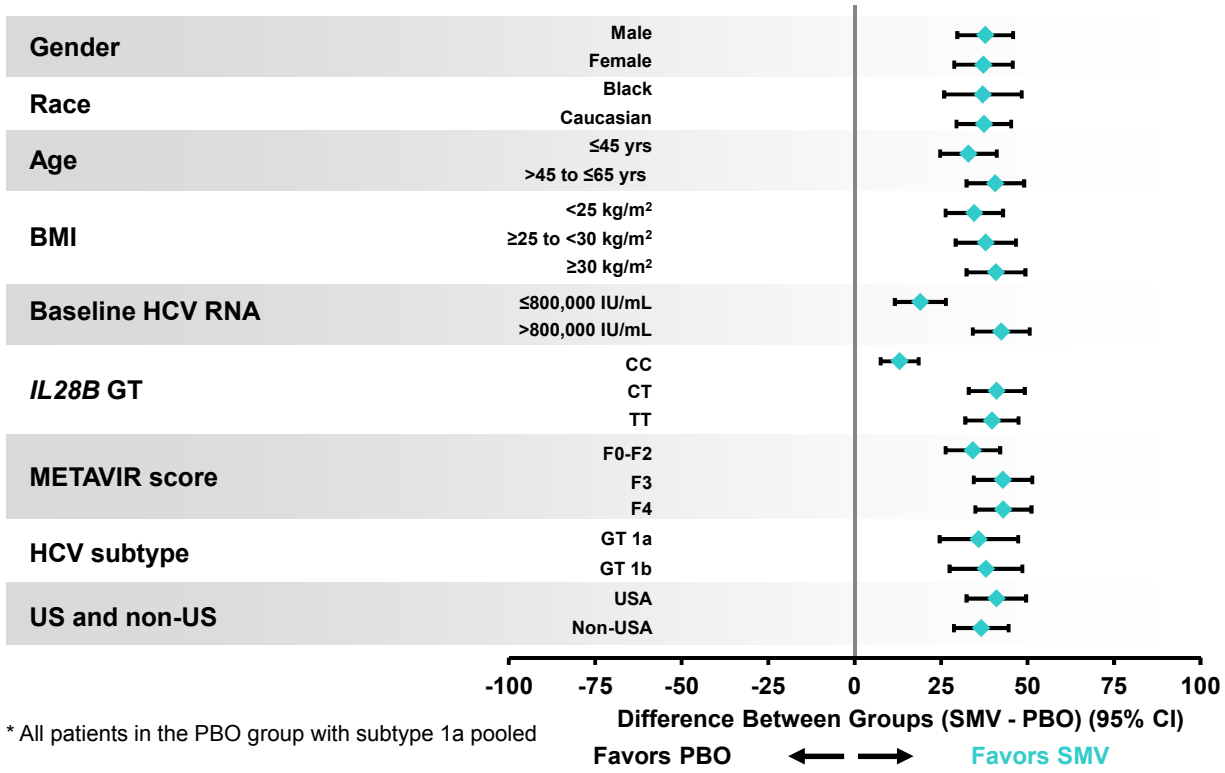
[b] Including 17 prior nonresponders and 1 'other', and 16 patients from selected Phase 1 studies.

Figure 32: Study Design Phase 2b Study with SMV and Sofosbuvir With or Without RBV – HPC2002



Appendix 2: Efficacy Results

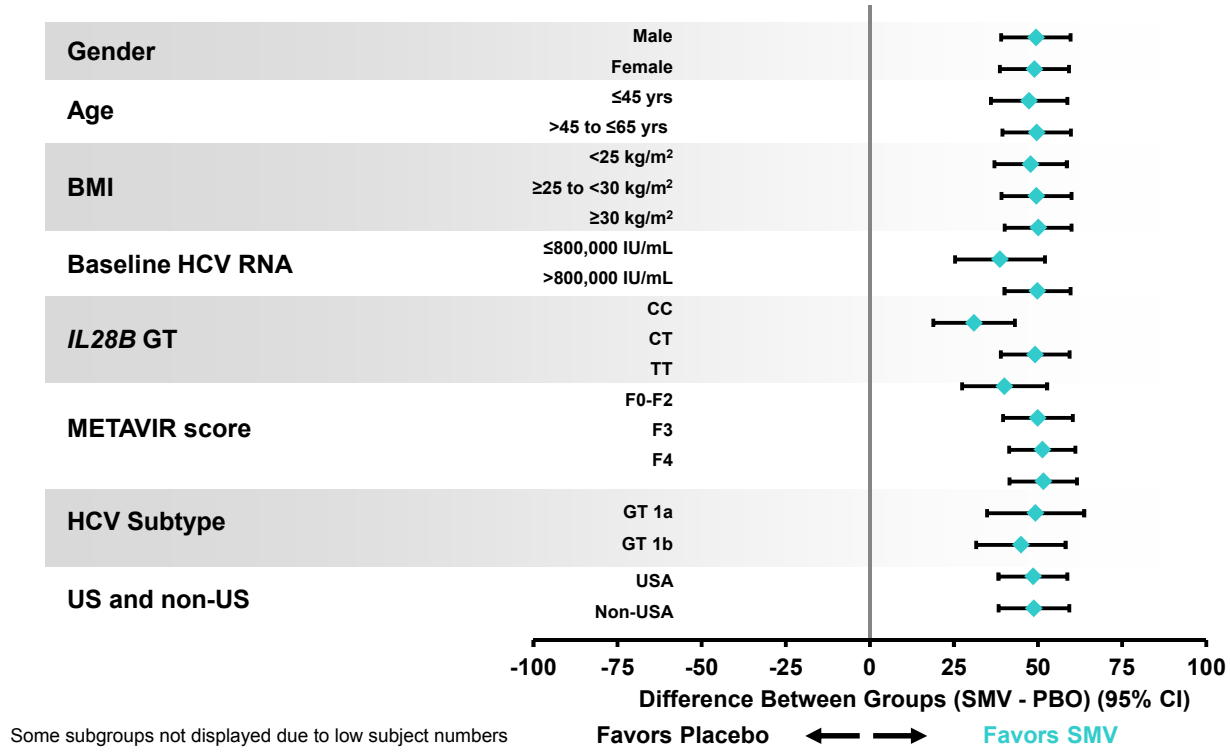
Figure 33: Subgroup Analyses SVR12 – Pooled C208/C216



