Attachment 1: Product information for AusPAR Olysio/Janssen Simeprevir, simeprevir (as sodium) Janssen Cilag Pty Ltd PM-2013-01557-1-2 Date of Finalisation 27 October 2014. This Product Information was approved at the time this AusPAR was published.

OLYSIO®

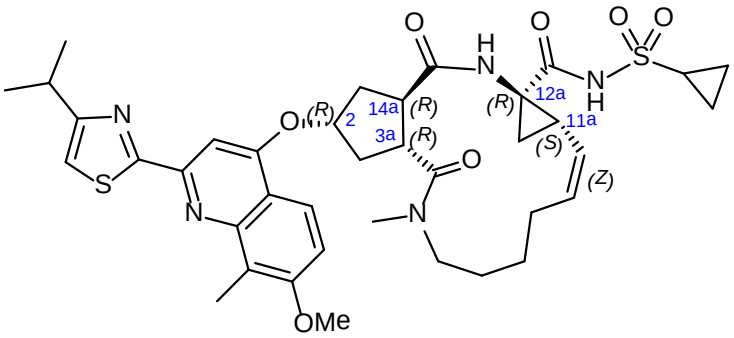
simeprevir

PRODUCT INFORMATION

NAME OF THE MEDICINE

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

Simeprevir has the following chemical structure:



Molecular formula: $C_{38}H_{47}N_5O_7S_2$ Molecular weight: 749.94
CAS Registry Number: 923604-59-5

DESCRIPTION

Simeprevir is a white to almost white powder.
Simeprevir is practically insoluble in water over a wide pH range, it is amphiprotic with a basic thiazole moiety (pKa = 2.85) and acidic sulfonyl carboxamide group (pKa = 5.24). The distribution coefficient (log D; using 1-octanol) was greater than 4.5 regardless of pH or aqueous buffered solution (at 22°C).

OLYSIO (simeprevir) is available as 150 mg hard capsules for oral use. The capsules are white with the body of the capsule marked with “TMC435 150” in black ink. Each capsule contains 154.4 mg simeprevir sodium salt equivalent to 150 mg simeprevir. Each 150 mg capsule also contains the following inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, lactose, sodium lauryl sulphate and magnesium stearate. Each capsule contains 78.4 mg lactose. The capsule shell contains gelatin and titanium dioxide (E171). Capsules are printed with ink containing iron oxide black (E172) and shellac (E904).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Direct-acting antiviral

Mechanism of action

Simeprevir is an inhibitor of the Hepatitis C Virus (HCV) NS3/4A protease which is essential for viral replication. In a biochemical assay, simeprevir inhibited the proteolytic activity of recombinant genotype 1a and 1b HCV NS3/4A proteases, with median K_i values of 0.5 nM and 1.4 nM, respectively.

Antiviral activity

The median simeprevir 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. Activity of simeprevir against a selection of genotype 1a and genotype 1b chimeric replicons carrying NS3 sequences derived from HCV PI-naïve patients resulted in median fold change (FC) in EC_{50} values of 1.4 (N=78) and 0.4 (N=59) compared to reference genotype 1b replicon, respectively. Genotype 1a and 1b isolates with a baseline Q80K polymorphism resulted in median FC in simeprevir EC_{50} of 11 (N=33) and 8.4 (N=2), respectively. Median simeprevir FC values against genotype 2, genotype 3, and genotype 4 baseline isolates tested were 25 (N=4), 1014 (N=2), and 0.3 (N=8), respectively. The presence of 50% human serum reduced simeprevir replicon activity by 2.4-fold. *In vitro* combination of simeprevir with interferon, ribavirin, NS5A or NS5B inhibitors resulted in additive or synergistic effects.

Resistance

Resistance in cell culture
Resistance to simeprevir was characterized in HCV genotype 1a and 1b replicon-containing cells. Ninety-six percent of simeprevir-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 simeprevir 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 simeprevir activity. Substitutions such as D168V or A, and R155K were usually associated with simeprevir treatment failure, and displayed high level resistance to simeprevir (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 simeprevir activity (FC in $EC_{50} \leq 2$). Amino acid substitutions at NS3 positions 80, 122, 155, and/or 168, associated with low level resistance to simeprevir when occurring alone, reduced simeprevir activity by more than 50-fold when present in combination.

Resistance in clinical studies
In a pooled analysis of patients treated with 150 mg OLYSIO in combination with peginterferon alfa and ribavirin who did not achieve sustained virologic response (SVR) in the controlled Phase 2b and Phase 3 clinical studies, emerging amino acid substitutions at NS3 positions 80, 122, 155 and/or 168 were observed in 180 out of 197 (91%) patients. Substitutions D168V and R155K alone or in combinations with other mutations at these positions emerged most frequently (Table 1). Most of these emerging substitutions have been shown to reduce simeprevir anti-HCV activity in cell culture replicon assays.

HCV genotype 1 subtype-specific patterns of simeprevir treatment-emergent amino acid substitutions were observed in patients not achieving SVR. Patients with HCV genotype 1a predominantly had emerging R155K alone or in combination with amino acid substitutions at NS3 positions 80, 122 and/or 168, while patients with HCV genotype 1b had most often an emerging D168V substitution (Table 1). In patients with HCV genotype 1a with a baseline Q80K amino acid substitution, an emerging R155K substitution was observed most frequently at failure.

Table 1: Treatment-Emergent Amino Acid Substitutions in Pooled Phase 2b and Phase 3 Studies: Patients Who Did Not Achieve SVR With 150 mg OLYSIO in Combination With Peginterferon Alfa and Ribavirin

Emerging Amino Acid Substitutions in NS3	All HCV Genotypes N=197 % (n)	Genotype 1a[1] N=116 % (n)	Genotype 1b N=81 % (n)
Any substitution at NS3 position 43, 80, 122, 155, 156, or 168[2]	91.4% (180)	94.8% (110)	86.4% (70)
D168E	15.7% (31)	14.7% (17)	17.3% (14)
D168V	31.0% (61)	10.3% (12)	60.5% (49)
Q80R[3]	7.6% (15)	4.3% (5)	12.3% (10)
R155K	45.2% (89)	76.7% (89)	0% (0)
Q80X+D168X[4]	8.1% (16)	4.3% (5)	13.6% (11)
R155X+D168X[4]	9.1% (18)	12.9% (15)	3.7% (3)
Q80K[3], S122A/G/I/T[3], S122R, R155Q, D168A, D168F[3], D168H, D168T	Less than 10%	Less than 10%	Less than 10%

[1] May include few patients with HCV non-genotype 1a/1b.
[2] Alone or in combination with other substitutions (includes mixtures).
[3] Substitutions only observed in combinations with other emerging substitutions at one or more of the NS3 positions 80, 122, 155 and/or 168.
[4] Patients with these combinations are also included in other rows describing the individual substitutions. X represents multiple amino acids. Other double or triple mutations were observed with lower frequencies.

Note: substitutions at NS3 position 43 and 156 associated with reduced simeprevir activity *in vitro* were not observed at time of failure. In addition, two patients had emerging single substitution I170T at time of failure.

In study HPC3011 in genotype 4 infected patients, 20 of 22 (91%) patients who did not achieve SVR had emerging amino acid substitutions at NS3 positions 80, 122, 155 and/or 168 (mainly D168V), similar to the emerging amino acid substitutions observed in genotype 1 infected patients.

Persistence of Resistance–Associated Substitutions
The persistence of simeprevir-resistant NS3 amino acid substitutions was assessed following treatment failure.

In the pooled analysis of patients receiving 150 mg OLYSIO in combination with peginterferon alfa and ribavirin in the Phase 2b and Phase 3 studies, treatment-emergent simeprevir-resistance variants were no longer detectable in 90 out of 180 patients (50%) at the end of the studies after a median follow-up of 28 weeks (range 0-70 weeks). In 32 out of 48 patients (67%) with emerging single D168V and in 34 out of 66 (52%) patients with emerging single R155K, the respective emerging variants were no longer detected at end of the studies. Data from an ongoing, long-term follow-up study (Study HPC3002) in patients who did not achieve SVR with a OLYSIO-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 88 weeks (range 47-147 weeks).

The long-term clinical impact of the emergence or persistence of simeprevir-resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses were conducted to explore the association between naturally-occurring baseline NS3/4A amino acid substitutions (polymorphisms) and treatment outcome.

Baseline polymorphisms at NS3 positions 43, 80, 122, 155, 156, and/or 168, associated with reduced simeprevir activity *in vitro* were generally uncommon (1.3%) in patients with HCV genotype 1 infection in the Phase 2b and Phase 3 studies (n=2007), with exception of the low-level resistance substitution Q80K. The observed prevalence of Q80K polymorphism at baseline in the overall population of the Phase 2b and Phase 3 studies was 14%, 30% in patients with HCV genotype 1a and 0.5% in patients with HCV genotype 1b. Q80K polymorphism in the clinical studies for Australia/New Zealand was 7% (n=11/155). The Q80K polymorphism was not observed in patients with genotype 4 (study HPC3011).

In the pooled analysis of the Phase 3 Studies C208 and C216, and in Study HPC3007, the presence of Q80K at baseline was associated with lower SVR rates in HCV genotype 1a OLYSIO-treated patients compared to HCV genotype 1a OLYSIO-treated patients without Q80K (Table 2).

Table 2: SVR12 Rates by HCV geno/subtype and Presence or Absence of Baseline Q80K Polymorphism in HCV Genotype 1 Patients

	All patients with HCV genotype 1a[1]	Patients with HCV genotype 1a[1] - Presence/Absence of Q80K polymorphism at baseline[2]		All patients with HCV genotype 1b
		Presence	Absence	
HCV mono infected patients (studies C208, C216, HPC3007 and C206)				
Treatment-naïve patients (pooled Studies C208 and C216)				
OLYSIO	75% (191/254)	58% (49/84)	84% (138/165)	85% (228/267)
Placebo	47% (62/131)	47% (62/131)		53% (70/133)
Prior relapser (Study HPC3007)				
OLYSIO	70% (78/111)	47% (14/30)	78% (62/79)	86% (128/149)
Placebo	28% (15/54)	28% (15/54)		43% (34/79)
Prior partial responder (Study C206)				
OLYSIO[3]	56% (14/25)	38% (3/8)	65% (11/17)	88% (38/43)
Placebo	13% (1/8)	13% (1/8)		7% (1/15)
Prior null responder (Study C206)				
OLYSIO[3]	42% (11/26)	75% (3/4)	38% (8/21)	58% (14/24)
Placebo	0% (0/7)	0% (0/7)		33% (3/9)
HCV/HIV 1 co infected patients (study C212)				
Treatment naïve patients				
OLYSIO	77% (33/43)	86% (12/14)	72% (21/29)	90% (9/10)
Prior relapsers				
OLYSIO	83% (10/12)	33% (1/3)	100% (9/9)	100% (3/3)
Prior partial responders				
OLYSIO	67% (6/9)	100% (1/1)	62% (5/8)	100% (1/1)
Prior null responders				
OLYSIO	54% (13/24)	50% (6/12)	58% (7/12)	75% (3/4)

[1] May include few patients with HCV non-genotype 1a/1b.
[2] Number of patients in the OLYSIO treatment group: only patients with sequence data available.
[3] Pooled 150 mg OLYSIO treatment group.
Note: In Studies C208, C216, HPC3007 and C206, three HCV genotype 1b infected patients had baseline Q80K polymorphism. All three patients had SVR12.

In the pooled analysis of Studies C208 and C216, 63% of OLYSIO-treated HCV genotype 1a infected patients (n=53/84) with Q80K polymorphism at baseline had undetectable HCV RNA at Week 4 (Rapid Virologic Response; RVR), and 79% of these patients (n=42/53) achieved SVR12. Among the OLYSIO-treated genotype 1a patients with Q80K and HCV RNA < 25 IU/mL detectable at Week 4 (13%; n=11/84), 45% (n=5/11) achieved SVR12.
In Study HPC3007, 43% of OLYSIO-treated HCV genotype 1a infected patients (n=13/30) with Q80K polymorphism at baseline had undetectable HCV RNA at Week 4 (RVR), and 77% of these patients (n=10/13) achieved SVR12. Among the OLYSIO-treated genotype 1a patients with Q80K and HCV RNA < 25 IU/mL detectable at Week 4 (40%; n=12/30), 33% (n=4/12) achieved SVR12.

