NEW ZEALAND DATA SHEET

1 HARVONI® (LEDIPASVIR 90 MG, SOFOSBUVIR 400 MG) TABLETS)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ledipasvir 90 mg and sofosbuvir 400 mg)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

HARVONI tablets are orange diamond shaped debossed with “GSI” on one side and the number “7985” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

HARVONI is indicated for the treatment of chronic hepatitis C (CHC) infection in adults and in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5 or 6 without cirrhosis or with compensated cirrhosis.

4.2 Dose and method of administration

4.2.1 Adults

The recommended dose of HARVONI tablets in adults is one tablet, taken orally, once daily with or without food.

Table 1 provides the recommended treatment duration of HARVONI and the recommended use of co-administered medicinal product for certain subgroups.

Table 1 Recommended treatment duration for HARVONI in Adult patients and the recommended use of co administered ribavirin in certain subgroups

Patient population*	Treatment	Duration
Patients with genotype 1, 2, 4, 5 or 6 CHC Mono-infected and HCV/HIV-1 Co-infected Patients		
Treatment-naïve without cirrhosis	HARVONI	8 or 12 weeks[a]
Treatment-naïve with cirrhosis	HARVONI	12 weeks
Treatment-experienced[b] without cirrhosis	HARVONI	12 weeks
Treatment-experienced[b] with cirrhosis	HARVONI	12 or 24 weeks[c]
Liver transplant recipients with compensated liver disease	HARVONI + ribavirin	12 Weeks
Patients with genotype 3 CHC		
Treatment-naïve with and without cirrhosis	HARVONI + ribavirin	12 weeks

* Includes patients co-infected with human immunodeficiency virus (HIV)

a. HARVONI for 8 weeks can be considered for treatment-naïve, non-cirrhotic patients with baseline HCV RNA <6 million IU/mL

b. Treatment-experienced patients who have failed treatment with either peginterferon alfa + ribavirin or an HCV protease inhibitor + peginterferon alfa + ribavirin.

c. Patients at high risk of clinical progression may be treated with HARVONI+ribavirin for 12 weeks or with HARVONI for 24 weeks.

In patients with genotype 1 CHC who have decompensated cirrhosis, irrespective of transplantation status, HARVONI with ribavirin for 12 weeks is recommended.

Concomitant Ribavirin Dose

When HARVONI is used in combination with ribavirin, the daily dose of ribavirin is 1,000 mg for patients weighing <75 kg and 1,200 mg for those weighing ≥75 kg, except for patients with decompensated cirrhosis who should receive 600 mg. Ribavirin is administered orally in two divided doses with food. Refer to ribavirin prescribing information for ribavirin dose modifications.

Elderly: Clinical trials of HARVONI included 351 patients aged 65 and over. The response rates observed for patients over 65 years of age were similar to that of younger patients across treatment groups. No dose adjustment of HARVONI is warranted in elderly patients. In general, caution should be exercised when administering HARVONI in elderly patients, reflecting the greater frequency of anaemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment: No dose adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety of HARVONI has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min) or end stage renal disease (ESRD) requiring haemodialysis (see section 5.2). When HARVONI is used in combination with ribavirin refer also to the product information for ribavirin for patients with creatinine clearance (CrCl) <50 mL/min

Hepatic impairment: No dose adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) (see section 5.2).

Dose modification of ribavirin in patients taking 1000-1200 mg daily

If HARVONI is used in combination with ribavirin, and a patient has a serious adverse reaction potentially related to this drug, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 2 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status.

Table 2 Ribavirin dose modification guideline for co-administration with HARVONI in Adult Patients

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day[a] If:	Discontinue Ribavirin If:[b]
Haemoglobin in patients with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Haemoglobin in patients with history of stable cardiac disease	≥ 2 g/dL decrease in haemoglobin during any 4 week period treatment	< 12 g/dL despite 4 weeks at reduced dose

a. The daily dose of ribavirin is administered orally in two divided doses with food.

b. Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1000 mg to 1200 mg daily).

4.2.2 Children and Adolescents up to 18 Years of Age

The recommended dosage of HARVONI in pediatric patients 12 years of age and older or weighing at least 35 kg is one tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally once daily with or without food for 12 weeks.

Table 3 shows the recommended HARVONI duration based on pediatric patient population.

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 3. Refer to Section 5.4 for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 3 Recommended treatment duration for HARVONI in Pediatric patients 12 years of age or older or weighing at least 35 kg with Genotype 1, 4, 5, or 6 HCV without cirrhosis or with compensated cirrhosis

Patient population*	Treatment	Duration
Patients with genotype 1		
Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI	12 weeks
Treatment-experienced[a] without cirrhosis	HARVONI	12 weeks
Treatment-experienced[a] with compensated cirrhosis (Child-Pugh A)	HARVONI	24 weeks
Patients with genotype 4, 5 or 6 CHC		
Treatment-naïve and treatment-experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI	12 weeks

* Includes patients co-infected with human immunodeficiency virus (HIV)

a. Treatment-experienced patients have failed an interferon based regimen with or without ribavirin

4.3 Contraindications

HARVONI tablets are contraindicated in patients with known hypersensitivity to the active substance or to any other component of the tablets.

HARVONI is a fixed-dose combination of ledipasvir and sofosbuvir. HARVONI should not be administered concurrently with other medicinal products containing any of the same active components.

4.4 Special warnings and precautions for use

Symptomatic Bradycardia When Coadministered with Amiodarone

Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown.

Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered HARVONI:

- Counsel patients about the risk of symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Patients who are taking HARVONI who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above.

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting HARVONI should also undergo similar cardiac monitoring as outlined above.

Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Hepatitis B Virus Reactivation

Cases of Hepatitis B virus (HBV) reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents (DAAs) in HCV/HBV co-infected patients. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment with HARVONI.

Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated.