* All patients in the PBO group with subtype 1a pooled

Source: Data on file, Janssen Research and Development

Figure 34: Subgroup Analyses SVR12 – HPC3007



Source: Data on file, Janssen Research and Development

Table 17: Viral Breakthrough Pooled Over Time – C206

Viral Breakthrough, n/N (%)	SMV12 PR48 100 mg N = 66	SMV24 PR48 100 mg N = 65	SMV48 PR48 100 mg N = 66	SMV12 PR48 150 mg N = 66	SMV24 PR48 150 mg N = 68	SMV48 PR48 150 mg N = 65	PBO N = 66
All Patients							
Before or at Week 12		19/197 (9.6)			14/199 (7.0)		0/66 (0.0)
Between Week 12 and 24	1/59 (1.7)	4/110 (3.6)		2/61 (3.3)	0/118 (0.0)		1/42 (2.4)
After Week 24	1/54 (1.9)	0/52 (0.0)	0/53 (0.0)	0/57 (0.0)	1/58 (1.7)	1/56 (1.8)	0/33 (0.0)

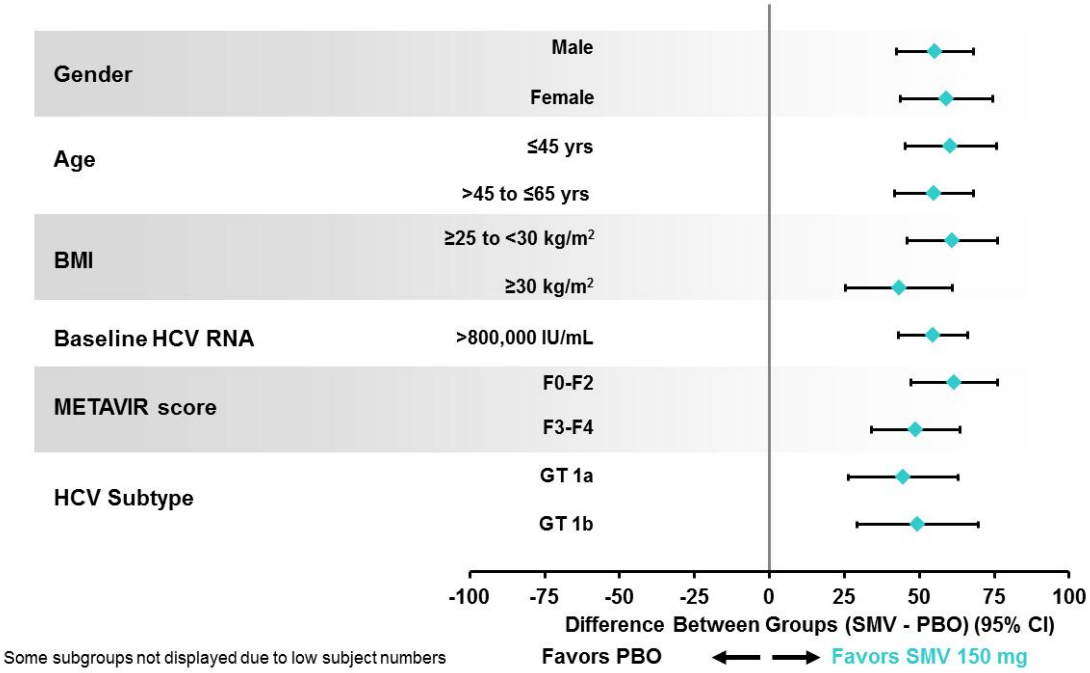
N: number of patients; n: number of patients with viral breakthrough
Source: Data on file, Janssen Research and Development.

Table 18: Viral Relapse – C206

n/N (%)	SMV12 PR48 100 mg N = 66	SMV24 PR48 100 mg N = 65	SMV48 PR48 100 mg N = 66	SMV12 PR48 150 mg N = 66	SMV24 PR48 150 mg N = 68	SMV48 PR48 150 mg N = 65	PBO N = 66
Total Population	5/54 (9.3)	7/51 (13.7)	9/50 (18.0)	6/51 (11.8)	8/57 (14.0)	3/55 (5.5)	12/27 (44.4)
Null responder	2/9 (22.2)	1/11 (9.1)	3/11 (27.3)	2/11 (18.2)	5/12 (41.7)	3/13 (23.1)	1/4 (25.0)
Partial responder	2/19 (10.5)	5/16 (31.3)	5/18 (27.8)	1/17 (5.9)	2/20 (10.0)	0/19 (0.0)	2/4 (50.0)
Relapser	1/26 (3.8)	1/24 (4.2)	1/21 (4.8)	3/23 (13.0)	1/25 (4.0)	0/23 (0.0)	9/19 (47.4)

N: number of patients with undetectable HCV RNA at EOT and with available follow-up data; n: number of patients with viral relapse
Source: Data on file, Janssen Research and Development.

Figure 35: Subgroup Analyses SVR12 – C206



Source: Data on file, Janssen Research and Development

Appendix 3: Virology/Resistance in Clinical Studies

Table 19: Number (%) of Patients with a Baseline Q80K Polymorphism, by Region; Intent-to-treat – Pooled C205/C206/C208/C216/HPC3007

	All HCV geno/subtypes	HCV geno/subtype 1a/other	HCV geno/subtype 1b
Analysis set: Intent-to-treat	2026	926	1100
All Regions	2026	926	1100
Patients with sequencing data	2007	911	1096
No Q80K	1733 (86.3%)	642 (70.5%)	1091 (99.5%)
Q80K	274 (13.7%)	269 (29.5%)	5 (0.5%)
Europe	1267	387	880
Patients with sequencing data	1254	377	877
No Q80K	1178 (93.9%)	304 (80.6%)	874 (99.7%)
Q80K	76 (6.1%)	73 (19.4%)	3 (0.3%)
North America	542	388	154
Patients with sequencing data	538	385	153
No Q80K	353 (65.6%)	200 (51.9%)	153 (100%)
Q80K	185 (34.4%)	185 (48.1%)	0 (0%)
South America	60	22	38
Patients with sequencing data	60	22	38
No Q80K	58 (96.7%)	20 (90.9%)	38 (100%)
Q80K	2 (3.3%)	2 (9.1%)	0 (0%)
United States	415	301	114
Patients with sequencing data	411	298	113
No Q80K	268 (65.2%)	155 (52.0%)	113 (100%)
Q80K	143 (34.8%)	143 (48.0%)	0 (0%)

Baseline polymorphisms are defined as changes from Con1 (AJ238799) and H77 (AF009606) for geno/subtype 1b and 1a/other respectively.