Cross-Resistance

Some of the treatment-emergent NS3 amino acid substitutions detected in OLYSIO-treated patients who did not achieve SVR in clinical studies (e.g., R155K) have been shown to reduce anti-HCV activity of telaprevir, boceprevir, and other NS3/4A PIs. The impact of prior exposure to simeprevir in patients not achieving SVR on the efficacy of subsequent HCV NS3/4A PI-based treatment regimens has not been established. There are no clinical data on the efficacy of OLYSIO in patients with a history of exposure to the NS3/4A PIs telaprevir or boceprevir. Simeprevir-resistant variants studied remained susceptible to representative HCV nucleoside and non-nucleoside polymerase inhibitors, and NS5A inhibitors. Variants carrying amino-acid substitutions conferring reduced susceptibility to NS5A inhibitors (Y93C/H, L31F/V), nucleoside inhibitors (S96T) and non-nucleoside inhibitors (C316N, M414I/L, P495A) remained susceptible to simeprevir *in vitro*.

Clinical study examining QT interval

The effect of simeprevir 150 mg once daily and 350 mg once daily for 7 days on the QT interval was evaluated in a randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg once daily), 4-way cross-over study in 60 healthy participants. No meaningful changes in QTc interval were observed with either the recommended dose of 150 mg once daily or the supratherapeutic dose of 350 mg once daily.

Pharmacokinetics

The pharmacokinetic properties of simeprevir have been evaluated in healthy adult participants and in adult HCV-infected patients. Plasma C_{max} and the area under the plasma concentration time curve (AUC) increased more than dose proportional after multiple doses between 75 mg and 200 mg once daily, with accumulation occurring following repeated dosing. Steady-state was reached after 7 days of once daily dosing. Plasma exposure of simeprevir (AUC) in HCV-infected patients was about 2- to 3-fold higher compared to that observed in healthy participants. Plasma C_{max} and AUC of simeprevir were similar during co-administration of peginterferon alfa and ribavirin compared with administration of simeprevir alone.

Absorption

Simeprevir is orally bioavailable. Maximum plasma concentrations (C_{max}) are typically achieved between 4 to 6 hours post dose. Administration of simeprevir with food to healthy participants increased the relative bioavailability (AUC) by 61% and 69% after a high-fat, high-caloric (928 kcal) and normal-caloric breakfast (533 kcal), respectively, and delayed the absorption by 1 hour and 1.5 hours, respectively.

In vitro experiments with human Caco-2 cells indicated that simeprevir is a substrate of P-gp.

For information on the inhibition potential of simeprevir on transporters, see *Interactions with other medicines*.

Distribution

Simeprevir is extensively bound to plasma proteins (> 99.9%), primarily to albumin and, to a lesser extent, alfa 1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Metabolism

Simeprevir is metabolized in the liver. *In vitro* experiments with human liver microsomes indicated that simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A system. Involvement of CYP2C8 and CYP2C19 cannot be excluded.

For information on the effects of CYP inhibitors or inducers on the pharmacokinetics of simeprevir and information on the inhibition potential of simeprevir on CYP enzymes, see *Interactions with other medicines*.

Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy participants, the majority of the radioactivity in plasma (up to 98%) was accounted for by unchanged drug and a small part of the radioactivity in plasma was related to metabolites (none being major metabolites). Metabolites identified in faeces were formed via oxidation at the macrocyclic moiety or aromatic moiety or both and by *O*-demethylation followed by oxidation.

Elimination

Elimination of simeprevir occurs via biliary excretion. Renal clearance plays an insignificant role in its elimination. Following a single oral administration of 200 mg ^{14}C-simeprevir to healthy participants, on average 91% of the total radioactivity was recovered in faeces. Less than 1% of the administered dose was recovered in urine. Unchanged simeprevir in faeces accounted for on average 31% of the administered dose.

The terminal elimination half-life of simeprevir was 10 to 13 hours in healthy participants and 41 hours in HCV-infected patients receiving 200 mg simeprevir.

Additional information on special populations

Paediatrics (below 18 years of age)
Studies characterising the pharmacokinetics of simeprevir in paediatric patients have not been performed.

Elderly (above 65 years of age)
There is limited data on the use of OLYSIO in patients older than 65 years. Age (18-73 years) had no clinically meaningful effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV-infected patients treated with OLYSIO. No dose adjustment of OLYSIO is required in elderly patients (see *Dosage and Administration*).

Renal impairment
Renal elimination of simeprevir is negligible.

Compared to healthy participants with normal renal function (classified using the Modification of Diet in Renal Disease [MDRD] eGFR formula; eGFR ≥ 80 mL/min), the mean steady-state AUC of simeprevir was 62% higher in participants with severe renal impairment (eGFR below 30 mL/min).

In a population pharmacokinetic analysis of mild or moderate renally impaired HCV-infected patients treated with OLYSIO 150 mg once daily, creatinine clearance was not found to influence the pharmacokinetic parameters of simeprevir. It is therefore not expected that renal impairment will have a clinically relevant effect on the exposure to simeprevir, and no dose adjustment of OLYSIO is needed in patients with mild, moderate or severe renal impairment. The safety and efficacy of OLYSIO have not been studied in HCV-infected patients with severe renal impairment or end-stage renal disease, including patients requiring dialysis (see *Dosage and Administration*).

As simeprevir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Refer to the respective product information for peginterferon alfa and ribavirin regarding use in patients with renal impairment.

Hepatic impairment
Simeprevir is primarily metabolized by the liver.

Compared to healthy participants with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in participants with moderate hepatic impairment (Child-Pugh Class B) and 5.2-fold higher in participants with severe hepatic impairment (Child-Pugh Class C). In clinical trials, higher simeprevir exposures have been associated with a higher incidence of adverse reactions, including rash (any type), pruritus and increased bilirubin. In addition, the safety and efficacy of OLYSIO have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) (see *Dosage and Administration*).

Based on a population pharmacokinetic analysis of HCV-infected patients treated with OLYSIO, liver fibrosis stage did not have a clinically relevant effect on the pharmacokinetics of simeprevir.

Refer to the respective product information for peginterferon alfa and ribavirin regarding use in patients with hepatic impairment.

Other populations
No dose adjustment is necessary based on gender, body weight or body mass index. These characteristics have no clinically relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV-infected patients treated with OLYSIO.

<u>Patients co-infected with HIV-1</u>
Pharmacokinetic parameters of simeprevir were comparable between patients with HCV genotype 1 infection with or without HIV-1 co-infection.

<u>Race</u>
No dose adjustment is necessary based on race.

Population pharmacokinetic estimates of exposure of simeprevir were comparable between Caucasian and African American HCV-infected patients.

From cross-study comparisons in healthy participants and HCV-infected patients, simeprevir plasma exposure in Asians ranged between 20% lower up to 2.4-fold higher compared to Caucasians. In the Phase 3 studies, the simeprevir plasma exposure in Asian patients was within the range observed in Caucasian patients. Given limited data, the potential risks and benefits of OLYSIO should be carefully considered prior to use in East Asian patients.

CLINICAL TRIALS

The efficacy of OLYSIO in patients with HCV genotype 1 infection was evaluated in two Phase 3 studies in treatment-naïve patients (Studies C208 and C216), one Phase 3 study in patients who relapsed after prior interferon-based therapy (Study HPC3007) and one Phase 2b study in patients who failed prior therapy with peginterferon and ribavirin (including prior relapsers, partial and null responders) (Study C206). In addition, on treatment response and preliminary SVR data are available from two ongoing Phase 3 studies in patients who are treatment-naïve or failed previous therapy: one in patients with HCV genotype 1 and HIV-1 co-infection, and one in patients with HCV genotype 4 infection. Prior relapsers were patients who had undetectable HCV RNA at the end of prior interferon-based therapy and detectable HCV RNA during follow-up; prior partial responders were patients with prior on-treatment ≥ 2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 and detectable HCV RNA at the end of prior therapy with peginterferon and ribavirin; and null responders were patients with prior on-treatment < 2 $\log_{10}$ reduction in HCV RNA from baseline at Week 12 during prior therapy with peginterferon and ribavirin. Patients in these studies had compensated liver disease (including cirrhosis), HCV RNA of at least 10000 IU/mL, and liver histopathology consistent with Chronic Hepatitis C (CHC).

In treatment-naïve and prior relapser patients, the overall duration of treatment with peginterferon alfa and ribavirin in the Phase 3 studies was response-guided. In these patients, the planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy (RGT) criteria were met: HCV RNA < 25 IU/mL detectable or undetectable at Week 4 AND undetectable HCV RNA at Week 12. Plasma HCV RNA levels were measured using the Roche COBAS® TaqMan® HCV test (version 2.0), for use with the High Pure System (25 IU/mL LLOQ and 15 IU/mL limit of detection). Treatment stopping rules for HCV therapy were used to ensure that patients with inadequate on-treatment virologic response discontinued treatment in a timely manner.

SVR (virologic cure) was defined as undetectable HCV RNA 24 weeks after planned end of treatment in the Phase 2b study and was defined as HCV RNA < 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment in the Phase 3 studies.

Efficacy in treatment-naïve adults with HCV genotype 1 infection

The efficacy of OLYSIO in treatment-naïve patients with HCV genotype 1 infection was demonstrated in two randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 studies (Study C208 [QUEST 1] and Study C216 [QUEST 2]). The design of both studies was similar. Patients received 12 weeks of once daily treatment with 150 mg OLYSIO or placebo, plus peginterferon alfa-2a (Studies C208 and C216) or peginterferon alfa-2b (Study C216) and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa and ribavirin in accordance with the on-treatment protocol-defined RGT criteria. Patients in the control groups received 48 weeks of peginterferon alfa-2a or -2b and ribavirin.

In the pooled analysis of Studies C208 and C216, the 785 enrolled patients had a median age of 47 years (range: 18 to 73 years); 56% were male; 91% were Caucasian, 7% African American, 1% Asian, and 17% Hispanic; 23% had a body mass index (BMI) ≥ 30 kg/m^2; 78% had HCV RNA levels > 800000 IU/mL; 74% had METAVIR fibrosis score F0, F1 or F2, 16% METAVIR fibrosis score F3, and 10% METAVIR fibrosis score F4 (cirrhosis); 48% had HCV genotype 1a, and 51% HCV genotype 1b; 29% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 15% *IL28B* TT genotype. In Study C208, all patients received peginterferon alfa-2a; in Study C216, 69% of the patients received peginterferon alfa-2a and 31% received peginterferon alfa-2b.

The proportion of patients who discontinued all treatment due to an adverse event was 2% in the OLYSIO with peginterferon alfa and ribavirin treatment group compared to 1% in the placebo with peginterferon alfa and ribavirin treatment group. Discontinuation of OLYSIO or placebo alone due to an adverse event was 1% in both treatments groups. Table 3 shows the response rates in treatment-naïve adult patients with HCV genotype 1 infection.

Table 3: Treatment Outcome in Treatment-naïve Adult Patients with HCV Genotype 1 Infection (Pooled Data Studies C208 and C216; Intent-to-Treat Analysis)

Treatment Outcome	OLYSIO N=521 % (n/N)	Placebo N=264 % (n/N)
Overall SVR12	80% (419/521)[1]	50% (132/264)
Outcome for patients without SVR12		
On-treatment failure[2]	8% (42/521)	33% (87/264)
Viral relapse[3]	11% (51/470)	23% (39/172)
Missing SVR12[4]	2% (13/521)	2% (6/264)

OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks.
SVR12: sustained virologic response 12 weeks after planned end of treatment (EOT).

1 $p < 0.001$

2 On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).

3 Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT. Includes 4 OLYSIO-treated patients who experienced relapse after SVR12.

4 Patients with missing data at the SVR assessment time point.

Eighty-eight percent (n=459/521) of the OLYSIO-treated patients met the protocol-defined RGT criteria (HCV RNA < 25 IU/mL detectable or undetectable at Week 4 and undetectable HCV RNA at Week 12) for shortened treatment duration (24 weeks); in these patients the SVR12 rate was 88%.

Seventy-eight percent (n=404/521) of OLYSIO-treated patients had undetectable HCV RNA at Week 4 (RVR); in these patients the SVR12 rate was 90%, while 8% with undetectable HCV RNA at end of treatment had viral relapse. The proportion of OLYSIO-treated patients with HCV RNA < 25 IU/mL detectable at Week 4 was 13% (n=70/521); 67% achieved SVR12, while 23% with undetectable HCV RNA at end of treatment had viral relapse. Seven percent (n=35/521) of OLYSIO-treated patients had HCV RNA ≥ 25 IU/mL at Week 4; in these patients the SVR12 rate was 20%.

In both C208 and C216 studies, addition of OLYSIO to peginterferon alfa and ribavirin did not increase severity of patient-reported fatigue, depressive symptoms or impairments in work and daily activities beyond what was observed in patients treated with peginterferon alfa and ribavirin alone. Additionally, OLYSIO-treated patients had significantly reduced time (weeks) with fatigue and impairments in work and daily activity as compared to peginterferon alfa and ribavirin alone.