Use with Potent P-gp Inducers

Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's Wort) may significantly decrease ledipasvir and sofosbuvir plasma concentration leading to reduced therapeutic effect of HARVONI. Rifampin and St. John's Wort should not be used with HARVONI.

Use with certain HIV antiretroviral regimens

HARVONI has been shown to increase tenofovir exposure. The potential risks and benefits associated with coadministration of tenofovir with HARVONI should be considered, particularly in patients at increased risk for renal dysfunction (See section 5.4).

Related products that are not recommended

The use of HARVONI with other medicinal products containing sofosbuvir is not recommended.

4.5 Interaction with other medicines and other forms of interaction

As HARVONI contains ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with HARVONI.

After oral administration of HARVONI, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Hydrolytic prodrug cleavage and sequential phosphorylation steps results in formation of the pharmacologically active uridine nucleoside analog triphosphate. Dephosphorylation of nucleotide metabolites results in conversion to the predominant circulating metabolite GS-331007 that accounts for approximately 85% of total systemic exposure. In clinical pharmacology studies, both sofosbuvir and GS-331007 were monitored for purposes of pharmacokinetic analyses.

Potential for HARVONI to Affect Other Drugs

Ledipasvir is an inhibitor of drug transporter P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir is an inhibitor of transporters OATP1B1, OATP1B3 and BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of transporters MRP2, MRP4, OCT2, OAT1, OAT3, MATE1, and OCT1. The drug-drug interaction potential of ledipasvir is primarily limited to the process of intestinal absorption. Clinically relevant transporter inhibition by ledipasvir in the systemic circulation is not expected due to its high protein binding. Sofosbuvir and GS-331007 are not inhibitors of drug transporters P-gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1 and GS-331007 is not an inhibitor of OAT1, OCT2, and MATE1.

Ledipasvir, sofosbuvir and GS-331007 are not inhibitors or inducers of CYP or UGT1A1 enzymes.

Potential for Other Drugs to Affect HARVONI

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g. rifampin or St. John's Wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and thus should not be used with HARVONI (see Precautions for Use: Use with Potent P-gp Inducers). Coadministration with drugs that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may be coadministered with P-gp and/or BCRP inhibitors. Neither ledipasvir nor sofosbuvir is a substrate for hepatic uptake transporters OCT1, OATP1B1 or OATP1B3. GS-331007 is not a substrate for renal transporters including organic anion transporter OAT1 or OAT3, or organic cation transporter OCT2.

Ledipasvir is subject to slow oxidative metabolism via an unknown mechanism. *In vitro*, no detectable metabolism of ledipasvir by CYP enzymes has been observed. Biliary excretion of unchanged ledipasvir is a major route of elimination. Sofosbuvir is not a substrate for CYP and UGT1A1 enzymes. Clinically significant drug interactions with HARVONI mediated by CYP or UGT1A1 enzymes are not expected.

Established and Other Potentially Significant Drug Interactions

Table 4 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either HARVONI, the components of HARVONI (ledipasvir and sofosbuvir) as individual agents, or are predicted drug interactions that may occur with HARVONI. This table is not all inclusive.

Table 4 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Acid Reducing Agents:	↓ ledipasvir ↔ sofosbuvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g. aluminum and magnesium hydroxide)	↔ GS-331007	It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists[c]		H_2-receptor antagonists may be administered simultaneously with or staggered from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c]		Proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with HARVONI. Proton-pump inhibitors should not be taken before HARVONI.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Coadministration of amiodarone with HARVONI may result in symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended (see section 4.4).
digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI.
Anticonvulsants carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. HARVONI should not be used with rifampin, a potent intestinal P-gp inducer.
Antiretrovirals: tenofovir disoproxil fumarate tipranavir/ritonavir	↑ tenofovir ↓ ledipasvir	HARVONI has been shown to increase tenofovir exposure. The potential risks and benefits associated with coadministration of tenofovir with HARVONI should be considered, particularly in patients at increased risk for renal dysfunction. Patients receiving tenofovir and HARVONI concomitantly should be monitored for adverse reactions associated with tenofovir . Refer to the tenofovir DF-containing product's prescribing information for recommendations on renal monitoring. Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir[c]	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. The safety and efficacy of HARVONI in combination with simeprevir have not been established.
Herbal Supplements: St. John's Wort (Hypericum perforatum)	↓ ledipasvir ↓ sofosbuvir	HARVONI should not be used with St. John's Wort, a potent intestinal P-gp inducer (see section 4.4)

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

a. This table is not all inclusive.

b. ↑ = increase, ↓ = decrease, ↔ = no effect

c. These interactions have been studied in healthy adults.

Drugs without Clinically Significant Interactions with HARVONI

Based on drug interaction studies conducted with the components of HARVONI (ledipasvir or sofosbuvir) or HARVONI, no clinically significant drug interactions have been either observed or are expected when HARVONI is combined with the following drugs: abacavir, atazanavir/ritonavir, cyclosporin, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus (see 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction: Other Forms of Interaction), tenofovir disoproxil fumarate or verapamil. For use of HARVONI with certain HIV antiretroviral regimens, see section 4.4.

Other Forms of Interaction

Improvement in hepatic function as a result of treatment of HCV with DAAs may require monitoring of relevant laboratory parameters in susceptible patients (e.g., International Normalized Ratio [INR] in patients taking vitamin K antagonists, blood glucose levels in diabetic patients). Concomitant medications significantly affected by changes in hepatic function (e.g., calcineurin inhibitors) may require monitoring or dose modification to ensure continued efficacy.