Source: data on file, Janssen Research and Development

Appendix 4: Safety Results

Table 20: AE Summary Table by METAVIR Fibrosis Score; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase					
	METAVIR Fibrosis Score					
	F0-F2		F3		F4	
	PBO	SMV 150 mg	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	290	545	55	126	51	87
Any AE	271 (93.4%)	512 (93.9%)	54 (98.2%)	124 (98.4%)	50 (98.0%)	86 (98.9%)
Worst grade 1 or 2 AE	202 (69.7%)	390 (71.6%)	42 (76.4%)	100 (79.4%)	34 (66.7%)	60 (69.0%)
Worst grade 1	117 (40.3%)	183 (33.6%)	22 (40.0%)	55 (43.7%)	19 (37.3%)	30 (34.5%)
Worst grade 2	85 (29.3%)	207 (38.0%)	20 (36.4%)	45 (35.7%)	15 (29.4%)	30 (34.5%)
Worst grade 3 or 4 AE	69 (23.8%)	122 (22.4%)	12 (21.8%)	24 (19.0%)	16 (31.4%)	26 (29.9%)
Worst grade 3	64 (22.1%)	106 (19.4%)	11 (20.0%)	22 (17.5%)	12 (23.5%)	23 (26.4%)
Worst grade 4	5 (1.7%)	16 (2.9%)	1 (1.8%)	2 (1.6%)	4 (7.8%)	3 (3.4%)
At least possibly related to SMV/PBO	15 (5.2%)	32 (5.9%)	2 (3.6%)	8 (6.3%)	3 (5.9%)	14 (16.1%)
Treatment-related AE	268 (92.4%)	502 (92.1%)	54 (98.2%)	122 (96.8%)	50 (98.0%)	85 (97.7%)
At least possibly related to SMV/PBO	160 (55.2%)	365 (67.0%)	35 (63.6%)	93 (73.8%)	33 (64.7%)	65 (74.7%)
At least possibly related to RBV	198 (68.3%)	399 (73.2%)	44 (80.0%)	105 (83.3%)	37 (72.5%)	72 (82.8%)
At least possibly related to PegIFN	265 (91.4%)	486 (89.2%)	54 (98.2%)	119 (94.4%)	50 (98.0%)	81 (93.1%)
Any AE with fatal outcome	0	0	0	0	0	0
Any SAE	4 (1.4%)	11 (2.0%)	2 (3.6%)	3 (2.4%)	4 (7.8%)	1 (1.1%)
At least possibly related to SMV/PBO	0	2 (0.4%)	0	1 (0.8%)	1 (2.0%)	0
AE leading to permanent stop[a]	11 (3.8%)	15 (2.8%)	2 (3.6%)	2 (1.6%)	5 (9.8%)	3 (3.4%)
SMV/PBO[b]	2 (0.7%)	11 (2.0%)	1 (1.8%)	1 (0.8%)	2 (3.9%)	2 (2.3%)
SMV/PBO only	1 (0.3%)	3 (0.6%)	0	0	1 (2.0%)	1 (1.1%)
SMV/PBO and PegIFN	0	0	0	0	0	0
SMV/PBO and RBV	0	0	0	0	0	0
SMV/PBO, PegIFN and RBV	1 (0.3%)	8 (1.5%)	1 (1.8%)	1 (0.8%)	1 (2.0%)	1 (1.1%)
PegIFN and/or RBV	9 (3.1%)	5 (0.9%)	1 (1.8%)	2 (1.6%)	3 (5.9%)	1 (1.1%)
PegIFN only	0	1 (0.2%)	0	0	0	0
RBV only	0	1 (0.2%)	0	1 (0.8%)	1 (2.0%)	0
PegIFN and RBV	9 (3.1%)	3 (0.6%)	1 (1.8%)	1 (0.8%)	3 (5.9%)	1 (1.1%)

[a]Permanent stop of at least one drug.
[b]Without regard to PegIFN and RBV.

Source: Data on file, Janssen Research and Development

Table 21: Number (%) of Patients with AEs in at Least 5% of Patients in the SMV Group During the First 12 Weeks Phase; Intent-to-treat – Primary Pooling