SVR12 rates were statistically significantly higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype subtype, baseline HCV RNA (less than or equal to 800000 IU/mL, greater than 800000 IU/mL), METAVIR fibrosis score, and *IL28B* genotype. Table 4 shows the SVR rates by METAVIR fibrosis score and *IL28B* genotype.

Table 4: SVR12 Rates by METAVIR Fibrosis Score and *IL28B* Genotype in Treatment-naïve Adult Patients with HCV Genotype 1 Infection (Pooled Data Studies C208 and C216)

Subgroup	OLYSIO % (n/N)	Placebo % (n/N)
METAVIR fibrosis score		
F0-2	84% (317/378)	55% (106/192)
F3-4	68% (89/130)	36% (26/72)
F4	60% (29/48)	34% (11/32)
IL28B genotype		
CC	95% (144/152)	80% (63/79)
CT	78% (228/292)	41% (61/147)
TT	61% (47/77)	21% (8/38)

OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

SVR12 rates were statistically significantly higher for patients receiving OLYSIO with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (88% and 78%, respectively) compared to patients receiving placebo with peginterferon alfa-2a or peginterferon alfa-2b and ribavirin (62% and 42%, respectively) (Study C216).

Efficacy in adults with HCV genotype 1 infection who failed prior therapy

Study HPC3007 (PROMISE) was a randomized, double-blind, placebo-controlled, 2-arm, multicenter, Phase 3 study in patients with HCV genotype 1 infection who **relapsed after prior interferon-based therapy**. Patients received 12 weeks of once daily treatment with 150 mg OLYSIO or placebo, plus peginterferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Patients in the control group received 48 weeks of peginterferon alfa-2a and ribavirin.

The 393 enrolled patients in Study HPC3007 had a median age of 52 years (range: 20 to 71 years); 66% were male; 94% were Caucasian, 3% African American, 2% Asian, and 7% Hispanic; 26% had a BMI ≥ 30 kg/m^2; 84% had HCV RNA levels > 800000 IU/mL; 69% had METAVIR fibrosis score F0, F1 or F2, 15% METAVIR fibrosis score F3, and 15% METAVIR fibrosis score F4 (cirrhosis); 42% had HCV genotype 1a, and 58% HCV genotype 1b; 24% had *IL28B* CC genotype, 64% *IL28B* CT genotype, and 12% *IL28B* TT genotype. The prior interferon-based HCV therapy was peginterferon alfa-2a/ribavirin (68%) or peginterferon alfa-2b/ribavirin (27%).

The proportion of patients who discontinued all treatment due to an adverse event was 0.4% in the OLYSIO with peginterferon alfa and ribavirin treatment group compared to none in the placebo with peginterferon alfa and ribavirin treatment group. None of the patients discontinued OLYSIO alone due to an adverse event. Table 5 shows the response rates for the OLYSIO and placebo treatment groups in adult patients with HCV genotype 1 infection who relapsed after prior interferon-based therapy.

Table 5: Treatment Outcome in Adult Patients with HCV Genotype 1 Infection Who Relapsed After Prior Interferon-Based Therapy (Study HPC3007; Intent-to-Treat Analysis)

Treatment Outcome	OLYSIO N=260 % (n/N)	Placebo N=133 % (n/N)
Overall SVR12	79% (206/260)[1]	37% (49/133)

Table 5: Treatment Outcome in Adult Patients with HCV Genotype 1 Infection Who Relapsed After Prior Interferon-Based Therapy (Study HPC3007; Intent-to-Treat Analysis)

Treatment Outcome	OLYSIO N=260 % (n/N)	Placebo N=133 % (n/N)
Outcome for patients without SVR12		
On-treatment failure[2]	3% (8/260)	27% (36/133)
Viral relapse[3]	19% (46/249)	48% (45/93)
Missing SVR12[4]	2% (5/260)	4% (5/133)

OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.

[1] $p < 0.001$

[2] On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough).

[3] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT and with at least one follow-up HCV RNA assessment. Includes 5 OLYSIO-treated patients who experienced relapse after SVR12.

[4] Patients with missing data at the SVR assessment time point.

Ninety-three percent (n=241/260) of the OLYSIO-treated patients met the protocol-defined RGT criteria (HCV RNA < 25 IU/mL detectable or undetectable at Week 4 and undetectable HCV RNA at Week 12); in these patients the SVR12 rate was 83%.

Seventy-seven percent (n=200/260) of OLYSIO-treated patients had undetectable HCV RNA at Week 4 (RVR); in these patients the SVR12 rate was 87%, while 13% with undetectable HCV RNA at end of treatment had viral relapse. The proportion of OLYSIO-treated patients with HCV RNA < 25 IU/mL detectable at Week 4 was 18% (n=47/260); 60% achieved SVR12, while 40% with undetectable HCV RNA at end of treatment had viral relapse. Five percent (n=12/260) of OLYSIO-treated patients had HCV RNA ≥ 25 IU/mL at Week 4; in these patients the SVR12 rate was 42%.

In Study HPC3007, the increases in severity of patient-reported fatigue, depressive symptoms and impairments in work and daily activities were comparable in both treatment groups. The increases lasted longer in patients treated with peginterferon alfa and ribavirin alone.

SVR12 rates were statistically significantly higher for the OLYSIO treatment group compared to the placebo treatment group by sex, age, race, BMI, HCV genotype subtype, baseline HCV RNA (less than or equal to 800000 IU/mL, greater than 800000 IU/mL), prior HCV therapy, METAVIR fibrosis score, and *IL28B* genotype. Table 6 shows the SVR rates by METAVIR fibrosis score and *IL28B* genotype.

Table 6: SVR12 Rates by METAVIR Fibrosis Score and *IL28B* Genotype in Adult Patients with HCV Genotype 1 Infection Who Relapsed After Prior Interferon-Based Therapy (Study HPC3007)

Subgroup	OLYSIO % (n/N)	Placebo % (n/N)
METAVIR fibrosis score		
F0-2	82% (137/167)	41% (40/98)
F3-4	73% (61/83)	24% (8/34)
F4	74% (29/39)	26% (5/19)
IL28B genotype		
CC	89% (55/62)	53% (18/34)
CT	78% (131/167)	34% (28/83)

Table 6: SVR12 Rates by METAVIR Fibrosis Score and *IL28B* Genotype in Adult Patients with HCV Genotype 1 Infection Who Relapsed After Prior Interferon-Based Therapy (Study HPC3007)

Subgroup	OLYSIO % (n/N)	Placebo % (n/N)
TT	65% (20/31)	19% (3/16)
OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 24 or 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR12: sustained virologic response 12 weeks after planned EOT.		

Study C206 (ASPIRE) was a randomized, double-blind, placebo-controlled, 7-arm, Phase 2b study in patients with HCV genotype 1 infection, who **failed prior therapy with peginterferon alfa and ribavirin** (including **prior relapsers, partial responders or null responders**). Patients received 12, 24 or 48 weeks of 100 mg or 150 mg OLYSIO in combination with 48 weeks of peginterferon alfa-2a and ribavirin, or 48 weeks of placebo in combination with 48 weeks of peginterferon alfa-2a and ribavirin.

The 462 enrolled patients in Study C206 had a median age of 50 years (range: 20 to 69 years); 67% were male; 93% were Caucasian, 5% African American, and 2% Asian; 25% had a BMI ≥ 30 kg/m^2; 86% had HCV RNA levels > 800000 IU/mL; 63% had METAVIR fibrosis score F0, F1 or F2, 19% METAVIR fibrosis score F3, and 18% METAVIR fibrosis score F4 (cirrhosis); 41% had HCV genotype 1a, and 58% HCV genotype 1b; 18% had *IL28B* CC genotype, 65% *IL28B* CT genotype, and 18% *IL28B* TT genotype (information available for 328 patients). Forty percent of patients were prior relapsers, 35% prior partial responders, and 25% prior null responders following prior therapy with peginterferon alfa and ribavirin. One hundred ninety-nine patients received OLYSIO 150 mg once daily (pooled analysis) of which 66 patients received OLYSIO for 12 weeks, and 66 patients received placebo in combination with peginterferon alfa and ribavirin.

The proportion of patients who discontinued all treatment due to an adverse event was 5% in both the 150 mg OLYSIO for 12 weeks and the placebo treatment groups; none of the patients discontinued OLYSIO or placebo alone. Table 7 shows the response rates for the OLYSIO and placebo treatment groups in prior partial responders and null responders.

Table 7: Treatment Outcome in Adult Patients with HCV Genotype 1 Infection Who Failed Prior Peginterferon alfa and Ribavirin Therapy (Study C206; Prior Partial and Null Responders)

Treatment Outcome	150 mg OLYSIO 12 weeks N=66 % (n/N)	Pooled 150 mg OLYSIO N=199 % (n/N)	Placebo N=66 % (n/N)
SVR24			
Prior partial responders	65% (15/23)	75% (52/69)[1]	9% (2/23)
Prior null responders	53% (9/17)	51% (26/51)[2]	19% (3/16)
Outcome for patients without SVR24			
On-treatment virologic failure[3]			
Prior partial responders	22% (5/23)	16% (11/69)	78% (18/23)
Prior null responders	35% (6/17)	29% (15/51)	75% (12/16)
Viral Relapse[4]			
Prior partial responders	6% (1/17)	5% (3/56)	50% (2/4)
Prior null responders	18% (2/11)	28% (10/36)	25% (1/4)

Table 7: Treatment Outcome in Adult Patients with HCV Genotype 1 Infection Who Failed Prior Peginterferon alfa and Ribavirin Therapy (Study C206; Prior Partial and Null Responders)

Treatment Outcome	150 mg OLYSIO 12 weeks N=66 % (n/N)	Pooled 150 mg OLYSIO N=199 % (n/N)	Placebo N=66 % (n/N)
150 mg OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; pooled 150 mg OLYSIO: 150 mg OLYSIO for 12, 24 or 48 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Placebo: placebo with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR24: sustained virologic response 24 weeks after planned EOT. [1] $p < 0.001$ [2] $p = 0.001$ [3] On-treatment virologic failure was defined as the proportion of patients who met the protocol-specified treatment stopping rules (including stopping rule due to viral breakthrough) or who had detectable HCV RNA at EOT (for patients who completed therapy). [4] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.			

In Study C206, no treatment-related differences in patient-reported fatigue severity were observed. Fatigue increased to similar extent and returned to baseline levels after Week 48 in all treatment arms.
SVR24 rates were higher in the OLYSIO-treated patients compared to patients receiving placebo in combination with peginterferon alfa and ribavirin, regardless of HCV geno/subtype, METAVIR fibrosis score, and *IL28B* genotype. Table 8 shows the SVR rates by METAVIR fibrosis score.

Table 8: SVR24 Rates by METAVIR Fibrosis Score in Adult Patients with HCV Genotype 1 Infection Who Failed Prior Peginterferon alfa and Ribavirin Therapy (Study C206; Prior Partial and Null Responders)

METAVIR Fibrosis Score	Prior Partial Responders		Prior Null Reponders	
	Pooled 150 mg OLYSIO % (n/N)	Placebo % (n/N)	Pooled 150 mg OLYSIO % (n/N)	Placebo % (n/N)
F0-2	79% (38/48)	8% (1/12)	66% (19/29)	23% (3/13)
F3-4	67% (14/21)	10% (1/10)	33% (7/21)	0% (0/3)
F4	82% (9/11)	0% (0/2)	31% (4/13)	0% (0/2)
pooled 150 mg OLYSIO: 150 mg OLYSIO for 12, 24 or 48 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Placebo: placebo for 12 weeks with peginterferon alfa-2a or -2b and ribavirin for 48 weeks. SVR24: sustained virologic response 24 weeks after planned EOT.				

Study HPC3001 was a randomized, double-blind, non-inferiority Phase 3 study in patients with HCV genotype 1 infection who were **null or partial responders to prior peginterferon alfa and ribavirin therapy**. Patients received 12 weeks of OLYSIO or telaprevir in combination with 48 weeks of peginterferon alfa-2a and ribavirin.

The 763 enrolled patients in Study HPC3001 had a median age of 51 years (range: 18 to 69 years); 61% were male; 94% were Caucasian, 5% African American; 23% had a BMI ≥ 30 kg/m^2; 88% had HCV RNA levels > 800000 IU/mL; 55% had METAVIR fibrosis score F0, F1 or F2, 28% METAVIR fibrosis score F3, and 17% METAVIR fibrosis score F4 (cirrhosis) (information available for 643 patients); 43% had HCV genotype 1a, and 57% HCV genotype 1b; 4% had *IL28B* CC genotype, 65% *IL28B* CT genotype, and 31% *IL28B* TT genotype (information available for 728 patients); 38% were prior partial responders, and 62% prior null responders following prior therapy with peginterferon alfa and ribavirin.