Assessment of Drug Interactions

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir and GS-331007 are shown in Table 5. The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 6.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[s]

Coadministered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
Abacavir/ lamivudine	600/300 once daily	90 once daily	400 once daily	13	ledipasvir	1.10 (1.01, 1.19)	1.18 (1.10, 1.28)	1.26 (1.17, 1.36)
					sofosbuvir	1.08 (0.85, 1.35))	1.21 (1.01, 1.35)	NA
					GS-331007	1.00 (0.94, 1.07)	1.05 (1.01, 1.09)	1.08 (1.01, 1.14)
Atazanavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine	300/100 + 300/200 once daily simultaneously with HARVONI[b]	90 once daily	400 once daily	24	ledipasvir	1.68 (1.54, 1.84)	1.96 (1.74, 2.21)	2.18 (1.91, 2.50)
					sofosbuvir	1.01 (0.88, 1.15)	1.11 (1.02, 1.21)	NA
					GS-331007	1.17 (1.12, 1.23)	1.31 (1.25, 1.36)	1.42 (1.34, 1.49)
Atazanavir/ ritonavir	300/100 once daily	90 once daily	400 once daily	30	ledipasvir	1.98 (1.78, 2.20)	2.13 (1.89, 2.40)	2.36 (2.08, 2.67)
					sofosbuvir	0.96 (0.88, 1.05)	1.08 (1.02, 1.15)	NA
					GS-331007	1.13 (1.08, 1.19)	1.23 (1.18, 1.29)	1.28 (1.21, 1.36)
Cyclosporin	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	N/A
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir/ ritonavir	800/100 once daily	90 once daily	ND	23	ledipasvir	1.45 (1.34, 1.56)	1.39 (1.28. 1.49)	1.39 (1.29, 1.51)
		ND	400 once daily	18	sofosbuvir	1.45 (1.10. 1.92)	1.34 (1.12, 1.59)	NA
					GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Darunavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine/	800/100 + 300/200 once daily simultaneously with HARVONI[b]	90 once daily	400 once daily	24	ledipasvir	1.11 (0.99, 1.24)	1.12 (1.00, 1.25)	1.17 (1.04, 1.31)
					sofosbuvir	0.63 (0.52, 0.75)	0.73 (0.65, 0.82)	NA
					GS-331007	1.10 (1.04, 1.16)	1.20 (1.16, 1.24)	1.26 (1.20, 1.32)
Dolutegravir + tenofovir disproxil fumarate/ emtricitabine	50 + 300/200 once daily	90 once daily	400 once daily	29	ledipasvir	0.85 (0.81, 0.90)	0.89 (0.84, 0.95)	0.89 (0.84, 0.95)
					sofosbuvir	1.06 (0.92, 1.21)	1.09 (1.00, 1.19)	N/A
					GS-331007	0.99 (0.95, 1.03)	1.06 (1.03, 1.09)	1.06 (1.03, 1.10)
Tenofovir disoproxil fumarate/ emtricitabin/ efavirenz[c]	300/200/600 once daily	90 once daily	400 single dose	14	ledipasvir	0.66 (0.59, 0.75)	0.66 (0.59, 0.75)	0.66 (0.57, 0.76)
					sofosbuvir	1.03 (0.87, 1.23)	0.94 (0.81, 1.10)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00			
						C_{max}	AUC	C_{min}
					GS-331007	0.86 (0.76, 0.96)	0.90 (0.83. 0.97)	1.07 (1.02, 1.13)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	150/150/200/10 once daily	90 once daily	400 once daily	30	ledipasvir	1.65 (1.53, 1.78)	1.79 (1.64, 1.96)	1.93 (1.74, 2.15)
					sofosbuvir	1.28 (1.13, 1.47)	1.47 (1.35,1.59)	NA
					GS-331007	1.29 (1.24, 1.35)	1.48 (1.44, 1.53)	1.66 (1.60, 1.73)
Tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine[d]	300/200/ 25 once daily	90 once daily	400 once daily	15	ledipasvir	1.01 (0.95, 1.07)	1.08 (1.02, 1.15)	1.16 (1.08, 1.25)
					sofosbuvir	1.05 (0.93, 1.20)	1.10 (1.01, 1.21)	NA
					GS-331007	1.06 (1.01, 1.11)	1.15 (1.11, 1.19)	1.18 (1.13, 1.24)
Famotidine	40 single dose simultaneously with HARVONI	90 single dose	400 single dose	12	ledipasvir	0.80 (0.69, 0.93)	0.89 (0.76, 1.06)	NA
					sofosbuvir	1.15 (0.88, 1.50)	1.11 (1.00, 1.24)	NA
					GS-331007	1.06 (0.97, 1.14)	1.06 (1.02, 1.11)	NA
	40 single dose 12 hours prior to HARVONI			12	ledipasvir	0.83 (0.69, 1.00)	0.98 (0.80, 1.20)	NA
					sofosbuvir	1.00 (0.76, 1.32)	0.95 (0.82, 1.10)	NA
					GS-331007	1.13 (1.07, 1.20)	1.06 (1.01, 1.12)	NA
Methadone	30 to 130 daily	ND	400 once daily	14	sofosbuvir	0.95 (0.68, 1.33)	1.30 (1.00, 1.69)	NA
					GS-331007	0.73 (0.65, 0.83)	1.04 (0.89, 1.22)	NA
Omeprazole	20 once daily simultaneously with HARVONI	90 single dose	400 single dose	16	ledipasvir	0.89 (0.61, 1.30)	0.96 (0.66, 1.39)	NA
					sofosbuvir	1.12 (0.88, 1.42)	1.00 (0.80, 1.25)	NA
					GS-331007	1.14 (1.01, 1.29)	1.03 (0.96, 1.12)	NA
Raltegravir	400 twice daily	90 once daily	ND	28	ledipasvir	0.92 (0.85, 1.00)	0.91 (0.84, 1.00)	0.89 (0.81, 0.98)
		ND	400 single dose	19	sofosbuvir	0.87 (0.71, 1.08)	0.95 (0.82, 1.09)	NA
					GS-331007	1.09 (0.99, 1.19)	1.02 (0.97, 1.08)	NA
Rifampin[e]	600 once daily	90 single dose	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA
Simeprevir	150 once daily	30 once daily	ND	22	ledipasvir	1.81 (1.69, 1.94)	1.92 (1.77, 2.07)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
					GS-331007	0.97	1.00	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Ledipasvir, Sofosbuvir and GS-331007 PK With/Without Coadministered Drug No Effect=1.00		
					C_{max}	AUC	C_{min}
					(0.83, 1.14)	(0.87, 1.13)	