	First 12 Weeks Phase		Entire Treatment Phase	
SOC PT	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	397	781	397	781
Any AE	376 (94.7%)	744 (95.3%)	382 (96.2%)	757 (96.9%)
General disorders and administration site conditions	317 (79.8%)	603 (77.2%)	329 (82.9%)	618 (79.1%)
Fatigue	157 (39.5%)	278 (35.6%)	167 (42.1%)	288 (36.9%)
Influenza like illness	84 (21.2%)	203 (26.0%)	88 (22.2%)	206 (26.4%)
Pyrexia	104 (26.2%)	184 (23.6%)	111 (28.0%)	194 (24.8%)
Asthenia	71 (17.9%)	125 (16.0%)	84 (21.2%)	141 (18.1%)
Chills	41 (10.3%)	68 (8.7%)	41 (10.3%)	71 (9.1%)
Injection site erythema	22 (5.5%)	44 (5.6%)	23 (5.8%)	47 (6.0%)
Skin and subcutaneous tissue disorders	151 (38.0%)	379 (48.5%)	215 (54.2%)	456 (58.4%)
Pruritus	54 (13.6%)	161 (20.6%)	92 (23.2%)	203 (26.0%)
Rash	44 (11.1%)	106 (13.6%)	64 (16.1%)	139 (17.8%)
Dry skin	27 (6.8%)	60 (7.7%)	47 (11.8%)	84 (10.8%)
Alopecia	21 (5.3%)	44 (5.6%)	59 (14.9%)	99 (12.7%)
Gastrointestinal disorders	158 (39.8%)	355 (45.5%)	194 (48.9%)	398 (51.0%)
Nausea	70 (17.6%)	173 (22.2%)	82 (20.7%)	186 (23.8%)
Diarrhoea	45 (11.3%)	86 (11.0%)	53 (13.4%)	104 (13.3%)
Vomiting	20 (5.0%)	51 (6.5%)	26 (6.5%)	59 (7.6%)
Nervous system disorders	176 (44.3%)	338 (43.3%)	191 (48.1%)	369 (47.2%)
Headache	141 (35.5%)	259 (33.2%)	148 (37.3%)	275 (35.2%)
Dizziness	20 (5.0%)	48 (6.1%)	24 (6.0%)	58 (7.4%)
Psychiatric disorders	151 (38.0%)	299 (38.3%)	183 (46.1%)	330 (42.3%)
Insomnia	67 (16.9%)	131 (16.8%)	85 (21.4%)	157 (20.1%)
Mood altered	46 (11.6%)	74 (9.5%)	56 (14.1%)	84 (10.8%)
Depression	29 (7.3%)	60 (7.7%)	45 (11.3%)	74 (9.5%)
Anxiety	17 (4.3%)	40 (5.1%)	22 (5.5%)	42 (5.4%)
Musculoskeletal and connective tissue disorders	115 (29.0%)	254 (32.5%)	152 (38.3%)	286 (36.6%)
Myalgia	53 (13.4%)	126 (16.1%)	62 (15.6%)	136 (17.4%)
Arthralgia	31 (7.8%)	80 (10.2%)	47 (11.8%)	91 (11.7%)
Back pain	17 (4.3%)	49 (6.3%)	31 (7.8%)	62 (7.9%)
Respiratory, thoracic and mediastinal disorders	85 (21.4%)	200 (25.6%)	121 (30.5%)	236 (30.2%)
Cough	36 (9.1%)	72 (9.2%)	63 (15.9%)	91 (11.7%)
Dyspnoea	22 (5.5%)	60 (7.7%)	25 (6.3%)	73 (9.3%)
Blood and lymphatic system disorders	81 (20.4%)	199 (25.5%)	126 (31.7%)	256 (32.8%)
Neutropenia	50 (12.6%)	109 (14.0%)	70 (17.6%)	140 (17.9%)
Anaemia	40 (10.1%)	93 (11.9%)	82 (20.7%)	129 (16.5%)
Metabolism and nutrition disorders	69 (17.4%)	141 (18.1%)	85 (21.4%)	162 (20.7%)
Decreased appetite	56 (14.1%)	120 (15.4%)	64 (16.1%)	128 (16.4%)
Infections and infestations	52 (13.1%)	137 (17.5%)	120 (30.2%)	217 (27.8%)
Investigations	59 (14.9%)	127 (16.3%)	83 (20.9%)	167 (21.4%)
Eye disorders	35 (8.8%)	67 (8.6%)	59 (14.9%)	90 (11.5%)
Injury, poisoning and procedural complications	9 (2.3%)	43 (5.5%)	26 (6.5%)	64 (8.2%)

Table 21: Number (%) of Patients with AEs in at Least 5% of Patients in the SMV Group During the First 12 Weeks Phase; Intent-to-treat – Primary Pooling

	First 12 Weeks Phase		Entire Treatment Phase	
SOC		SMV		SMV
PT	PBO	150 mg	PBO	150 mg

AEs are coded using MedDRA version 15.0

Source: Data on file, Janssen Research and Development

Table 22: Number (%) of Patients by Completions and Discontinuations of Study Drug and Reasons for Discontinuation; Intent-to-treat – Primary Pooling

	PBO	SMV 150 mg
Analysis Set: ITT	397	781
SMV/PBO		
N	397	781
Completed	133 (33.5%)	729 (93.3%)
Discontinued	264 (66.5%)	52 (6.7%)
Adverse event[a]	5 (1.3%)	14 (1.8%)
Lost to follow-up	1 (0.3%)	2 (0.3%)
Withdrawal by subject	2 (0.5%)	9 (1.2%)
Subject non-compliant	1 (0.3%)	7 (0.9%)
Subject reached a virologic endpoint[b]	255 (64.2%)	19 (2.4%)
Other	0	1 (0.1%)
RBV		
N	397	781
Completed	255 (64.2%)	708 (90.7%)
Discontinued	142 (35.8%)	73 (9.3%)
Adverse event	29 (7.3%)	22 (2.8%)
Lost to follow-up	5 (1.3%)	4 (0.5%)
Withdrawal by subject	15 (3.8%)	14 (1.8%)
Subject non-compliant	4 (1.0%)	7 (0.9%)
Subject reached a virologic endpoint[b]	85 (21.4%)	25 (3.2%)
Other	4 (1.0%)	1 (0.1%)
PegIFN		
N	397	781
Completed	256 (64.5%)	709 (90.8%)
Discontinued	141 (35.5%)	72 (9.2%)
Adverse event	27 (6.8%)	21 (2.7%)
Lost to follow-up	5 (1.3%)	4 (0.5%)
Withdrawal by subject	15 (3.8%)	14 (1.8%)
Subject non-compliant	5 (1.3%)	7 (0.9%)
Subject reached a virologic endpoint[b]	85 (21.4%)	25 (3.2%)
Other	4 (1.0%)	1 (0.1%)

[a] Could include subjects who stopped SMV because they had to stop RBV and/or PegIFN due to an AE.

[b] Subject met a treatment stopping rule.

Source: Data on file, Janssen Research and Development

Table 23: AE Summary Table for *Increased Bilirubin*; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	397	781	397	781
Any AE	11 (2.8%)	62 (7.9%)	12 (3.0%)	64 (8.2%)
Worst grade 1 or 2 AE	9 (2.3%)	46 (5.9%)	9 (2.3%)	48 (6.1%)
Worst grade 1	2 (0.5%)	18 (2.3%)	2 (0.5%)	19 (2.4%)
Worst grade 2	7 (1.8%)	28 (3.6%)	7 (1.8%)	29 (3.7%)
Worst grade 3 or 4 AE	2 (0.5%)	16 (2.0%)	3 (0.8%)	16 (2.0%)
Worst grade 3	2 (0.5%)	14 (1.8%)	3 (0.8%)	14 (1.8%)
Worst grade 4	0	2 (0.3%)	0	2 (0.3%)
At least possibly related to SMV/PBO	0	14 (1.8%)	0	14 (1.8%)
Treatment-related AE	9 (2.3%)	60 (7.7%)	9 (2.3%)	61 (7.8%)
At least possibly related to SMV/PBO	7 (1.8%)	47 (6.0%)	7 (1.8%)	47 (6.0%)
At least possibly related to RBV	6 (1.5%)	42 (5.4%)	6 (1.5%)	42 (5.4%)
At least possibly related to PegIFN	0	19 (2.4%)	0	20 (2.6%)
Any AE with fatal outcome	0	0	0	0
Any SAE	0	0	0	0
At least possibly related to SMV/PBO	0	0	0	0
AE leading to permanent stop[a]	0	1 (0.1%)	0	1 (0.1%)
SMV/PBO[b]	0	1 (0.1%)[c]	0	1 (0.1%)
SMV/PBO only	0	1 (0.1%)	0	1 (0.1%)
SMV/PBO and PegIFN	0	0	0	0
SMV/PBO and RBV	0	0	0	0
SMV/PBO, PegIFN and RBV	0	0	0	0
PegIFN and/or RBV	0	0	0	0
PegIFN only	0	0	0	0
RBV only	0	0	0	0
PegIFN and RBV	0	0	0	0