The proportion of patients who discontinued OLYSIO or teleprevir due to an adverse event was 2% in the OLYSIO treatment group and 8% in the telaprevir treatment group. Table 9 shows the response rates for the OLYSIO and telaprevir treatment group in adult patients with HCV genotype 1 infection who were null or partial responders to prior peginterferon alfa and ribavirin therapy.

Table 9: Treatment Outcome in Prior Partial and Prior Null Responder Adult Patients with HCV Genotype 1 Infection (Study HPC3001; Intent-To-Treat Analysis Set)

Treatment Outcome	OLYSIO N=379 % (n/N)	Telaprevir N=384 % (n/N)
SVR12		
Overall	54% (203/379)[1]	55% (210/384)
Prior partial responders	70% (101/145)	68% (100/146)
Prior null responders	44% (102/234)	46% (110/238)
Outcome for patients without SVR12		
On-treatment virologic failure[2]		
Overall	34% (130/379)	32% (124/384)
Prior partial responders	21% (30/145)	17% (25/146)
Prior null responders	43% (100/234)	42% (99/238)
Viral relapse[3]		
Overall	18% (43/246)	17% (43/256)
Prior partial responders	12% (14/115)	14% (16/118)
Prior null responders	22% (29/131)	20% (27/138)
Missing SVR[4]		
Overall	1% (3/379)	2% (9/384)
Prior partial responders	0	4% (6/146)
Prior null responders	1% (3/234)	1% (3/238)

OLYSIO: 150 mg OLYSIO for 12 weeks with peginterferon alfa-2a and ribavirin for 48 weeks; Telaprevir: telaprevir with peginterferon alfa-2a and ribavirin for 48 weeks. SVR12: sustained virologic response 24 weeks after planned EOT.

[1] $p < 0.001$; non-inferiority of OLYSIO versus telaprevir met.

[2] On-treatment virologic failure was defined as the proportion of patients who had detectable HCV RNA at EOT.

[3] Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at EOT and with at least one follow-up HCV RNA assessment.

[4] Patients with missing data at the SVR assessment time point.

Long-term efficacy in adults with HCV genotype 1 infection

Interim data from an ongoing 3-year follow-up study (Study HPC3002) in patients who achieved SVR with a OLYSIO-based regimen in previous Phase 2b studies showed that all patients (n=166) maintained undetectable HCV RNA during a median follow-up time of 16 months.

Efficacy in adults with HCV genotype 1 infection and HIV-1 co-infection

Study C212 is an ongoing open-label, single-arm Phase 3 study in HIV-1 patients co-infected with HCV genotype 1 who are treatment-naïve or failed prior HCV therapy with peginterferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Non-cirrhotic treatment-naïve patients or prior relapsers received 12 weeks of once daily treatment with 150 mg OLYSIO plus peginterferon alfa-2a and ribavirin, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Prior non-responder patients (partial and null response) and all cirrhotic patients (METAVIR fibrosis score F4) received 36 weeks of peginterferon alfa-2a and ribavirin after the initial 12 weeks of OLYSIO in combination with peginterferon alfa-2a and ribavirin.

The 106 enrolled patients in Study C212 had a median age of 48 years (range: 27 to 67 years); 85% were male; 82% were Caucasian, 14% African American, 1% Asian, and 6% Hispanic; 12% had a BMI ≥ 30 kg/m^2; 86% had HCV RNA levels > 800000 IU/mL; 68% had METAVIR fibrosis score F0, F1 or F2, 19% METAVIR fibrosis score F3, and 13% METAVIR fibrosis score F4; 82% had HCV genotype 1a, and 17% HCV genotype 1b; 27% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 17% *IL28B* TT genotype; 50% (n=53) were HCV treatment-naïve patients, 14% (n=15) prior relapsers, 9% (n=10) prior partial responders, and 26% (n=28) prior null responders. Eighty-eight percent (n=93) of the patients were on highly active antiretroviral therapy (HAART), with nucleoside reverse transcriptase inhibitors and the integrase inhibitor raltegravir being the most commonly used HIV antiretroviral. The median baseline HIV-1 RNA levels and CD4+ cell count in patients not on HAART were 4.18 $\log_{10}$ copies/mL (range: 1.3-4.9 $\log_{10}$ copies/mL) and 677 x 10^6 cells/L (range: 489-1076 x 10^6 cells/L), respectively. The median baseline CD4+ cell count in patients on HAART was 561 x 10^6 cells/mL (range: 275-1407 x 10^6 cells/mL).

The proportion of patients who discontinued all treatment due to an adverse event was 3%. The proportion of patients who discontinued simeprevir alone treatment due to an adverse event was 1%. Table 10 shows the response rates in treatment naïve, prior relapsers, prior partial responders and prior null responders.

Table 10: Treatment outcome in adult patients with HCV genotype 1 infection and HIV 1 co infection (study C212; Intent To Treat analysis set)

Treatment outcome[1]	Treatment-naïve patients N=53 % (n/N)	Prior relapsers N=15 % (n/N)	Prior partial responders N=10 % (n/N)	Prior null responders N=28 % (n/N)
SVR12	79% (42/53)[2]	87% (13/15)	70% (7/10)	57% (16/28)[2]
Outcome for patients without SVR12				
On-treatment failure[3]	9% (5/53)	0% (0/15)	20% (2/10)	39% (11/28)
Viral relapse[4]	10% (5/48)	13% (2/15)	0% (0/7)	12% (2/17)
Missing SVR12[5]	2% (1/53)	0% (0/15)	10% (1/10)	0% (0/28)

1 150 mg simeprevir for 12 weeks with peginterferon alfa 2a and ribavirin for 24 or 48 weeks.
2 $p < 0.001$ compared to historical control of peginterferon alfa and ribavirin.
3 On treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol specified treatment stopping rules and/or experienced viral breakthrough).
4 Viral relapse rates are calculated with a denominator of patients with undetectable HCV RNA at actual EOT and with at least one follow up HCV RNA assessment. Includes one prior null responder who experienced relapse after SVR12.
5 Patients with missing data at the SVR assessment time point.

Eighty nine percent (54/61) of the simeprevir treated treatment naïve patients and prior relapsers without cirrhosis were eligible for 24 weeks of treatment by meeting the protocol defined RGT criteria (HCV RNA < 25 IU/ml detectable or undetectable at week 4 and undetectable HCV RNA at week 12); in these patients the SVR12 rate was 87%.

Seventy percent (37/53), 93% (14/15), 80% (8/10) and 36% (10/28) of simeprevir treated treatment naïve patients, prior relapsers, prior partial responders and prior null responders had undetectable HCV RNA at week 4 (RVR). In these patients the SVR12 rates were 89%, 93%, 75% and 90%, respectively.

Six percent (3/53), 0% (0/15), 20% (2/10) and 25% (7/28) of simeprevir treated treatment naïve patients, prior relapsers, prior partial responders and prior null responders, respectively, had HCV RNA ≥ 25 IU/ml at week 4. The SVR12 rates were 0% in treatment naïve patients, prior relapsers and prior null responders and 50% (1/2) in prior partial responders.

Table 11 shows the SVR rates by METAVIR fibrosis scores and IL28B genotype.

Table 11: SVR12 rates by METAVIR fibrosis score and *IL28B* genotype in adult patients with HCV genotype 1 infection and HIV 1 co infection (study C212)

Subgroup	Treatment-naïve patients % (n/N)	Prior relapsers % (n/N)	Prior partial responders % (n/N)	Prior null responders % (n/N)
METAVIR fibrosis score				
F0-2	89% (24/27)	78% (7/9)	50% (1/2)	57% (4/7)
F3-4	57% (4/7)	100% (2/2)	67% (2/3)	60% (6/10)
F4	100% (2/2)	100% (1/1)	100% (1/1)	60% (3/5)
IL28B genotype				
CC	100% (15/15)	100% (7/7)	100% (1/1)	80% (4/5)
CT	70% (19/27)	100% (6/6)	71% (5/7)	53% (10/19)
TT	80% (8/10)	0% (0/2)	50% (1/2)	50% (2/4)

Two patients had HIV virologic failure defined as confirmed HIV 1 RNA ≥ 200 copies/ml after previous < 50 copies/ml; these failures occurred 36 and 48 weeks after end of simeprevir treatment.

Efficacy in adults with HCV genotype 4 infection

Study HPC3011 (RESTORE) is an open-label, single-arm Phase 3 study in patients with HCV genotype 4 infection who are treatment-naïve or failed prior therapy with peginterferon alfa and ribavirin (including prior relapsers, partial responders or null responders). Treatment-naïve patients or prior relapsers received once daily treatment with 150 mg OLYSIO plus peginterferon alfa-2a and ribavirin for 12 weeks, followed by 12 or 36 weeks of therapy with peginterferon alfa-2a and ribavirin in accordance with the protocol-defined RGT criteria. Prior non-responder patients (partial and null response) received once daily treatment with 150 mg OLYSIO plus peginterferon alfa-2a and ribavirin for 12 weeks, followed by 36 weeks of peginterferon alfa-2a and ribavirin.

The 107 enrolled patients in Study HPC3011 with HCV genotype 4 had a median age of 49 years (range: 27 to 69 years); 79% were male; 72% were Caucasian, 28% African American, and 7% Hispanic; 14% had a BMI ≥ 30 kg/m^2; 60% had HCV RNA levels > 800000 IU/mL; 57% had METAVIR fibrosis score F0, F1 or F2, 14% METAVIR fibrosis score F3, and 29% METAVIR fibrosis score F4; 42% had HCV genotype 4a, and 24% had HCV genotype 4d; 8% had *IL28B* CC genotype, 58% *IL28B* CT genotype, and 35% *IL28B* TT genotype 33% (n=35) were treatment-naïve HCV patients, 21% (n=22) prior relapsers, 9% (n=10) prior partial responders, and 37% (n=40) prior null responders.

The proportion of patients who discontinued all treatment due to an adverse event was 3%. The proportion of patients who discontinued simeprevir due to an adverse event was 1%. Table 12 shows the response rates in treatment naïve, prior relapsers, prior partial responders and null responders.

Table 12: Treatment Outcome in Adult Patients with HCV Genotype 4 Infection (Study HPC3011; Intent-To-Treat Analysis Set)

Treatment Outcome[1]	Treatment-naïve patients N=35 % (n/N)	Prior relapsers N=22 % (n/N)	Prior partial responders N=10 % (n/N)	Prior null responders N=40 % (n/N)
SVR12	83% (29/35)	86% (19/22)	60% (6/10)	40% (16/40)[2]
Outcome for patients without SVR12				
On-treatment failure[3]	9% (3/35)	9% (2/22)	20% (2/10)	45% (18/40)
Viral relapse[4]	9% (3/35)	5% (1/22)	20% (2/10)	15% (6/40)
Missing SVR12[5]	0% (0/35)	0% (0/22)	0% (0/10)	0% (0/40)

Table 12: Treatment Outcome in Adult Patients with HCV Genotype 4 Infection (Study HPC3011; Intent-To-Treat Analysis Set)

Treatment Outcome[1]	Treatment-naïve patients N=35 % (n/N)	Prior relapsers N=22 % (n/N)	Prior partial responders N=10 % (n/N)	Prior null responders N=40 % (n/N)
[1] 150 mg TRADENAME for 12 weeks with peginterferon alfa-2a and ribavirin for 24 or 48 weeks. [3] On-treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol-specified treatment stopping rules and/or experienced viral breakthrough). [4] Viral relapse rates are calculated with a denominator of patients with undetectable (or unconfirmed detectable) HCV RNA at actual EOT. [5] Patients with missing data at the SVR assessment time point.				

Table 13 shows the SVR rates by METAVIR fibrosis scores and *IL28B* genotype.

Table 13: SVR12 Rates by METAVIR Fibrosis Score and *IL28B* genotype in Adult Patients with HCV Genotype 4 Infection (Study HPC3011)

Treatment Outcome	Treatment-Naïve Patients % (n/N)	Prior Relapsers % (n/N)	Prior Partial Responders % (n/N)	Prior Null Responders % (n/N)
METAVIR fibrosis score				
F0-2	85% (22/26)	91% (10/11)	100% (5/5)	47% (8/17)
F3-4	78% (7/9)	82% (9/11)	20% (1/5)	35% (7/20)
F4	50% (1/2)	78% (7/9)	20% (1/5)	36% (5/14)
IL28B genotype				
CC	100% (7/7)	100% (1/1)	-	-
CT	82% (14/17)	82% (14/17)	60% (3/5)	41% (9/22)
TT	80% (8/10)	100% (4/4)	60% (3/5)	39% (7/18)

INDICATIONS

OLYSIO is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with other medicinal products for the treatment of CHC infection (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS).