NA = not available/not applicable, ND = not dosed.

a. All interaction studies conducted in healthy volunteers

b. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) of atazanavir/ritonavir+ tenofovir disoproxil fumarate/emtricitabine or darunavir/ritonavir+ tenofovir disoproxil fumarate/emtricitabine and HARVONI provided similar results.

c. Administered as ATRIPLA.

d Administered as EVIPLERA.

e. This study was conducted in the presence of two other investigational HCV direct-acting agents.

Table 6 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir or HARVONI[a]

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
Abacavir /lamivudine	Abacavir 600 once daily	90 once daily	400once daily	15	0.92 (0.87, 0.97)	0.90 (0.85, 0.94)	NA
	Lamivudine 300 once daily				0.93 (0.87, 1.00)	0.94 (0.90, 0.98)	1.12 (1.05, 1.20)
Atazanavir/ ritonavir	Atazanavir 300/ once daily	90 once daily	400 once daily	30	1.07 (1.00, 1.15)	1.33 (1.25, 1.42)	1.75 (1.58, 1.93)
	Ritonavir 100 once daily				0.93 (0.84, 1.02)	1.05 (0.98, 1.11)	1.56 (1.42, 1.71)
Atazanavir/ ritonavir + tenofovir disoproxil fumarate emtricitabine simultaneously with HARVONI[b,c]	atazanavir 300 once daily	90 once daily	400 once daily	24	1.07 (0.99, 1.14)	1.27 (1.18, 1.37)	1.63 (1.45, 1.84)
	ritonavir 100 once daily				0.86 (0.79, 0.93)	0.97 (0.89, 1.05)	1.45 (1.27, 1.64)
	emtricitabine 200 once daily				0.98 (0.94, 1.02)	1.00 (0.97, 1.04)	1.04 (0.96, 1.12)
	tenofovir disoproxil fumarate 300 once daily				1.47 (1.37, 1.58)	1.35 (1.29, 1.42)	1.47 (1.38, 1.57)
Darunavir/ ritonavir + tenofovir disoproxil fumarate/ emtricitabine simultaneously with HARVONI[b,d]	ritonavir 100 once daily	90 once daily	400 once daily	23	1.17 (1.01, 1.35)	1.25 (1.15, 1.36)	1.48 (1.34, 1.63)
	Darunavir 800 once daily				1.01 (0.96, 1.06)	1.04 (0.99, 1.08)	1.08 (0.98, 1.20)
	Emtricitabine 200 once daily				1.02 (0.96, 1.08)	1.04 (1.00, 1.08)	1.03 (0.97, 1.10)
	tenofovir disoproxil fumarate 300 once daily				1.64 (1.54, 1.74)	1.50 (1.42, .59)	1.59 (1.49, 1.70)
Cyclosporin	600 single dose	ND	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Darunavir	800/100 once daily	90 once	ND	23	1.02	0.96	0.97

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
(boosted by ritonavir)		daily			(0.88, 1.19)	(0.84, 1.11)	(0.86, 1.10)
		ND	400 single dose	18	0.97 (0.94, 1.01)	0.97 (0.94, 1.00)	0.86 (0.78, 0.96)
Dolutegravir + tenofovir disoproxil fumarate/ emtricitabine[e]	dolutegravir 50 once daily	90 once daily	400 once daily	29	1.15 (1.07, 1.23)	1.13 (1.06, 1.20)	1.13 (1.06, 1.21)
	emtricitabine 200 once daily				1.02 (0.95, 1.08)	1.07 (1.04, 1.10)	1.05 (1.02, 1.09)
	Tenofovir disoproxil fumarate 300 once daily				1.61 (1.51, 1.72)	1.65 (1.59, 1.71)	2.15 (2.05, 2.26)
Tenofovir disoproxil fumarate/ emtricitabine/ efavirenz[e]	tenofovir disoproxil fumarate 300 once daily	90 once daily	400 once daily	15	1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)
	emtricitabine 200 once daily				1.08 (0.97, 1.21)	1.05 (0.98, 1.11)	1.04 (0.98, 1.11)
	efavirenz 600 once daily				0.87 (0.79, 0.97)	0.90 (0.84, 0.96)	0.91 (0.83, 0.99)
Tenofovir alafenamide/ elvitegravir/ cobicistat/ emtricitabine	tenofovir alafenamide 10 once daily	90 once daily	400 once daily	30	0.90 (0.73, 1.11)	0.86 (0.78, 0.95)	NA
	elvitegravir 150 once daily				0.98 (0.90, 1.07)	1.11 (1.02, 1.20)	1.46 (1.28, 1.66)
	cobicistat 150 once daily				1.23 (1.15, 1.32)	1.53 (1.45, 1.62)	3.25 (2.88, 3.67)
	emtricitabine 200 once daily				1.03 (0.96, 1.11)	0.97 (0.93, 1.00)	0.95 (0.91, 0.99)
Tenofovir disoproxil fumarate/ emtricitabine/ rilpivirine[f]	tenofovir disoproxil fumarate 300 once daily	90 once daily	400 once daily	14	1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)
	emtricitabine once 200 daily				1.02 (0.98, 1.06)	1.05 (1.02, 1.08)	1.06 (0.97, 1.15)
	rilpivirine 25 once daily				0.97 (0.88, 1.07)	1.02 (0.94, 1.11)	1.12 (1.03, 1.21)
R-Methadone	30 to 130 daily	ND	400 once daily	14	0.99 (0.85, 1.16)	1.01 (0.85, 1.21)	0.94 (0.77, 1.14)
S-Methadone					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)
Norelgestromin	Norgestimate 0.180/0.215/0.25/	90 once daily	ND	15	1.02 (0.89, 1.16)	1.03 (0.90, 1.18)	1.09 (0.91, 1.31)