[a]Permanent stop of at least one drug.
[b]Without regard to PegIFN and RBV.
[c]Patient stopped due to a grade 4 increased blood bilirubin, not associated with any transaminase increases and any other sign for liver decompensation. The patient stopped as required by a clinical study protocol defined toxicity management guideline.
Increased bilirubin includes MedDRA PTs: bilirubin conjugated abnormal, bilirubin conjugated increased, bilirubin excretion disorder, bilirubinuria, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinemia, icterus index increased, jaundice, jaundice cholestatic, jaundice extrahepatic obstructive, jaundice hepatocellular, ocular icterus, urine bilirubin increased, and yellow skin.
Source: Data on file, Janssen Research and Development

Table 24: AE Summary Table for *Rash (Any Type)*; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	397	781	397	781
Any AE	67 (16.9%)	181 (23.2%)	99 (24.9%)	218 (27.9%)
Worst grade 1 or 2 AE	67 (16.9%)	176 (22.5%)	99 (24.9%)	213 (27.3%)
Worst grade 1	52 (13.1%)	118 (15.1%)	78 (19.6%)	141 (18.1%)
Worst grade 2	15 (3.8%)	58 (7.4%)	21 (5.3%)	72 (9.2%)
Worst grade 3 or 4 AE	0	5 (0.6%)	0	5 (0.6%)
Worst grade 3	0	5 (0.6%)	0	5 (0.6%)
At least possibly related to SMV/PBO	0	2 (0.3%)	0	2 (0.3%)
Treatment-related AE	61 (15.4%)	163 (20.9%)	86 (21.7%)	196 (25.1%)
At least possibly related to SMV/PBO	37 (9.3%)	149 (19.1%)	37 (9.3%)	150 (19.2%)
At least possibly related to RBV	47 (11.8%)	129 (16.5%)	69 (17.4%)	165 (21.1%)
At least possibly related to PegIFN	43 (10.8%)	83 (10.6%)	63 (15.9%)	104 (13.3%)
Any AE with fatal outcome	0	0	0	0
Any SAE	0	2 (0.3%)	0	2 (0.3%)
At least possibly related to SMV/PBO	0	2 (0.3%)	0	2 (0.3%)
AE leading to permanent stop[a]	1 (0.3%)	7 (0.9%)	2 (0.5%)	7 (0.9%)
SMV/PBO[b]	1 (0.3%)	6 (0.8%)	1 (0.3%)	6 (0.8%)
SMV/PBO only	1 (0.3%)	2 (0.3%)	1 (0.3%)	2 (0.3%)
SMV/PBO and PegIFN	0	0	0	0
SMV/PBO and RBV	0	0	0	0
SMV/PBO, PegIFN and RBV	0	4 (0.5%)	0	4 (0.5%)
PegIFN and/or RBV	0	2 (0.3%)	1 (0.3%)	2 (0.3%)
PegIFN only	0	0	0	0
RBV only	0	1 (0.1%)	1 (0.3%)	1 (0.1%)
PegIFN and RBV	0	1 (0.1%)	0	1 (0.1%)

[a]Permanent stop of at least one drug.
[b]Without regard to PegIFN and RBV.
Rash (Any Type) includes MedDRA HLTs: "Erythemas", "Papulosquamous conditions", "Rashes, eruptions and exanthems NEC", "Photosensitivity conditions", MedDRA SMQ "Severe cutaneous adverse reaction": narrow scope) and selected terms of the broad scope.
Source: Data on file, Janssen Research and Development

Table 25: AE Summary Table for *Photosensitivity Conditions*; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	397	781	397	781
Any AE	2 (0.5%)	26 (3.3%)	2 (0.5%)	26 (3.3%)
Worst grade 1 or 2 AE	2 (0.5%)	25 (3.2%)	2 (0.5%)	25 (3.2%)
Worst grade 1	2 (0.5%)	21 (2.7%)	2 (0.5%)	21 (2.7%)
Worst grade 2	0	4 (0.5%)	0	4 (0.5%)
Worst grade 3 or 4 AE	0	1 (0.1%)	0	1 (0.1%)
Worst grade 3	0	1 (0.1%)	0	1 (0.1%)
At least possibly related to SMV/PBO	0	1 (0.1%)	0	1 (0.1%)
Treatment-related AE	1 (0.3%)	24 (3.1%)	1 (0.3%)	24 (3.1%)
At least possibly related to SMV/PBO	1 (0.3%)	22 (2.8%)	1 (0.3%)	22 (2.8%)
At least possibly related to RBV	1 (0.3%)	13 (1.7%)	1 (0.3%)	13 (1.7%)
At least possibly related to PegIFN	0	14 (1.8%)	0	14 (1.8%)
Any AE with fatal outcome	0	0	0	0
Any SAE	0	2 (0.3%)	0	2 (0.3%)
At least possibly related to SMV/PBO	0	2 (0.3%)	0	2 (0.3%)
AE leading to permanent stop[a]	0	0	0	0
SMV/PBO[b]	0	0	0	0
SMV/PBO only	0	0	0	0
SMV/PBO and PegIFN	0	0	0	0
SMV/PBO and RBV	0	0	0	0
SMV/PBO, PegIFN and RBV	0	0	0	0
PegIFN and/or RBV	0	0	0	0
PegIFN only	0	0	0	0
RBV only	0	0	0	0
PegIFN and RBV	0	0	0	0

[a]Permanent stop of at least one drug.
[b]Without regard to PegIFN and RBV.
Photosensitivity conditions include MedDRA HLT "Photosensitivity conditions".