CONTRAINDICATIONS

Hypersensitivity to simeprevir or to any of the excipients.

OLYSIO in combination with peginterferon alfa and ribavirin is contraindicated in:

- women who are or may become pregnant. Ribavirin may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug treatment, the patient should be apprised of the potential hazard to a fetus (see PRECAUTIONS, Pregnancy and contraception requirements and Use in Pregnancy).
- men whose female partners are pregnant.

Refer to the respective product information for a list of the contraindications for peginterferon alfa and ribavirin.

PRECAUTIONS

General

OLYSIO must not be administered as monotherapy. OLYSIO must be prescribed in combination with both peginterferon alfa and ribavirin. The product information for peginterferon alfa and ribavirin must therefore be consulted before starting therapy with OLYSIO.

The safety and efficacy of OLYSIO in combination with anti-HCV medicinal products other than peginterferon and ribavirin have not been established.

Precautions related to peginterferon alfa and ribavirin also apply to OLYSIO combination treatment.

Use in patients with HCV genotype 1a

Sustained virologic response (SVR) rates of OLYSIO in combination with peginterferon alfa and ribavirin were reduced in patients with hepatitis C genotype 1a with NS3 Q80K polymorphism compared to patients without Q80K polymorphism (see Pharmacodynamics).

Rash

Rash has been observed with OLYSIO combination treatment (see ADVERSE EFFECTS).

The recommendations for monitoring and management of cutaneous reactions are summarised in the table below:

Extent and features of Cutaneous Reactions	Recommendations for Monitoring and Management of Cutaneous Reactions
Mild to moderate rash	Monitor for progression, mucosal signs or systemic symptoms until the rash is resolved.
Severe rash	OLYSIO, peginterferon alfa, and ribavirin should be discontinued and the patients should be monitored until the symptoms have resolved
Serious skin reactions including rash with systemic symptoms, progressive severe rash and suspicion or diagnosis of generalized bullous eruption, DRESS, Stevens-Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, erythema multiforme	Immediate and permanent discontinuation of OLYSIO, peginterferon alfa, and ribavirin. Consult with a specialist in dermatology.

Pregnancy and contraception requirements

Because OLYSIO must be used in combination with peginterferon alfa and ribavirin, the contraindications and warnings regarding pregnancy and contraception requirements applicable to those medicinal products also apply to OLYSIO combination treatment.

Ribavirin may cause birth defects and/or death of the exposed fetus. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients (see Use in Pregnancy). Refer also to the product information for ribavirin.

Female patients of childbearing potential and their male partners as well as male patients and their female partners must use 2 effective contraceptive methods during treatment and after completion of treatment for a duration as specified in the product information for ribavirin (see Use in Pregnancy).

Effects on fertility

Use of OLYSIO with ribavirin and peginterferon alfa

In fertility studies in animals, ribavirin caused reversible testicular toxicity in males, while peginterferon alfa may impair fertility in females. Refer to product information for ribavirin and peginterferon alfa for additional information.

There are no data on the effect of simeprevir on human fertility. A fertility study in rats at doses up to 500 mg/kg/day showed no motile sperm, small testes and epididymides in 3 males (2/24 at 50 mg/kg/day and 1/24 at 500 mg/kg/day) that resulted in infertility in 2 out of the 3 males. The simprevir exposure multiple, based on AUC, was 0.2 at 50 mg/kg/day.

Use in Pregnancy

Category X – Use of OLYSIO with Ribavirin and Peginterferon alfa

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; and therefore ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant (see CONTRAINDICATIONS and ribavirin Product Information). Interferons have abortifacient effects in animals and should be assumed to have abortifacient potential in humans (see peginterferon alfa Product Information). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients - both during treatment and for 6 months after the completion of all treatment. OLYSIO combination treatment should not be started unless a female patient has a negative pregnancy test immediately prior to initiation of treatment. Pregnancy testing should occur monthly during OLYSIO combination treatment and for 6 months after all treatment has ended. Pregnancy testing in non-pregnant female partners is recommended before OLYSIO combination therapy, every month during OLYSIO combination therapy and for 6 months after ribavirin therapy has ended.

Category B3– OLYSIO capsules

There are no adequate and well-controlled studies with OLYSIO alone or in combination with peginterferon alfa and ribavirin in pregnant women. Simeprevir was not teratogenic in embryofetal studies in mice and rats at respective exposures, based on AUC, of 6x and 0.5x the mean exposure in humans at the recommended dose. A mouse embryofetal study showed some maternal deaths, significantly increased post-implantation loss, and significantly decreased fetal weights at the high-dose of 1000 mg/kg/day, 6x the mean exposure in humans at the recommended dose. A rat pre-postnatal study, in which maternal rats were treated from gestation day 6 to day 20 of lactation, showed some maternal deaths at the high-dose of 1000 mg/kg/day (estimated exposure multiple ~1), and significant reductions in bodyweight gain at 150 mg/kg/day and above. The rat offspring showed significantly decreased bodyweight gains at 150 mg/kg/day and above (estimated exposure multiple 0.7x), and delayed physical growth and development (motor activity) at a maternal dose of 1000 mg/kg/day, Subsequent survival, behaviour and fertility were unaffected. In pregnant rats, the simeprevir concentration in the placenta was lower compared to that observed in blood. In fetal liver and fetus, levels of simeprevir or its metabolite were below the limit of detection.

Use in Lactation

Refer to the respective product information for peginterferon alfa and ribavirin regarding breast-feeding.

It is not known whether simeprevir or its metabolites are excreted in human milk. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from OLYSIO therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Paediatric Use
The safety and efficacy of OLYSIO have not been established in pediatric patients (below 18 years of age).

Elderly
There are limited data on the safety and efficacy of OLYSIO in patients older than 65 years. No dose adjustment of OLYSIO is required in elderly patients (see *Pharmacokinetic Properties*).

Genotoxicity
Ribavirin was genotoxic in in vitro and in vivo assays. See the product information for ribavirin. Simeprevir was not genotoxic in a series of *in vitro* and *in vivo* tests.

Carcinogenicity
Ribavirin was not tumourigenic in a 6-month p53+/- transgenic mouse study or a 2-year carcinogenicity study in rats. See the product information for ribavirin.
Carcinogenicity studies with simeprevir have not been conducted.

Photosensitivity
Photosensitivity reactions (which were mostly mild or moderate) have been observed with OLYSIO in combination with peginterferon alfa and ribavirin (see Adverse Effects).

Use appropriate sun protective measures during treatment with OLYSIO. Avoid excess exposure to sun and use of tanning devices during treatment with OLYSIO.

Laboratory testing

HCV RNA levels should be monitored at Weeks 4 and 12 and as clinically indicated (see also guidelines for treatment duration and stopping rules; *Dosage and Administration*). Use of a quantitative HCV RNA assay for monitoring HCV RNA levels during treatment is recommended.

Refer to the product information of peginterferon alfa and ribavirin for baseline, on-treatment and post-treatment laboratory testing requirements including haematology, biochemistry (including hepatic enzymes and bilirubin), and pregnancy testing requirements.

Use in patients who have failed previous therapy with direct-acting antivirals against HCV

The safety and efficacy of OLYSIO have not been studied in patients who have failed previous therapy with OLYSIO or other direct-acting antivirals against HCV.

Use in patients with other HCV genotypes

Clinical data are insufficient to support the use of OLYSIO in patients with HCV genotypes 2, 3, 5 or 6.

Interactions with medicinal products

Co-administration of OLYSIO with substances that moderately or strongly induce or inhibit cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively.

For information on interactions with medicinal products, see *Interactions with other medicines*.

Hepatitis B Virus (HBV) co-infection

The safety and efficacy of OLYSIO alone or in combination with peginterferon alfa and ribavirin for the treatment of HCV infection in patients co-infected with HBV have not been studied.

Organ transplantation

The safety and efficacy of OLYSIO alone or in combination with peginterferon alfa and ribavirin have not been studied in organ transplant patients.

INTERACTIONS WITH OTHER MEDICINES

In vitro assessment of interactions

The primary enzyme involved in the biotransformation of simeprevir is CYP3A (see *Pharmacokinetics*) and clinically relevant effects of other medicinal products on the pharmacokinetics of simeprevir via CYP3A may occur.

Simeprevir does not induce CYP1A2 or CYP3A4 in human hepatocytes. *In vitro* studies show that simeprevir is a moderate inhibitor of CYP2A6, CYP2C8 and CYP2D6 (IC_{50} values > 32 µg/mL) and a mild inhibitor of CYP2C19 and CYP3A (IC_{50} values > 64 µg/mL). Simeprevir is not a clinically relevant inhibitor of cathepsin A enzyme activity (IC_{50} > 37 µg/mL).

In vitro experiments show that simeprevir is a substrate for the drug transporters P-glycoprotein (P-gp), MRP2, BCRP, OATP1B1, OATP2B1 and OATP1B3. Simeprevir inhibits the uptake transporters OATP1B1 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. OATP1B1 and MRP2 are involved in the transport of bilirubin into and out of hepatocytes.

In vivo assessment of interactions

Specific drug interaction studies were conducted to investigate the effects of inhibitors or inducers of CYP enzymes on the pharmacokinetics of simeprevir. Co-administration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir, while co-administration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy (see Table 14). Therefore, co-administration of OLYSIO with substances that moderately or strongly inhibit or induce CYP3A is not recommended (see PRECAUTIONS).

A drug interaction study in healthy participants was conducted to assess the effects of simeprevir on various CYP enzymes via simultaneous administration of substrates for CYP1A2 (caffeine, orally), CYP2C9 (warfarin, orally), CYP2C19 (omeprazole, orally), CYP2D6 (dextromethorphan, orally) and CYP3A4 (midazolam, administered orally and intravenously to investigate the effect on intestinal and hepatic CYP3A activity, respectively). Simeprevir does not affect CYP2C9; the inhibition of CYP2C19 and CYP2D6 observed *in vitro* is not observed *in vivo*. Simeprevir mildly inhibits the CYP1A2 activity and intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Co-administration of OLYSIO with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs (see Table 14).

A drug interaction study in healthy participants showed that co-administration of digoxin or rosuvastatin with simeprevir resulted in increased plasma exposure of digoxin and rosuvastatin, likely due to inhibition of P-gp and OATP1B1, respectively. Co-administration of OLYSIO with drugs that are substrates for OATP1B1 and P-gp transporters may result in increased plasma concentrations of such drugs (see Table 14).

Known and theoretical interactions between simeprevir and selected medicinal products are listed in Table 14 (least square mean ratios with 90% confidence intervals are presented, increase is indicated as "↑", decrease as "↓", no change as "↔", and not assessed as "NA"). Interaction studies have been performed in healthy adults with the recommended dose of 150 mg simeprevir once daily unless otherwise noted.

Refer to the respective product information for peginterferon alfa and ribavirin regarding the interactions for those medicinal products.