Co-administered Drug	Dose of Coadministered Drug (mg)	LDV Dose (mg)	SOF Dose (mg)	N	Mean Ratio (90% CI) of Coadministered drug PK With/Without Ledipasvir, Sofosbuvir or HARVONI No Effect=1.00		
					C_{max}	AUC	C_{min}
		ND	400 once daily		1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel		90 once daily	ND		1.03 (0.87, 1.23)	0.99 (0.82, 1.20)	1.00 (0.81, 1.23)
		ND	400 once daily		1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol		90 once daily	ND		1.40 (1.18, 1.66)	1.20 (1.04, 1.39)	0.98 (0.79, 1.22)
		ND	400 once daily		1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	90 once daily	ND	28	0.82 (0.66, 1.02)	0.85 (0.70, 1.02)	1.15 (0.90, 1.46)
		ND	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Simeprevir	150 once daily	30 once daily	ND	28	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Tacrolimus	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Tenofovir disoproxil fumarate	300 once daily[e]	90 once daily	400 once daily	15	1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)
	300 once daily[f]			14	1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)

NA = not available/not applicable, ND = not dosed.

a. All interaction studies conducted in healthy volunteers.

b. Data generated from simultaneous dosing with HARVONI. Staggered administration (12 hours apart) of atazanavir/ritonavir+ tenofovir disoproxil fumarate/emtricitabine or darunavir/ritonavir+ tenofovir disoproxil fumarate/ emtricitabine and HARVONI provided similar results.

c. Administered as atazanavir/ritonavir+ tenofovir disoproxil fumarate/emtricitabine

d. Administered as darunavir/ritonavir+ tenofovir disoproxil fumarate/emtricitabine

e. Administered as ATRIPLA.

f. Administered as EVIPLERA.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B1

There are no adequate and well-controlled studies with HARVONI in pregnant women. Because animal reproduction studies are not always predictive of human response, HARVONI should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Pregnancy: Use with ribavirin (Pregnancy Category X)

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. When HARVONI is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for a period of time after the treatment has concluded as recommended in the prescribing information for ribavirin. Refer to ribavirin prescribing information for additional information. There are no data on the effectiveness of systemic hormonal contraceptives in women taking HARVONI. Therefore, two effective non-hormonal methods of contraception should be used during treatment with HARVONI and concomitant ribavirin.

Ledipasvir: No effects on foetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to ledipasvir was 5- and 2-fold, respectively, the exposure in humans at the recommended clinical dose

In a rat pre- and postnatal study, at a maternally toxic dose, the developing rat offspring exhibited mean decreased body weight and body weight gain when exposed *in utero* (via maternal dosing) and during lactation (via maternal milk) at a maternal exposure approximately 4 times the exposure in humans at the recommended clinical dose. There were no effects on survival, physical and behavioural development and reproductive performance in the offspring at maternal exposures similar to the exposure in humans at the recommended clinical dose.

Sofosbuvir: No effect on foetal development has been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 was approximately 6-fold and 16-fold the exposure in humans at the recommended clinical dose, respectively.

Breast-feeding

When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to excretion of ledipasvir via milk. Ledipasvir had no effects on the nursing pups. The predominant circulating metabolite of sofosbuvir (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups. It is not known whether ledipasvir, sofosbuvir or metabolites of sofosbuvir are present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with HARVONI, taking into account the importance of the therapy to the mother.

Fertility

Ledipasvir: Ledipasvir had no adverse effects on mating and fertility. In female rats, the mean number of corpora lutea and implantation sites were slightly reduced at maternal exposures 6-fold the exposure in humans at the recommended clinical dose. At the no observed effect level, AUC

exposure to ledipasvir was approximately 7- and 3-fold, in males and females, respectively, the human exposure at the recommended clinical dose.

Sofosbuvir: Sofosbuvir had no effects on embryo-foetal viability or on fertility when evaluated in rats. At the highest dose tested, AUC exposure to the predominant circulating metabolite GS 331007 was approximately 5-fold the exposure in humans at the recommended clinical dose.

4.7 Effects on ability to drive and use machines

No studies on the effects of HARVONI on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trials

4.8.1 Adults

The safety assessment of HARVONI in patients with genotype 1 CHC is based on pooled data from three Phase 3 clinical trials (ION-3, ION-1 and ION-2) including 215, 539 and 326 patients who received HARVONI for 8, 12 and 24 weeks, respectively; and 216, 328 and 328 patients who received HARVONI + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

The proportion of patients who permanently discontinued treatment due to adverse events was 0%, <1% and 1% for patients receiving HARVONI for 8, 12 and 24 weeks, respectively; and <1%, 0%, and 2% for patients receiving HARVONI + ribavirin combination therapy for 8, 12 and 24 weeks, respectively.

No adverse drug reactions specific to HARVONI have been identified. In clinical trials, ION-1, ION-2, and ION-3, fatigue, headache and nausea were the most common (incidence ≥ 10%) treatment emergent adverse events reported in patients treated with 8 or 12 weeks of HARVONI which are the recommended regimens for patients (see section 4.2). The type of treatment emergent adverse events observed during 24 weeks of treatment with HARVONI was consistent with those observed during 8 or 12 weeks of treatment but the frequency of adverse events is generally higher in the 24 week treatment group than the 8 or 12 week treatment groups. When HARVONI was studied with ribavirin, the most frequent adverse drug reactions to HARVONI + ribavirin combination therapy were consistent with the known safety profile of ribavirin, without increasing the frequency or severity of the expected adverse drug reactions.