Source: Data on file, Janssen Research and Development

Table 26: Number (%) of Patients with Events of Interest by Geographical Region, First 12 Weeks Phase; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks							
	Geographical Region							
	Europe		North America		South America		Asia/Pacific	
	PBO	SMV 150mg	PBO	SMV 150mg	PBO	SMV 150mg	PBO	SMV 150mg
Analysis set: Intent-to-treat	232	460	119	221	19	41	27	59
Events of special interest	9 (3.9%)	44 (9.6%)	1 (0.8%)	16 (7.2%)	1 (5.3%)	1 (2.4%)	0	1 (1.7%)
Increased Bilirubin	9 (3.9%)	44 (9.6%)	1 (0.8%)	16 (7.2%)	1 (5.3%)	1 (2.4%)	0	1 (1.7%)
Events of clinical interest	85 (36.6%)	235 (51.1%)	51 (42.9%)	115 (52.0%)	10 (52.6%)	28 (68.3%)	15 (55.6%)	41 (69.5%)
Rash (Any Type)	19 (8.2%)	93 (20.2%)	32 (26.9%)	50 (22.6%)	5 (26.3%)	11 (26.8%)	11 (40.7%)	27 (45.8%)
Pruritus	39 (16.8%)	106 (23.0%)	12 (10.1%)	39 (17.6%)	2 (10.5%)	9 (22.0%)	6 (22.2%)	18 (30.5%)
Photosensitivity conditions	0	17 (3.7%)	2 (1.7%)	5 (2.3%)	0	2 (4.9%)	0	2 (3.4%)
Neutropenia	37 (15.9%)	73 (15.9%)	15 (12.6%)	34 (15.4%)	6 (31.6%)	11 (26.8%)	2 (7.4%)	11 (18.6%)
Anemia	17 (7.3%)	53 (11.5%)	21 (17.6%)	40 (18.1%)	5 (26.3%)	7 (17.1%)	0	5 (8.5%)

Patients are counted only once for any given event, regardless of the number of times they actually reported the same event.
Adverse events are coded using MedDRA version 15.0

Source: Data on file, Janssen Research and Development

Table 27: AE Summary Table for *Pruritus*; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis set: Intent-to-treat	397	781	397	781
Any AE	59 (14.9%)	172 (22.0%)	99 (24.9%)	217 (27.8%)
Worst grade 1 or 2 AE	59 (14.9%)	171 (21.9%)	99 (24.9%)	215 (27.5%)
Worst grade 1	56 (14.1%)	147 (18.8%)	87 (21.9%)	179 (22.9%)
Worst grade 2	3 (0.8%)	24 (3.1%)	12 (3.0%)	36 (4.6%)
Worst grade 3 or 4 AE	0	1 (0.1%)	0	2 (0.3%)
Worst grade 3	0	1 (0.1%)	0	2 (0.3%)
At least possibly related to SMV/PBO	0	1 (0.1%)	0	1 (0.1%)
Treatment-related AE	54 (13.6%)	160 (20.5%)	87 (21.9%)	198 (25.4%)
At least possibly related to SMV/PBO	34 (8.6%)	129 (16.5%)	34 (8.6%)	131 (16.8%)
At least possibly related to RBV	49 (12.3%)	139 (17.8%)	78 (19.6%)	172 (22.0%)
At least possibly related to PegIFN	39 (9.8%)	122 (15.6%)	63 (15.9%)	147 (18.8%)
Any AE with fatal outcome	0	0	0	0
Any SAE	0	0	0	0
At least possibly related to SMV/PBO	0	0	0	0
AE leading to permanent stop[a]	0	1 (0.1%)	0	2 (0.3%)
SMV/PBO[b]	0	1 (0.1%)	0	1 (0.1%)
SMV/PBO only	0	0	0	0
SMV/PBO and PegIFN	0	0	0	0
SMV/PBO and RBV	0	0	0	0
SMV/PBO, PegIFN and RBV	0	1 (0.1%)	0	1 (0.1%)
PegIFN and/or RBV	0	0	0	1 (0.1%)
PegIFN only	0	0	0	0
RBV only	0	0	0	1 (0.1%)
PegIFN and RBV	0	0	0	0

[a]Permanent stop of at least one drug.
[b]Without regard to PegIFN and RBV.
Pruritus includes MedDRA HLT "Pruritus NEC".
Source: Data on file, Janssen Research and Development

Table 28: Number (%) of Patients with Selected[a] Laboratory Parameters (Worst Toxicity Grade[b]); Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	397	781	397	781
Chemistry				
Hepatic parameters				
ALT				
N	395	780	396	780
Grade 1	30 (7.6%)	47 (6.0%)	42 (10.6%)	57 (7.3%)
Grade 2	11 (2.8%)	23 (2.9%)	17 (4.3%)	36 (4.6%)
Grade 3	8 (2.0%)	10 (1.3%)	15 (3.8%)	14 (1.8%)
Grade 4	0	0	1 (0.3%)	3 (0.4%)
AST				
N	395	780	396	780
Grade 1	49 (12.4%)	65 (8.3%)	59 (14.9%)	84 (10.8%)
Grade 2	13 (3.3%)	28 (3.6%)	28 (7.1%)	36 (4.6%)
Grade 3	5 (1.3%)	8 (1.0%)	9 (2.3%)	18 (2.3%)
Grade 4	0	0	1 (0.3%)	1 (0.1%)
GGT				
N	387	767	393	768
Grade 1	35 (9.0%)	36 (4.7%)	41 (10.4%)	51 (6.6%)
Grade 2	17 (4.4%)	16 (2.1%)	27 (6.9%)	32 (4.2%)
Grade 3	5 (1.3%)	2 (0.3%)	13 (3.3%)	14 (1.8%)
Grade 4	2 (0.5%)	1 (0.1%)	2 (0.5%)	4 (0.5%)
Hyperbilirubinemia				
N	395	780	396	780
Grade 1	61 (15.4%)	208 (26.7%)	64 (16.2%)	208 (26.7%)
Grade 2	36 (9.1%)	143 (18.3%)	35 (8.8%)	142 (18.2%)
Grade 3	6 (1.5%)	32 (4.1%)	7 (1.8%)	33 (4.2%)
Grade 4	0	3 (0.4%)	0	3 (0.4%)
Lipids and glucose				
Hyperglycemia				
N	395	780	396	780
Grade 1	55 (13.9%)	108 (13.8%)	92 (23.2%)	145 (18.6%)
Grade 2	9 (2.3%)	23 (2.9%)	15 (3.8%)	28 (3.6%)
Grade 3	3 (0.8%)	6 (0.8%)	4 (1.0%)	11 (1.4%)
Grade 4	0	0	0	0
General biochemistry				
Amylase				
N	395	780	396	780
Grade 1	57 (14.4%)	116 (14.9%)	65 (16.4%)	132 (16.9%)
Grade 2	22 (5.6%)	38 (4.9%)	27 (6.8%)	49 (6.3%)
Grade 3	11 (2.8%)	27 (3.5%)	16 (4.0%)	33 (4.2%)
Grade 4	0	0	1 (0.3%)	0