Table 14: Summary of Drug Interactions With Simeprevir

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
ANALEPTIC					
Caffeine[1]	150 mg	caffeine	↔ 1.12 (1.06-1.19)	↑ 1.26 (1.21-1.32)	NA
	No dose adjustment is required when OLYSIO is co-administered with caffeine.				
ANTIARRHYTHMICS					
Digoxin[1]	0.25 mg	digoxin	↑ 1.31 (1.14-1.51)	↑ 1.39 (1.16-1.67)	NA
	Concomitant use of OLYSIO with digoxin resulted in increased concentrations of digoxin due to inhibition of P-gp by simeprevir. Concentrations of digoxin should be monitored and used for titration of digoxin dose to obtain the desired clinical effect when co-administered with OLYSIO.				
Amiodarone Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Quinidine	Concomitant use of OLYSIO with these antiarrhythmics may result in mild increases in concentrations of these antiarrhythmics due to intestinal CYP3A4 inhibition by simeprevir. Caution is warranted and therapeutic drug monitoring for these antiarrhythmics, if available, is recommended when co-administered with OLYSIO.				
ANTICOAGULANTS					
Warfarin[1]	10 mg	S-warfarin	↔ 1.00 (0.94-1.06)	↔ 1.04 (1.00-1.07)	NA
	No dose adjustment is required when OLYSIO is co-administered with warfarin. However, it is recommended that the international normalised ratio (INR) be monitored.				
ANTICONVULSANTS					
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Concomitant use of OLYSIO with carbamazepine, oxcarbazepine, phenobarbital or phenytoin may result in significantly decreased plasma concentrations of simeprevir due to strong CYP3A induction by these anticonvulsants. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with these anticonvulsants.				
ANTIDEPRESSANTS					
Escitalopram[1]	10 mg once daily	escitalopram	↔ 1.03 (0.99-1.07)	↔ 1.00 (0.97-1.03)	↔ 1.00 (0.95-1.05)
		simeprevir	¯ 0.80 (0.71-0.89)	¯ 0.75 (0.68-0.83)	¯ 0.68 (0.59-0.79)
	Concomitant use of OLYSIO with escitalopram resulted in decreased plasma concentrations of simeprevir. This decrease is not considered to be clinically relevant. No dose adjustment is necessary for either drug when OLYSIO is co-administered with escitalopram.				
ANTIHISTAMINES					

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
Astemizole Terfenadine	Astemizole and terfenadine have the potential for cardiac arrhythmias. Concomitant use of OLYSIO with astemizole and terfenadine may result in mild increases in concentrations of these antihistamines due to intestinal CYP3A4 inhibition by simeprevir. It is not recommended to co-administer OLYSIO with astemizole or terfenadine.				
ANTI-INFECTIVES					
Antibiotics					
Erythromycin[1]	500 mg three times a day	erythromycin	- 1.59 (1.23-2.05)	- 1.90 (1.53-2.36)	- 3.08 (2.54-3.73)
		simeprevir	- 4.53 (3.91-5.25)	- 7.47 (6.41-8.70)	- 12.74 (10.19-15.93)
	Concomitant use of OLYSIO with erythromycin resulted in significantly increased plasma concentrations of both erythromycin and simeprevir due to inhibition of CYP3A and P-gp by both erythromycin and simeprevir. It is not recommended to co-administer OLYSIO with erythromycin.				
Clarithromycin Telithromycin	Concomitant use of OLYSIO with clarithromycin or telithromycin may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by these antibiotics. It is not recommended to co-administer OLYSIO with clarithromycin or telithromycin.				
Antifungals (oral administration)					
Itraconazole Ketoconazole Posaconazole	Concomitant use of OLYSIO with systemic itraconazole, ketoconazole or posaconazole may result in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by these antifungals. It is not recommended to co-administer OLYSIO with systemic itraconazole, ketoconazole or posaconazole.				
Voriconazole	Concomitant use of OLYSIO with voriconazole may result in increased plasma concentrations of simeprevir due to mild to moderate CYP3A inhibition by voriconazole. It is not recommended to co-administer OLYSIO with voriconazole.				
Fluconazole	Concomitant use of OLYSIO with fluconazole is not expected to affect plasma exposure of simeprevir. No dose adjustment is required when OLYSIO is co-administered with fluconazole.				
Antimycobacterials					
Rifampicin/ Rifampin[1,2]	600 mg once daily	rifampin	↔ 0.92 (0.80-1.07)	↔ 1.00 (0.93-1.08)	NA
		25-desacetyl-rifampin	↔ 1.08 (0.98-1.19)	- 1.24 (1.13-1.36)	NA
		simeprevir	- 1.31 (1.03-1.66)	¯ 0.52 (0.41-0.67)	¯ 0.08 (0.06-0.11)
	Concomitant use of OLYSIO with rifampicin/rifampin resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A4 induction by rifampicin/rifampin. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with rifampicin/rifampin.				
Rifabutin Rifapentine	Concomitant use of OLYSIO with rifabutin or rifapentine may result in significantly decreased plasma concentrations of simeprevir due to CYP3A4 induction by these antimycobacterials. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with rifabutin or rifapentine.				
ANTITUSSIVE					
Dextromethorphan (DXM)[1]	30 mg	DXM	↑ 1.21 (0.93-1.57)	↑ 1.08 (0.87-1.35)	NA
		dextrorphan	↔ 1.03 (0.93-1.15)	↔ 1.09 (1.03-1.15)	NA

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
	No dose adjustment is required when OLYSIO is co-administered with dextromethorphan.				
CALCIUM CHANNEL BLOCKERS					
Amlodipine Bepridil Diltiazem Felodipine Nicardipine Nifedipine Nisoldipine Verapamil	Concomitant use of OLYSIO with calcium channel blockers may result in increased plasma concentrations of calcium channel blockers due to intestinal CYP3A4 and/or P-gp inhibition by simeprevir. Caution is warranted and clinical monitoring of patients is recommended when OLYSIO is co-administered with calcium channel blockers.				
CORTICOSTEROIDS					
Systemic Dexamethasone	Concomitant use of OLYSIO with systemic dexamethasone may result in decreased plasma concentrations of simeprevir due to moderate induction of CYP3A4 by dexamethasone. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with systemic dexamethasone.				
Budesonide Fluticasone Methylprednisolone Prednisone	No dose adjustment is required when OLYSIO is co-administered with budesonide, fluticasone, methylprednisolone or prednisone.				
GASTROINTESTINAL PRODUCTS					
Antacids					
e.g., Aluminium or Magnesium hydroxide, Calcium carbonate	Concomitant use of OLYSIO with antacids is not expected to result in a clinically relevant interaction. No dose adjustment is required when OLYSIO is co-administered with antacids.				
H_2-receptor antagonists					
e.g., Cimetidine, Nizatidine, Ranitidine	Concomitant use of OLYSIO with H_2-receptor antagonists is not expected to result in a clinically relevant interaction. No dose adjustment is required when OLYSIO is co-administered with H_2-receptor antagonists.				
Propulsive					
Cisapride	Cisapride has the potential to cause cardiac arrhythmias. Concomitant use of OLYSIO with cisapride may result in increased plasma concentrations of cisapride due to intestinal CYP3A4 inhibition by simeprevir. It is not recommended to co-administer OLYSIO with cisapride.				
Proton pump inhibitors					
Omeprazole[1]	40 mg	omeprazole	- 1.14 (0.93-1.39)	- 1.21 (1.00-1.46)	NA
	Concomitant use of OLYSIO with omeprazole resulted in increased plasma concentrations of omeprazole. However, this increase is not expected to be clinically relevant. No dose adjustment is required when OLYSIO is co-administered with omeprazole.				
Other proton pump inhibitors; e.g., Dexlansoprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole	Concomitant use of OLYSIO with proton pump inhibitors is not expected to result in a clinically relevant interaction. No dose adjustment is required when OLYSIO is co-administered with proton pump inhibitors.				
HCV PRODUCTS					
Antiviral					
Sofosbuvir[3]	400 mg once daily	sofosbuvir	- 1.91 (1.26-2.90)	- 3.16 (2.25-4.44)	NA

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
		GS-331007	¯ 0.69 (0.52-0.93)	↔ 1.09 (0.87-1.37)	NA
		simeprevir	↔ 0.96 (0.71-1.30)	↔ 0.94 (0.67-1.33)	NA
	Concomitant use of simeprevir with sofosbuvir resulted in increased plasma concentrations of sofosbuvir, with no change in exposure of the nucleotide metabolite GS-331007 or simeprevir. The increase in sofosbuvir exposure is not clinically relevant due to the low transient exposure to these analytes relative to the total drug-related material.				
HERBAL PRODUCTS					
Milk thistle (*Silybum marianum*)	Concomitant use of OLYSIO with milk thistle may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by milk thistle. It is not recommended to co-administer OLYSIO with milk thistle.				
St John's wort (*Hypericum perforatum*)	Concomitant use of OLYSIO with products containing St John's wort may result in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by St John's wort. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with products containing St John's wort.				
HIV PRODUCTS					
Cobicistat	Concomitant use of OLYSIO and cobicistat may result in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by cobicistat. It is not recommended to co-administer OLYSIO with cobicistat.				
Antiretroviral – CCR5 antagonist					
Maraviroc	Concomitant use of OLYSIO with maraviroc is not expected to result in a clinically relevant interaction. No dose adjustment is required for either drug when OLYSIO is co-administered with maraviroc.				
Antiretroviral – integrase inhibitor					
Raltegravir[1]	400 mg twice daily	raltegravir	↔ 1.03 (0.78-1.36)	- 1.08 (0.85-1.38)	- 1.14 (0.97-1.36)
		simeprevir	↔ 0.93 (0.85-1.02)	↔ 0.89 (0.81-0.98)	¯ 0.86 (0.75-0.98)
	No dose adjustment is required for either drug when OLYSIO is co-administered with raltegravir.				
Antiretroviral – non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Efavirenz[1]	600 mg once daily	efavirenz	↔ 0.97 (0.89-1.06)	↔ 0.90 (0.85-0.95)	↔ 0.87 (0.81-0.93)
		simeprevir	¯ 0.49 (0.44-0.54)	¯ 0.29 (0.26-0.33)	¯ 0.09 (0.08-0.12)
	Concomitant use of OLYSIO with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz. This may result in loss of therapeutic effect of OLYSIO. It is not recommended to co-administer OLYSIO with efavirenz.				
Rilpivirine[1]	25 mg once daily	rilpivirine	↔ 1.04 (0.95-1.13)	↔ 1.12 (1.05-1.19)	- 1.25 (1.16-1.35)
		simeprevir	- 1.10 (0.97-1.26)	↔ 1.06 (0.94-1.19)	↔ 0.96 (0.83-1.11)
	No dose adjustment is required for either drug when OLYSIO is co-administered with rilpivirine.				
Other NNRTIs (Delavirdine, Etravirine, Nevirapine)	Concomitant use of OLYSIO with delavirdine, etravirine or nevirapine may result in altered plasma concentrations of simeprevir due to CYP3A inhibition (delavirdine) or induction (etravirine and nevirapine) by these medicinal products. It is not recommended to co-administer OLYSIO with delavirdine, etravirine or nevirapine.				
Antiretroviral – nucleoside or nucleotide reverse transcriptase inhibitors (N(t)RTIs)					

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
Tenofovir disoproxil fumarate[1]	300 mg once daily	tenofovir	- 1.19 (1.10-1.30)	↔ 1.18 (1.13-1.24)	- 1.24 (1.15-1.33)
		simeprevir	¯ 0.85 (0.73-0.99)	¯ 0.86 (0.76-0.98)	¯ 0.93 (0.78-1.11)
	No dose adjustment is required for either drug when OLYSIO is co-administered with tenofovir disoproxil fumarate.				
Other NRTIs (Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Zidovudine)	Concomitant use of OLYSIO with these NRTIs is not expected to result in a clinically relevant interaction based on different elimination routes for these NRTIs and simeprevir. No dose adjustment is required when OLYSIO is co-administered with these NRTIs.				
Antiretroviral – protease inhibitors (PIs)					
Darunavir/ritonavir[1,4]	800/100 mg once daily	darunavir	↔ 1.04 (0.99-1.10)	- 1.18 (1.11-1.25)	- 1.31 (1.13-1.52)
		simeprevir	- 1.79 (1.55-2.06)	- 2.59 (2.15-3.11)	- 4.58 (3.54-5.92)
	Concomitant use of OLYSIO with darunavir/ritonavir resulted in increased plasma concentrations of simeprevir due to CYP3A inhibition by darunavir/ritonavir. It is not recommended to co-administer darunavir/ritonavir and OLYSIO.				
Ritonavir[1,2]	100 mg twice daily	simeprevir	- 4.70 (3.84-5.76)	- 7.18 (5.63-9.15)	- 14.35 (10.29-20.01)
	Concomitant use of OLYSIO with ritonavir resulted in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by ritonavir. It is not recommended to co-administer OLYSIO with ritonavir.				
Other ritonavir-boosted or unboosted HIV PIs, e.g., Atazanavir, (Fos)amprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir	Concomitant use of OLYSIO with ritonavir-boosted or unboosted HIV PIs may result in altered plasma concentrations of simeprevir due to CYP3A inhibition or induction by these HIV PIs. It is not recommended to co-administer OLYSIO with any HIV PI, with or without ritonavir.				
HMG CO-A REDUCTASE INHIBITORS					
Rosuvastatin[1]	10 mg	rosuvastatin	↑ 3.17 (2.57-3.91)	↑ 2.81 (2.34-3.37)	NA
	Concomitant use of OLYSIO with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1 by simeprevir. Titrate the rosuvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.				
Pitavastatin Pravastatin	Concomitant use of OLYSIO with pitavastatin or pravastatin may result in increased plasma concentrations of pitavastatin and pravastatin due to inhibition of OATP1B1 by simeprevir. Titrate the pitavastatin and pravastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.				
Atorvastatin[1]	40 mg	atorvastatin	↑ 1.70 (1.42-2.04)	↑ 2.12 (1.72-2.62)	NA
		2-hydroxy-atorvastatin	↑ 1.98 (1.70-2.31)	↑ 2.29 (2.08-2.52)	NA