The safety of HARVONI with or without ribavirin in treatment-experienced genotype-1 patients with compensated cirrhosis was compared to placebo in Study SIRIUS. Patients were randomised to receive 24 weeks of HARVONI without ribavirin or 12 weeks of placebo followed by 12 weeks of HARVONI+ribavirin. Table 7 presents the adverse reactions, as defined above, that were reported more frequently (≥5%) in patients during the first 12 weeks of treatment in the HARVONI 24 week treatment group or in patients treated with 12 weeks of HARVONI + ribavirin, compared with those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 7 were Grade 1 or 2 in severity.

Table 7 Adverse Reactions Reported ≥5% More Frequent in Treatment-Experienced Patients with Cirrhosis Receiving HARVONI for the First 12 Weeks in the HARVONI 24 Week Treatment Arm or HARVONI+RBV for 12 Weeks Than Placebo for 12 weeks

	HARVONI (first 12 weeks of 24 week treatment) (N=78)	HARVONI+RBV 12 weeks (N=76)	Placebo 12 weeks (N=77)
Fatigue[a]	41%	38%	25%
Headache	27%	13%	16%
Cough	4%	11%	1%
Irritability	8%	7%	1%
Dyspnea	1%	9%	1%

a. Includes preferred terms fatigue and asthenia.

No adverse drug reactions specific to HARVONI were identified from the clinical trials conducted in patients with genotype 2, 3, 4, 5 or 6 CHC.

HCV/HIV-1 Coinfection

No adverse drug reactions specific to HARVONI were identified from an open-label trial (ION-4) in which patients with HCV/HIV-1 coinfection received treatment with HARVONI for 12 weeks (N=335).

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

No adverse drug reactions specific to HARVONI were identified from two open-label trials (SOLAR-1 and SOLAR-2) in which liver transplant recipients and/or patients with decompensated cirrhosis received HARVONI with ribavirin for 12 or 24 weeks (N=670). The adverse events observed were consistent with expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known toxicity profile of ribavirin.

Decreases in haemoglobin to less than 10 mg/dL and 8.5 mg/dL during treatment were experienced by 39% and 13% of patients treated with HARVONI+ribavirin, respectively. Ribavirin was discontinued in 15% of the subjects.

Due to improved organ function, 7% of liver transplant recipients had a dose modification of their immunosuppressive agents.

4.8.2 Pediatrics

The safety assessment of HARVONI in pediatric patients 12 years of age or older is based on data from a Phase 2, open-label clinical trial (Study 1116) that enrolled 100 patients who were treated with HARVONI for 12 weeks. The adverse reactions observed were consistent with those observed in clinical studies of HARVONI in adults (see Section 4.8.1).

POST MARKETING SURVEILANCE

In addition to adverse reactions from clinical studies, the following possible adverse reactions were also identified during postapproval use of HARVONI. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders

Symptomatic bradycardia (when amiodarone is coadministered with HARVONI) (Seesection 4.4**)**

Hepatobiliary Disorders

Hepatitis B Reactivation (See section 4.4)

Skin and Subcutaneous Tissue Disorders

Angioedema, rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdosage

The highest documented doses of ledipasvir and sofosbuvir were 120 mg twice daily for 10 days and a single dose of 1200 mg, respectively. In these healthy volunteer studies, there were no untoward effects observed at these dose levels, and adverse events were similar in frequency and severity to those reported in the placebo groups. The effects of higher doses/exposures are not known.

No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with HARVONI consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Haemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Haemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%.

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use; direct acting antivirals, other antivirals, ATC code: J05AX65.

Mechanism of action

Ledipasvir is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition of ledipasvir is not currently possible as NS5A has no enzymatic function. *In vitro* resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir is a pangenotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated by HCV NS5B and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with an IC_{50} value ranging from 0.7 to 2.6 µM. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

Antiviral activity *in vitro*

In HCV replicon assays, the EC_{50} values of ledipasvir against full-length replicons from genotype 1a and 1b were 0.031 nM and 0.004 nM, respectively. The median EC_{50} of ledipasvir against chimeric replicons encoding NS5A sequences from clinical isolates was 0.018 nM for genotype 1a (range 0.009-0.085 nM; N=30) and 0.006 nM for genotype 1b (range 0.004-0.007 µM; N=3). In addition, ledipasvir has various levels of antiviral activity against genotype 2 to 6 replicons, with EC_{50} values ranging from 0.15 to 530 nM. The presence of 40% human serum reduced anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicon.

In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 µM. The mean ± SD EC_{50} of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.068 ± 0.024 µM for genotype 1a (N=67), 0.11 ± 0.029 µM for genotype 1b (N=29), 0.035 ± 0.018 µM for genotype 2 (N=15) and 0.085 ± 0.034 µM for genotype 3a (N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 µM, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Evaluation of sofosbuvir in combination with ledipasvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Drug Resistance

In Cell Culture:

HCV replicons with reduced susceptibility to ledipasvir have been selected in cell culture for genotype 1a and 1b. Reduced susceptibility to ledipasvir was associated with the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally a Q30E substitution emerged in genotype 1a replicons. Site-directed mutagenesis of the Y93H in both genotype 1a and 1b as well as the Q30E substitution in genotype 1a conferred high levels of reduced susceptibility to ledipasvir (fold change in EC_{50} greater than 500-fold).

HCV replicons with reduced susceptibility to sofosbuvir have been selected in cell culture for multiple genotypes including 1b, 2a, 2b, 3a, 4a, 5a and 6a. Reduced susceptibility to sofosbuvir was associated with the primary NS5B substitution S282T in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes including 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication capacity by 89% to 99% compared to the corresponding wild-type. In biochemical assays, recombinant NS5B polymerase from genotypes 1b, 2a, 3a and 4a expressing the S282T substitution showed reduced susceptibility to GS-461203 compared to respective wild-types.