Table 28: Number (%) of Patients with Selected[a] Laboratory Parameters (Worst Toxicity Grade[b]); Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
Hypercalcemia				
N	395	780	396	780
Grade 1	1 (0.3%)	7 (0.9%)	4 (1.0%)	7 (0.9%)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	1 (0.3%)	0
Hypocalcemia				
N	395	780	396	780
Grade 1	12 (3.0%)	29 (3.7%)	39 (9.8%)	54 (6.9%)
Grade 2	6 (1.5%)	3 (0.4%)	6 (1.5%)	4 (0.5%)
Grade 3	0	0	1 (0.3%)	3 (0.4%)
Grade 4	0	0	0	0
Hypophosphatemia				
N	395	780	396	780
Grade 1	77 (19.5%)	164 (21.0%)	107 (27.0%)	219 (28.1%)
Grade 2	11 (2.8%)	29 (3.7%)	26 (6.6%)	60 (7.7%)
Grade 3	4 (1.0%)	0	6 (1.5%)	3 (0.4%)
Grade 4	0	0	0	0
Triacylglycerol Lipase				
N	395	780	396	780
Grade 1	8 (2.0%)	19 (2.4%)	11 (2.8%)	21 (2.7%)
Grade 2	6 (1.5%)	6 (0.8%)	9 (2.3%)	12 (1.5%)
Grade 3	3 (0.8%)	5 (0.6%)	3 (0.8%)	5 (0.6%)
Grade 4	0	0	1 (0.3%)	0
Hematology				
Hematology differential counts				
Neutrophils and Precursors				
N	395	780	396	780
Grade 1	149 (37.7%)	314 (40.3%)	135 (34.1%)	295 (37.8%)
Grade 2	93 (23.5%)	159 (20.4%)	101 (25.5%)	173 (22.2%)
Grade 3	52 (13.2%)	96 (12.3%)	82 (20.7%)	136 (17.4%)
Grade 4	11 (2.8%)	23 (2.9%)	20 (5.1%)	33 (4.2%)
Hematology coagulation				
Activated PTT				
N	395	780	396	780
Grade 1	42 (10.6%)	90 (11.5%)	82 (20.7%)	131 (16.8%)
Grade 2	2 (0.5%)	4 (0.5%)	2 (0.5%)	9 (1.2%)
Grade 3	1 (0.3%)	0	2 (0.5%)	0
Grade 4	1 (0.3%)	1 (0.1%)	1 (0.3%)	1 (0.1%)
Prothrombin Time				
N	395	780	396	780
Grade 1	13 (3.3%)	18 (2.3%)	26 (6.6%)	34 (4.4%)
Grade 2	3 (0.8%)	2 (0.3%)	5 (1.3%)	2 (0.3%)
Grade 3	4 (1.0%)	3 (0.4%)	9 (2.3%)	6 (0.8%)
Grade 4	1 (0.3%)	1 (0.1%)	1 (0.3%)	1 (0.1%)

Table 28: Number (%) of Patients with Selected[a] Laboratory Parameters (Worst Toxicity Grade[b]); Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 weeks Phase		Entire Treatment Phase	
	PBO	SMV 150 mg	PBO	SMV 150 mg
General hematology				
Hemoglobin				
N	395	780	396	780
Grade 1	59 (14.9%)	121 (15.5%)	98 (24.7%)	173 (22.2%)
Grade 2	19 (4.8%)	41 (5.3%)	48 (12.1%)	75 (9.6%)
Grade 3	7 (1.8%)	6 (0.8%)	12 (3.0%)	8 (1.0%)
Grade 4	0	0	0	0
Platelet				
N	395	780	396	780
Grade 1	54 (13.7%)	101 (12.9%)	64 (16.2%)	127 (16.3%)
Grade 2	37 (9.4%)	44 (5.6%)	42 (10.6%)	55 (7.1%)
Grade 3	3 (0.8%)	13 (1.7%)	13 (3.3%)	22 (2.8%)
Grade 4	0	0	0	1 (0.1%)

[a]Reaching at least grade 3 in at least 1 patient.
[b]According to the WHO toxicity grading scale .

Source: Data on file, Janssen Research and Development

Table 29: Statistical Analysis of the AUC_{60} for the Fatigue Severity Scale and the WPAI Productivity, Activity Impairment, and Absenteeism Scores Using a Piecewise Linear Model Approach; Intent-to-treat – Pooled C208/C216/HPC3007