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
	Concomitant use of OLYSIO with atorvastatin resulted in increased plasma concentrations of atorvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Titrate the atorvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.				
Simvastatin[1]	40 mg	simvastatin	↑ 1.46 (1.17-1.82)	↑ 1.51 (1.32-1.73)	NA
		simvastatin acid	↑ 3.03 (2.49-3.69)	↑ 1.88 (1.63-2.17)	NA
	Concomitant use of OLYSIO with simvastatin resulted in increased plasma concentrations of simvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Titrate the simvastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.				
Lovastatin	Concomitant use of OLYSIO with lovastatin may result in increased plasma concentrations of lovastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Titrate the lovastatin dose carefully and use the lowest necessary dose while monitoring for safety when co-administered with OLYSIO.				
Fluvastatin	Concomitant use of OLYSIO with fluvastatin is not expected to result in a clinically relevant interaction. No dose adjustment is required when OLYSIO is co-administered with fluvastatin.				
HORMONAL CONTRACEPTIVES					
Ethinylestradiol[1] Norethindrone[1]	0.035 mg once daily	ethinylestradiol	↑ 1.18 (1.09-1.27)	↔ 1.12 (1.05-1.20)	↔ 1.00 (0.89-1.13)
	1 mg once daily	norethindrone	↔ 1.06 (0.99-1.14)	↔ 1.15 (1.08-1.22)	↑ 1.24 (1.13-1.35)
	No dose adjustment is required when OLYSIO is co-administered with estrogen- and/or progesterone-based contraceptives. Due to significant teratogenic and/or embryocidal effects with ribavirin, two effective methods of contraception must be used during treatment with ribavirin (see *Warnings and Precautions*).				
IMMUNOSUPPRESSANTS					
Cyclosporin[1]	100 mg	cyclosporin	↑ 1.16 (1.07-1.26)	↑ 1.19 (1.13-1.26)	NA
	No dose adjustment is required when OLYSIO is co-administered with cyclosporin. Monitoring of blood concentrations of cyclosporin is recommended.				
Tacrolimus[1]	2 mg	tacrolimus	¯ 0.76 (0.65-0.90)	¯ 0.83 (0.59-1.16)	NA
	No dose adjustment is required when OLYSIO is co-administered with tacrolimus. Monitoring of blood concentrations of tacrolimus is recommended.				
Sirolimus	Concomitant use of OLYSIO and sirolimus may result in mild increased or decreased plasma concentrations of sirolimus. Monitoring of blood concentrations of sirolimus is recommended.				
NARCOTIC ANALGESICS					
Methadone[5]	30-150 mg once daily, individualised dose	R(-) methadone	↔ 1.03 (0.97-1.09)	↔ 0.99 (0.91-1.09)	↔ 1.02 (0.93-1.12)
	No dose adjustment is required when OLYSIO is co-administered with methadone.				
Buprenorphine Naloxone	No dose adjustment is required when OLYSIO is co-administered with buprenorphine or naloxone.				
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS					

Co-administered medicinal product	Dose of co-administered medicinal product	Medicinal product assessed	C_{max}	AUC	C_{min}
Sildenafil Tadalafil Vardenafil	Concomitant use of OLYSIO with PDE-5 inhibitors may result in mild increases in concentrations of PDE-5 inhibitors due to intestinal CYP3A4 inhibition by simeprevir. No dose adjustment is required when OLYSIO is co-administered with doses of sildenafil, vardenafil, or tadalafil indicated for the treatment of erectile dysfunction. Dose adjustment of the PDE-5 inhibitor may be required when OLYSIO is co-administered with sildenafil or tadalafil administered chronically at doses used for the treatment of pulmonary arterial hypertension. Consider starting with the lowest dose of the PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate.				
SEDATIVES/ANXIOLYTICS					
Midazolam[1]	0.075 mg/kg oral	midazolam	- 1.31 (1.19-1.45)	- 1.45 (1.35-1.57)	NA
	0.025 mg/kg intravenous		¯ 0.78 (0.52-1.17)	- 1.10 (0.95-1.26)	NA
	Concomitant use of OLYSIO with orally administered midazolam resulted in increased plasma concentrations of midazolam due to mild inhibition of intestinal CYP3A4 by simeprevir. Plasma concentrations of midazolam were not affected when administered intravenously as simeprevir does not inhibit hepatic CYP3A4. Caution is warranted when this medicinal product with narrow therapeutic index is co-administered with OLYSIO via the oral route.				
Triazolam	Concomitant use of OLYSIO with orally administered triazolam may result in mild increases in concentrations of triazolam due to intestinal CYP3A4 inhibition by simeprevir. Caution is warranted when this medicinal product with narrow therapeutic index is co-administered with OLYSIO via the oral route.				
STIMULANTS					
Methylphenidate	No dose adjustment is required when OLYSIO is co-administered with methylphenidate.				

The direction of the arrow (↑=increase, ↓=decrease, ↔=no change) for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 0.80-1.25 range.

[1] The interaction between OLYSIO and the drug was evaluated in a pharmacokinetic study in healthy adults. All other drug interactions shown are predicted.

[2] This interaction study has been performed with a dose higher than the recommended dose for OLYSIO assessing the maximal effect on the co-administered drug. The dosing recommendation is applicable to the recommended dose of OLYSIO 150 mg once daily.

[3] Comparison based on historic controls. The interaction between simeprevir and the drug was evaluated in a preliminary pharmacokinetic substudy within a Phase 2 study in 22 HCV-infected patients. The safety and efficacy of OLYSIO in combination with sofosbuvir have not been established.

[4] The dose of OLYSIO in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir, compared to 150 mg in the OLYSIO alone treatment group.

[5] The interaction between OLYSIO and the drug was evaluated in a pharmacokinetic study in opioid-dependent adults on stable methadone maintenance therapy.

Effect on Ability to Drive or Operate Machinery

OLYSIO has no known effect on the ability to drive and use machines. No specific studies on the effects of OLYSIO on the ability to drive and use machines have been performed.

Combination treatment of OLYSIO, peginterferon alfa and ribavirin may affect a patient's ability to drive and use machines. Refer to the product information for peginterferon alfa and ribavirin regarding their potential effect on the ability to drive and use machines.

ADVERSE EFFECTS

OLYSIO must be administered with peginterferon alfa and ribavirin. Please note the following risks have been identified for the combination of peginterferon alfa and ribavirin: anaemia, lymphopenia/neutropenia, thrombocytopenia, psychiatric disorders, diabetes mellitus, thyroid disorders and specific skin disorders (cutaneous leukocytoclastic vasculitis, lichen planus, polyarteritis nodosa and porphyria cutanea tarda). Refer to the product information of peginterferon alfa and ribavirin for a complete list of their adverse reactions.

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of OLYSIO based on the comprehensive assessment of the available adverse event information. A causal relationship with OLYSIO cannot be reliably established in individual cases. Further, because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of OLYSIO in combination with peginterferon alfa and ribavirin in patients with HCV genotype 1 infection who were treatment-naïve or who failed prior interferon therapy with or without ribavirin is based on pooled data from 2 clinical Phase 2b studies (Studies C205 and C206) and 3 clinical Phase 3 studies (Studies C208, C216 and HPC3007). The pooled data from the Phase 2b and Phase 3 studies included 1486 patients who received OLYSIO in combination with peginterferon alfa and ribavirin (of which 924 patients were to receive OLYSIO 150 mg once daily for 12 weeks) and 540 patients who received placebo with peginterferon alfa and ribavirin.

Table 15 lists adverse reactions of at least moderate severity (≥ Grade 2) reported in patients during the 12 weeks of treatment with OLYSIO 150 mg once daily or placebo in combination with peginterferon alfa and ribavirin in the pooled Phase 3 studies (Studies C208, C216 and HPC3007). The adverse reactions are listed by system organ class (SOC) and frequency. No additional adverse reactions were identified in the other clinical studies.

In the pooled Phase 3 safety data, the majority of the adverse reactions reported during 12 weeks treatment with OLYSIO were Grade 1 to 2 in severity. Grade 3 or 4 adverse reactions were reported in 2.8% of patients receiving OLYSIO with peginterferon alfa and ribavirin versus 0.5% of patients receiving placebo with peginterferon alfa and ribavirin. Serious adverse reactions were reported in 0.3% of OLYSIO-treated patients and in none of the patients receiving placebo with peginterferon alfa and ribavirin. Discontinuation of OLYSIO or placebo due to adverse reactions occurred in 0.9% and 0.3% of patients receiving OLYSIO with peginterferon alfa and ribavirin and patients receiving placebo with peginterferon alfa and ribavirin, respectively.

Table 15: Adverse Reactions of at Least Moderate Severity (Grades 2 to 4[1]) Reported in Adult Patients with HCV Genotype 1 Infection (Pooled Phase 3 Studies C208, C216 and HPC3007; First 12 Weeks of Treatments; Intent-to-Treat Analysis)

System Organ Class, Grouped Term	OLYSIO + Peginterferon alfa + Ribavirin N=781 n (%)	Placebo + Peginterferon alfa + Ribavirin N=397 n (%)
Gastrointestinal disorders		
Constipation[2]	2 (0.3%)	2 (0.5%)
Hepatobiliary disorders		
Blood bilirubin increased[3]	42 (5.4%)	9 (2.3%)
Skin and subcutaneous tissue disorders		

Table 15: Adverse Reactions of at Least Moderate Severity (Grades 2 to 4[1]) Reported in Adult Patients with HCV Genotype 1 Infection (Pooled Phase 3 Studies C208, C216 and HPC3007; First 12 Weeks of Treatments; Intent-to-Treat Analysis)

System Organ Class, Grouped Term	OLYSIO + Peginterferon alfa + Ribavirin N=781 n (%)	Placebo + Peginterferon alfa + Ribavirin N=397 n (%)
Rash[4]	59 (7.6%)	15 (3.8%)
Pruritus[5]	24 (3.1%)	3 (0.8%)
Photosensitivity reaction[6]	6 (0.8%)	0 (0.0%)

[1] According to the WHO toxicity grading scale.
[2] Grouped term 'constipation' included the preferred term constipation.
[3] Grouped term 'blood bilirubin increased' included the preferred terms bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[4] Grouped term 'rash' included the preferred terms blister, drug eruption, erythema, erythema of eyelid, exfoliative rash, generalised erythema, macule, palmar erythema, papule, pityriasis rosea, polymorphic light eruption, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, scrotal erythema, skin exfoliation, skin irritation, skin reaction, toxic skin eruption, umbilical erythema and vasculitic rash.
[5] Grouped term 'pruritus' included the preferred terms eyelids pruritus, prurigo, pruritus and pruritus generalized.
[6] Grouped term 'photosensitivity reaction' included the preferred terms photodermatosis, photosensitivity reaction, solar dermatitis and sunburn.

Rash and pruritus
During the 12 weeks treatment with OLYSIO, rash and pruritus were observed in 21.8% and 21.9% of OLYSIO-treated patients, compared to 16.6% and 14.6% in patients treated with placebo, peginterferon alfa and ribavirin, respectively (all grades; pooled Phase 3). Most of the rash and pruritus events in OLYSIO-treated patients were of mild or moderate severity (Grade 1 or Grade 2). Grade 3 rash or pruritus occurred in 0.5% and 0.1% of OLYSIO-treated patients, respectively. There were no reports of Grade 4 rash or pruritus. Discontinuation of OLYSIO due to rash or pruritus occurred in 0.8% and 0.1% of OLYSIO-treated patients, compared to 0.3% and no patients treated with placebo, peginterferon alfa and ribavirin, respectively.

Blood bilirubin increased
During the 12 weeks treatment with OLYSIO, 'blood bilirubin increased' was reported in 7.4% of OLYSIO-treated patients, compared to 2.8% in patients treated with placebo, peginterferon alfa and ribavirin (all grades; pooled Phase 3). In 2% and 0.3% of the OLYSIO-treated patients Grade 3 or Grade 4 'blood bilirubin increased' was reported, respectively (pooled Phase 3 studies). Discontinuation of OLYSIO due to 'blood bilirubin increased' was rare (0.1%; n=1). The elevations in direct and indirect bilirubin were mostly of mild or moderate severity and were reversible. Bilirubin elevations were generally not associated with elevations in liver transaminases and are attributed to a decrease in bilirubin elimination related to inhibition of the hepatocyte transporters OATP1B1 and MRP2 by simeprevir. These changes are not considered to be clinically relevant.