In Clinical Studies:

Adults

Genotype 1

In a pooled analysis of patients who received HARVONI in Phase 3 trials (ION-3, ION-1 and ION-2), 37 patients (29 with genotype 1a and 8 with genotype 1b) qualified for resistance analysis due to virologic failure or early study drug discontinuation and having HCV RNA > 1000 IU/ml. Post-baseline NS5A and NS5B deep sequencing data (assay cutoff of 1%) were available for 37/37 and 36/37 patients, respectively.

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients not achieving SVR. Of the 29 genotype 1a patients who qualified for resistance testing, 22/29 (76%) patients harbored one or more NS5A RAVs at positions K24, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R, Y93H, L31M, Y93N and Q30H. Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harbored one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H. Among the 8 patients who had no NS5A RAVs at failure, 7 patients received 8 weeks of treatment (N=3 with HARVONI; N=4 with HARVONI + ribavirin) and 1 patient received HARVONI for 12 weeks. In phenotypic analyses, post-baseline isolates from patients who harbored NS5A RAVs at failure showed 20- to >243-fold reduced susceptibility to ledipasvir.

Among post-transplant patients with compensated liver disease or patients with decompensated liver disease (pre- and post-transplant) (SOLAR-1 and SOLAR-2 trials), relapse was associated with the detection of one or more of the following NS5A RAVs: K24R, M28T, Q30R/H/K, L31V, H58D and Y93H/C in 12/14 genotype 1a patients, and L31M, Y93H/N in 6/6 genotype 1b patients.

The NS5B nucleoside inhibitor resistance associated variants (NS5B NI RAVs) L159F and V321A were each detected in one patient with genotype 1a infection in the Phase 3 trials (ION-1, ION-2, ION-3). The single L159F and V321A variants demonstrated 1.2- and 1.2-fold change in EC50 to sofosbuvir in genotype 1a replicon, respectively. A NS5B substitution E237G at a conserved position was detected in 3 patients (1 genotype 1b and 2 genotype 1a) in the Phase 3 trials (ION-3, ION-1 and ION-2) and 3 patients (all genotype 1a) in the phase 2 trials of patients with advanced liver disease (SOLAR-1 and SOLAR-2) at the time of relapse. The E237G substitution showed a 1.3-fold reduction in susceptibility to sofosbuvir in the genotype 1a replicon assay. The clinical significance of these substitutions is currently unknown.

The NS5B NI RAV S282T in NS5B was not detected in any failure isolate from ION-1, ION-2, ION-3, SOLAR-1 or SOLAR-2 trials. However, the NS5B S282T substitution in combination with NS5A RAVs L31M, Y93H and Q30L were detected in one patient at failure following 8 week treatment with HARVONI from the Phase 2 trial LONESTAR. This patient was subsequently retreated with HARVONI + ribavirin for 24 weeks and achieved SVR following retreatment.

Genotype 2, 3, 4, 5, and 6

Resistance analysis was performed for virologic failures in clinical trials with genotype 2, 3, 4, 5 and 6 CHC. Patients in these trials were treated with HARVONI or HARVONI+RBV for 12 weeks (see section 5.1).

Genotype 2: None of the genotype 2 patients experienced virologic failure in the LEPTON study.

Genotype 3: Of the 17 patients who experienced virologic failures in the ELECTRON-2 study, one patient developed the NS5A RAV Y93C (1.1%), one patient developed the NS5B NI RAV S282T and one patient developed the NS5B NI RAV L159F.

Genotype 4: Of the 3 patients who experienced virologic failure in Study 1119, one patient developed the NS5B NI RAV S282T along with the NS5A RAV Y93C. In SOLAR-2 trial, one patient with genotype 4d developed NS5B substitution E237G at the time of relapse. The clinical significance of this substitution is currently unknown.

Genotype 5: NS5A sequencing was successful in 1 of 2 virologic failure patients in Study 1119. This patient developed NS5B NI RAVs S282T (1.6%) and M289I (16%).

Genotype 6: Virologic failure occurred in one patient in the ELECTRON-2 study who discontinued treatment early at approximately Week 8 and subsequently relapsed in Study ELECTRON-2. This patient developed NS5B NI RAV S282T.

Effect of Baseline HCV Polymorphisms on Treatment Outcome

Adults

Genotype 1

Analyses were conducted to explore the association between pre-existing baseline NS5A resistance-associated variants (RAVs) and treatment outcome. In the pooled analysis of the Phase 3 trials (ION-1, ION-2 and ION-3), 256/1618 (16%) patients had baseline NS5A RAVs identified by population or deep sequencing irrespective of subtype.

In treatment-naïve patients in ION-3 with NS5A RAVs, SVR12 rates of 89% (34/38) after 8 weeks and 96% (66/69) after 12 weeks of therapy were observed with HARVONI. No association between any individual NS5A RAV or group of RAVs and treatment outcome was observed.

In treatment-experienced patients in ION-2 who had baseline NS5A RAVs, an SVR12 rate of 76% (13/17) after 12 weeks of therapy was observed with HARVONI. No association between any individual NS5A RAV and treatment outcome was observed. When NS5A RAVs were grouped by their EC_{50} fold change from wild-type, among those treatment-experienced patients with any NS5A RAV conferring <100-fold resistance *in vitro*, 4/4 (100%) patients achieved SVR following 12 weeks of treatment with HARVONI. Among those treatment experienced patients with any NS5A RAV conferring ≥100-fold resistance, 9/13 (69%) patients achieved SVR following 12 weeks of treatment with HARVONI. The group of NS5A RAVs that conferred >100-fold shift were defined as any of the following substitutions in genotype 1a (M28A/G, Q30E/G/H/K/R, L31I/M/V, P32L, H58D, Y93C/H/N/S) or in genotype 1b (P58D, A92K, Y93H). In another study in treatment-experienced patients with compensated cirrhosis (SIRIUS, N=77), 8/8 (100%) patients with baseline NS5A RAVs conferring >100-fold reduced susceptibility to ledipasvir achieved SVR following 12 weeks of treatment with HARVONI+ribavirin.