	SMV + PR			PBO + PR			Difference in	95% CI	P-value
PRO Endpoints	N	LS Mean	95% CI	N	LS Mean	95% CI	AUC_{60}		
Fatigue Severity Scale Score*									
C208	260	214.9	(205.8; 223.9)	130	235.5	(224.1; 247.0)	-20.7	(-32.7; -8.6)	< 0.001
C216	256	208.4	(199.4; 217.3)	133	225.0	(213.6; 236.4)	-16.7	(-29.1; -4.3)	0.009
HPC3007	257	226.1	(217.3; 234.9)	130	253.0	(241.7; 264.2)	-26.9	(-39.1; -14.7)	< 0.001
Pooled Phase 3	773	214.1	(208.3; 220.0)	393	235.6	(228.4; 242.7)	-21.4	(-28.5; -14.4)	< 0.001
WPAI Productivity Impairment Score**									
C208	260	1555.4	(1415.9;1694.9)	130	1791.2	(1604.4;1978.1)	-235.9	(-448.3; -23.4)	0.030
C216	256	1626.7	(1487.7;1765.6)	133	1909.0	(1726.1;2092.0)	-282.4	(-491.5; -73.2)	0.008
HPC3007	257	1680.1	(1534.5;1825.8)	130	2228.0	(2040.8;2415.3)	-547.9	(-751.9;-343.9)	< 0.001
Pooled Phase 3	773	1554.4	(1461.9;1646.8)	393	1904.2	(1788.4;2020.1)	-349.9	(-470.5;-229.2)	< 0.001
WPAI Activity Impairment Score***									
C208	260	1515.6	(1377.5;1653.7)	130	1795.0	(1609.5;1980.4)	-279.4	(-490.9; -67.8)	0.010
C216	256	1579.1	(1441.3;1716.9)	133	1862.0	(1680.3;2043.8)	-282.9	(-491.1; -74.7)	0.008
HPC3007	257	1655.2	(1510.8;1799.5)	130	2238.0	(2051.8;2424.1)	-582.8	(-786.6;-379.0)	< 0.001
Pooled Phase 3	773	1519.8	(1428.3;1611.4)	393	1894.7	(1779.7;2009.7)	-374.9	(-495.1;-254.6)	< 0.001
WPAI Absenteeism Score****									
C208	164	443.6	(321.2; 565.9)	76	404.6	(231.7; 577.5)	39.0	(-165.0; 242.9)	0.708
C216	179	663.3	(510.1; 816.6)	86	847.8	(631.1;1064.5)	-184.5	(-436.7; 67.7)	0.151
HPC3007	171	554.3	(413.4; 695.2)	78	600.1	(397.9; 802.4)	-45.9	(-280.1; 188.4)	0.701
Pooled Phase 3	514	522.5	(432.4; 612.5)	240	595.0	(473.7; 716.3)	-72.6	(-206.5; 61.4)	0.288

* The fatigue severity score (FSS) total score ranges from 1 to 7, with higher scores indicating worse outcome.

** Work Productivity and Activity Impairment (WPAI) productivity scores range from 0 to 100, with higher scores indicating more impairment in work and/or daily activities; WPAI Productivity score is available for all patients who completed the questionnaire; for patients who were not employed during the study, the score is based only on individual Question 6 (multiplied by 10).

*** WPAI Activity Impairment score is based on WPAI Question 6: "During the past 7 days, how much did HCV affect your ability to do your regular daily activities"; scores range from 0 (no effect on activities) to 10 (completely prevented me from doing my daily activities); for the purpose of the analysis, the score was multiplied by 10; this score is available for all patients who completed the questionnaire.

**** WPAI Absenteeism score is the number of hours missed from work because of HCV divided by the total number of hours supposed to work, and expressed as a percentage and is based on Question 2: "In the last 7 days, how many hours were you absent from your job because of problems that are related to your HCV?" WPAI Absenteeism score is only provided for patients who were in the labor force at baseline.

Table 30: Number (%) of Patients with Events of Interest by METAVIR Fibrosis Score; Intent-to-treat – Pooled C208/C216/HPC3007

	First 12 Weeks Phase					
	METAVIR Fibrosis Score					
	F0-F2		F3		F4	
	PBO	SMV 150 mg	PBO	SMV 150 mg	PBO	SMV 150 mg
Analysis Set: Intent-to-treat	290	545	55	126	51	87
Events of special interest						
Increased bilirubin	8 (2.8%)	37 (6.8%)	2 (3.6%)	8 (6.3%)	1 (2.0%)	13 (14.9%)
Events of clinical interest						
Rash (Any Type)	44 (15.2%)	121 (22.2%)	11 (20.0%)	29 (23.0%)	12 (23.5%)	26 (29.9%)
Photosensitivity conditions	1 (0.3%)	16 (2.9%)	1 (1.8%)	6 (4.8%)	0	3 (3.4%)
Pruritus	39 (13.4%)	117 (21.5%)	8 (14.5%)	24 (19.0%)	12 (23.5%)	26 (29.9%)
Neutropenia	41 (14.1%)	89 (16.3%)	8 (14.5%)	18 (14.3%)	10 (19.6%)	17 (19.5%)
Anemia	27 (9.3%)	61 (11.2%)	9 (16.4%)	23 (18.3%)	7 (13.7%)	19 (21.8%)

Source: Data on file, Janssen Research and Development

Appendix 5: Events of Interest – Grouped Terms

Event of Interest:

Increased Bilirubin

The event of special interest *increased bilirubin* included:

> MedDRA PTs: bilirubin conjugated abnormal, bilirubin conjugated increased, bilirubin excretion disorder, bilirubinuria, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinemia, icterus index increased, jaundice, jaundice cholestatic, jaundice extrahepatic obstructive, jaundice hepatocellular, ocular icterus, urine bilirubin increased, and yellow skin.

Rash (Any Type)

The event of clinical interest *rash (any type)* included the following terms:

> MedDRA HLT: erythemas, papulosquamous conditions, rashes, eruptions and exanthems not elsewhere classified (NEC), and photosensitivity conditions. Note: the PTs of the MedDRA HLT photosensitivity conditions are also included in the separate grouped term *photosensitivity conditions*.
>
> MedDRA SMQ: Severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope (acquired epidermolysis bullosa, blister, bullous impetigo, drug eruption, drug rash with eosinophilia and systemic symptoms, epidermolysis, epidermolysis bullosa, mucocutaneous ulceration, Nikolsky's sign, pemphigoid, pemphigus, skin erosion, and skin exfoliation).

Photosensitivity Conditions

The event of clinical interest *photosensitivity conditions* included:

> MedDRA HLT: photosensitivity conditions. The PTs included are application site photosensitivity reaction, Hartnup disease, Hutchinson’s summer prurigo, infusion site photosensitivity reaction, injection site photosensitivity reaction, juvenile spring eruption, photodermatosis, photosensitivity allergic reaction, photosensitivity reaction, polymorphic light eruption, and solar dermatitis.

Note, all PTs of the grouped term *photosensitivity conditions* are also included in the grouped term *rash (any type)*.

Pruritus

The event of clinical interest *pruritus* included:

> MedDRA HLT: pruritus NEC.

Neutropenia

The event of clinical interest *neutropenia* included:

> MedDRA PTs: neutropenia and neutrophil count decreased.

Anemia

The event of clinical interest *anemia* included:

> MedDRA PTs: anemia, hemoglobin decreased, and hemolytic anemia.

Dyspnea

The grouped term dyspnea included the following PTs: acute respiratory distress syndrome, cardiorespiratory arrest, dyspnea, dyspnea exertional, dyspnea at rest, dyspnea paroxysmal nocturnal, hyperventilation, nocturnal dyspnea, orthopnea, respiratory arrest, respiratory distress, and tachypnea.