Photosensitivity reactions
During the 12 weeks treatment with OLYSIO, photosensitivity reactions were reported in 4.7% of OLYSIO-treated patients compared to 0.8% in patients treated with placebo, peginterferon alfa and ribavirin (all grades; pooled Phase 3). Most photosensitivity reactions in OLYSIO-treated patients were of mild or moderate severity (Grade 1 or 2); 0.1% of the OLYSIO-treated patients experienced Grade 3 photosensitivity reactions. There were no Grade 4 photosensitivity reactions reported. None of the patients discontinued treatment due to photosensitivity reactions.

Laboratory abnormalities

There were no differences in hemoglobin, neutrophils or platelets between both treatment groups. Treatment-emergent laboratory abnormalities that were observed at a higher incidence in OLYSIO-treated patients than in patients treated with placebo, peginterferon alfa and ribavirin are given in Table 16.

Table 16: Treatment-Emergent Laboratory Abnormalities (WHO Worst Toxicity Grades 1 to 4) Observed at a Higher Incidence in OLYSIO-Treated Patients (Pooled Phase 3 Studies C208, C216 and HPC3007; First 12 Weeks of Treatments; Intent-to-Treat Analysis)

Laboratory Parameter	WHO Toxicity Range	OLYSIO + Peginterferon alfa + Ribavirin N=781 n (%)	Placebo+ Peginterferon alfa + Ribavirin N=397 n (%)
Chemistry			
Alkaline Phosphatase			
Grade 1	≥ 1.25 to ≤ 2.50 x ULN	26 (3.3%)	5 (1.3%)
Grade 2	> 2.50 to ≤ 5.00 x ULN	1 (0.1%)	0 (0%)
Hyperbilirubinemia			
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	208 (26.7%)	61 (15.4%)
Grade 2	> 1.5 to ≤ 2.5 x ULN	143 (18.3%)	36 (9.1%)
Grade 3	> 2.5 to ≤ 5.0 x ULN	32 (4.1%)	6 (1.5%)
Grade 4	> 5.0 x ULN	3 (0.4%)	0 (0%)
ULN= Upper Limit of Normal No Grade 3 or 4 changes in alkaline phosphatase were observed.			

Additional information on special populations

Patients co-infected with HIV-1
The safety profile of OLYSIO is comparable in patients with HCV genotype 1 infection with (N=106) and without HIV-1 co-infection.

Safety in adults with HCV genotype 4 infection
The safety profile of OLYSIO is comparable in patients with HCV genotype 4 infection (N=107) and genotype 1 infection.

DOSAGE AND ADMINISTRATION

OLYSIO must be administered in combination with peginterferon alfa and ribavirin.
For dosage instructions for peginterferon alfa and ribavirin, refer to the product information for these medicinal products.

Dosage – Adults (≥ 18 years)

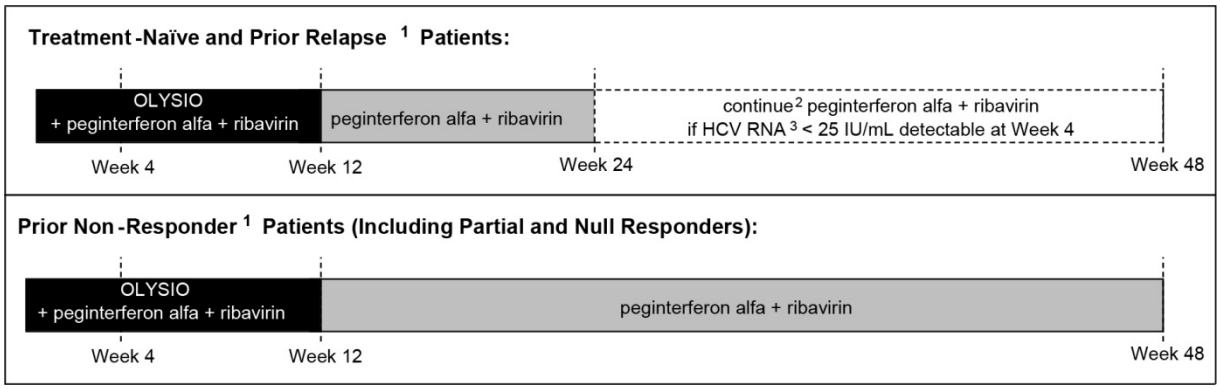
The recommended dosage of OLYSIO is 150 mg once daily for 12 weeks, taken with food.
In all patients, treatment with OLYSIO must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks. Hepatitis C virus (HCV) RNA levels should be assessed at treatment Week 4 to determine the total treatment duration with peginterferon alfa and ribavirin. The recommended duration of treatment with OLYSIO, peginterferon alfa and ribavirin is presented in Figure 1. Refer to Table 17 for treatment stopping rules.

- Treatment-naïve and prior relapse patients with undetectable HCV RNA at treatment Week 4 receive an additional 12 weeks of peginterferon alfa and ribavirin after completing 12 weeks of treatment with OLYSIO, peginterferon alfa and ribavirin (total treatment duration of 24 weeks).

- In treatment-naïve and prior relapse patients with HCV RNA < 25 IU/mL detectable at treatment Week 4, an additional 36 weeks of peginterferon alfa and ribavirin is recommended after completing 12 weeks of treatment with OLYSIO, peginterferon alfa and ribavirin (total treatment duration of 48 weeks).

- Prior non-responder patients (including partial and null responders) with undetectable HCV RNA or HCV RNA < 25 IU/mL detectable at treatment Week 4 receive an additional 36 weeks of peginterferon alfa and ribavirin after completing 12 weeks of treatment with OLYSIO, peginterferon alfa and ribavirin (total treatment duration of 48 weeks).

Figure 1: Duration of Treatment with OLYSIO, Peginterferon Alfa and Ribavirin



Note: Duration of treatment: provided that a patient does not meet a treatment stopping rule (see Table 16).

[1] Relapse or non-response following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin (see *Pharmacodynamics*).

[2] In patients with HCV RNA < 25 IU/mL detectable at treatment Week 4, a total treatment duration of 48 weeks of peginterferon alfa and ribavirin is recommended.

[3] In clinical studies, HCV RNA in plasma was measured with a COBAS® TaqMan® real-time polymerase chain reaction (RT-PCR) assay with a lower limit of quantification (LLOQ) of 25 IU/mL and a limit of detection of 15 IU/mL (see *Pharmacodynamics*). HCV RNA < 25 IU/mL detectable corresponds to HCV below the LLOQ, but target detected; undetectable HCV RNA corresponds to a result of target not detected.

Treatment discontinuation in patients with inadequate on-treatment virologic response
It is unlikely that patients with inadequate on-treatment virologic response will achieve a sustained virologic response (SVR), therefore discontinuation of treatment is recommended in these patients. The HCV RNA thresholds that trigger discontinuation of treatment (i.e., guidelines for discontinuation) are presented in Table 17.

Table 17: Guideline for discontinuation in Patients with Inadequate On-Treatment Virologic Response

HCV RNA	Action
Treatment Week 4: ≥ 25 IU/mL	Discontinue OLYSIO, peginterferon alfa and ribavirin
Treatment Week 12: detectable[1]	Discontinue peginterferon alfa and ribavirin (treatment with OLYSIO is complete at Week 12)
[1] Re-evaluation of HCV RNA is recommended in case of detectable HCV RNA after previous undetectable HCV RNA to confirm HCV RNA levels prior to discontinuing HCV treatment.	

Testing at week 24 may be considered in addition to the tests at week 4 and week 12. Patients with HCV RNA detectable at week 24 should discontinue peginterferon alfa and ribavirin.
If peginterferon alfa or ribavirin is discontinued for any reason, OLYSIO must also be discontinued.

Dosage adjustment or interruption of OLYSIO treatment
To prevent treatment failure, the dose of OLYSIO must not be reduced or interrupted. If treatment with OLYSIO is discontinued because of adverse reactions or inadequate on-treatment virologic response, OLYSIO treatment must not be reinitiated.

Dosage adjustment or interruption of peginterferon alfa and/or ribavirin treatment
If adverse reactions, potentially related to peginterferon alfa and/or ribavirin, require dosage adjustment or interruption of either medicinal product, refer to the instructions outlined in the respective product information for these medicinal products.

Missed dose(s)
If a dose of OLYSIO is missed and the patient remembers within 12 hours of the usual dosing time, the patient should take the missed dose of OLYSIO with food as soon as possible and then take the next dose of OLYSIO at the regularly scheduled time. If a dose of OLYSIO is missed by more than 12 hours after the usual dosing time, the patient should not take the missed dose of OLYSIO, and should resume dosing of OLYSIO with food at the regularly scheduled time.

Special populations

Paediatrics (below 18 years of age)
The safety and efficacy of OLYSIO have not been established in pediatric patients.

Elderly (above 65 years of age)
There are limited data on the safety and efficacy of OLYSIO in patients older than 65 years. No dose adjustment of OLYSIO is required in elderly patients (see *Pharmacokinetics*).

Renal impairment
No dose adjustment of OLYSIO is required in patients with mild, moderate or severe renal impairment (see *Pharmacokinetics*). The safety and efficacy of OLYSIO have not been studied in HCV-infected patients with severe renal impairment (creatinine clearance below 30 mL/min) or end-stage renal disease, including patients requiring dialysis. Simeprevir is highly protein bound, therefore dialysis is unlikely to result in significant removal of simeprevir (see *Pharmacokinetics*).

Refer to the respective product information for peginterferon alfa and ribavirin regarding use in patients with renal impairment. Ribavirin is contraindicated, or to be used with extreme caution in patients with CrCl < 50 ml/min (see the Product Information for ribavirin).

Hepatic impairment
No dose adjustment of OLYSIO is required in patients with mild hepatic impairment (Child-Pugh Class A). However, moderate and severe hepatic impairment (Child-Pugh Class B or C) are associated with increases in simeprevir exposure (see Pharmacokinetics). In addition, the safety and efficacy of OLYSIO have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). Therefore, the potential risks and benefits of simeprevir should be carefully considered prior to use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

Refer to the respective product information for peginterferon alfa and ribavirin which are contraindicated in patients with decompensated cirrhosis (Child-Pugh Class B or C). Refer also to the Product Information for peginterferon alfa and ribavirin which are contraindicated in patients with liver cirrhosis and a Child-Pugh score ≥ 6.

Race
Given limited data, the potential risks and benefits of OLYSIO should be carefully considered prior to use in East Asian patients (see Pharmacokinetics).

Human immunodeficiency virus type 1 (HIV-1) co-infection
No dose adjustment of OLYSIO is required in patients with HCV genotype 1 or genotype 4 co-infection with HIV-1 (see *Adverse Effects*, *Clinical Trials*, *Pharmacokinetics* sections). For information on interactions with antiretroviral agents, see *Interactions with other medicines*.

Administration

OLYSIO should be taken orally once a day with food. The type of food does not affect exposure to simeprevir (see *Pharmacokinetics*). The capsule should be swallowed as a whole.

OLYSIO must be used in combination with peginterferon alfa and ribavirin. For peginterferon alfa and ribavirin dosage instructions, see the respective product information.

OVERDOSAGE

Symptoms and signs

Human experience of overdose with OLYSIO is limited. OLYSIO was generally well tolerated when given as single doses up to 600 mg or once daily doses up to 400 mg for 5 days in healthy adult participants, and as 200 mg once daily for 4 weeks in adult patients with HCV. OLYSIO mildly inhibits intestinal CYP3A, but not hepatic CYP3A. Coadministration of OLYSIO with orally administered drugs that are solely dependent on CYP3A4 for their elimination may result in increased plasma concentrations of such drugs and may cause life threatening consequences in case of drugs with narrow therapeutic index.

Treatment

There is no specific antidote for overdose with OLYSIO. In the event of an overdose, it is recommended to employ the usual supportive measures and observing the patient's clinical status.

Simeprevir is highly protein bound, therefore dialysis is unlikely to result in significant removal of simeprevir (see *Pharmacokinetics*).

PRESENTATION AND STORAGE CONDITIONS

OLYSIO 150 mg capsules are white (white body/white cap), with "TMC435 150" printed in black ink.

OLYSIO capsules are provided in a polyvinylchloride/polyethylene/polyvinylidenechloride (PVC/PE/PVDC) aluminium push-through blister strips of 7 capsules contained within an outer carton. OLYSIO is available in pack sizes of 7 or 28 capsules*.
*Not all pack sizes may be available.

Store below 30°C. Store in the original container. Protect from light.

NAME AND ADDRESS OF SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia
NZ Office: Auckland New Zealand

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG

18 July 2014