Among post-transplant patients with compensated liver disease (SOLAR-1 and SOLAR-2 studies), no relapse occurred in patients with baseline NS5A RAVs (N=23) following 12 weeks of treatment with HARVONI+ribavirin. Among patients with decompensated liver disease (pre- and post-transplant), 4/16 (25%) patients with NS5A RAVs conferring >100-fold resistance relapsed after 12 weeks treatment with HARVONI+RBV compared to 7/120 (6%) in those without any baseline NS5A RAVs or RAVs conferring a fold-change of ≤100.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials (ION-1, ION-2, ION-3) by population or deep sequencing. SVR was achieved in all 24 patients (N=21 with L159F and N=3 with N142T) who had baseline NS5B NI RAVs.

Genotype 2, 3, 4, 5 and 6

Baseline NS5A RAVs did not have a clinically meaningful effect on treatment outcome in clinical studies of patients with genotype 2, 4, 5 or 6 CHC. For patients with genotype 3 CHC, the role of baseline NS5A RAVs varied depending on the patient population.

For patients with genotype 2, 4, 5 and 6 CHC, SVR was achieved in 14/14 (100%), 25/28 (89%), 7/8 (88%) and 17/18 (94%) patients who had baseline NS5A RAVs following 12 weeks treatment with HARVONI, respectively. The specific baseline NS5A RAVs observed in patients with virologic failure were L28M/V and L30R for genotype 4, L31M for genotype 5 and F28V for genotype 6.

Among treatment-naïve patients with genotype 3 CHC who were treated with HARVONI+RBV for 12 weeks, SVR was achieved in 4/4 (100%) patients with baseline NS5A RAVs. Among treatment-experienced patients with genotype 3 CHC, SVR was achieved in 4/6 (67%) and 37/44 (84%) patients with or without baseline NS5A RAVs, respectively. The specific baseline NS5A RAVs observed in patients with virologic failure were S24G, A30K, L31M and Y93H.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient with genotype 2, 3, 4, 5 or 6 CHC in clinical trials by population or deep sequencing. For patients

with genotype 2, 3 and 5 CHC, SVR was achieved in all 14 patients who had baseline NS5B NI RAVs (N=4 with M289I in genotype 2; N=1 with N142T in genotype 3; N=7 with N142T and N=2 with M289I in genotype 5).

Relapse occurred in 2/3 genotype 4 patients who had the baseline NS5B NI RAV V321I along with two baseline NS5A RAVs.

In patients with genotype 6 CHC, SVR was achieved in one patient each with the baseline NS5B NI RAVs M289L+S282G or M289L+V321A and 13/14 patients with M289L/I.

Pediatrics

The presence of NS5A and NS5B RAVs did not impact treatment outcome; all patients with baseline NS5A or NS5B NI RAVs achieved SVR following 12 weeks treatment with HARVONI

Cross-resistance:

Ledipasvir was fully active against the sofosbuvir-associated resistance substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Both sofosbuvir and ledipasvir were fully active against substitutions associated with resistance to other classes of direct acting antivirals with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors.

Clinical Data

Overview of Clinical Studies

Adults

Genotype 1 CHC

The efficacy of HARVONI was evaluated in 2105 patients with genotype 1 CHC in four trials including one trial conducted in noncirrhotic treatment-naïve patients (ION-3), one trial in cirrhotic and noncirrhotic treatment-naïve patients (ION-1), and one trial in cirrhotic and noncirrhotic patients who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor (ION-2) and one trial in patients with cirrhosis who failed prior therapy with a Peg-IFN+ribavirin regimen followed by a Peg-IFN+ribavirin+HCV protease inhibitor regimen (SIRIUS). Patients in these trials had compensated liver disease. All four trials evaluated efficacy of HARVONI with or without ribavirin.

Genotype 2, 3, 4, 5 or 6

The efficacy of HARVONI in patients with genotype 2, 3 ,4, 5 and 6 CHC was evaluated in the following clinical trials:

- Genotype 2 (LEPTON): treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=26)
- Genotype 3 (ELECTRON-2): treatment-naïve and treatment-experienced patients with or without cirrhosis (N=101)
- Genotype 4:

    - Study 1119: treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=44)
    - ION-4: HCV/HIV-1 coinfected patients, with or without cirrhosis (N=8)
- Genotype 5 (Study 1119): treatment-naive and treatment-experienced patients, with or without cirrhosis (N=25)
- Genotype 6 (ELECTRON-2): treatment-naïve and treatment-experienced patients, with or without cirrhosis (N=25)

For patients with genotype 2, 4, 5, or 6 CHC, HARVONI was administered for 12 weeks without ribavirin. For patients–with genotype 3 CHC, HARVONI with or without ribavirin was administered for 12 weeks in treatment-naive patients and HARVONI with ribavirin was administered for 12 weeks in treatment-experienced patients.

HCV/HIV-1 Coinfection

The efficacy of HARVONI in HCV/HIV-1 coinfected patients was evaluated in an open-label Phase 3 trial (ION-4) that enrolled 335 patients with genotype 1 or 4 CHC, with or without cirrhosis, coinfected with HIV-1. All patients in the trial were treated with HARVONI for 12 weeks.

Patients Who Failed Prior Treatment with SOVALDI and Ribavirin, with or without Interferon

The efficacy of HARVONI in genotype 1 CHC patients who failed prior treatment with regimens containing SOVALDI was evaluated in two clinical trials. In Study 1118, patients who had previously failed SOVALDI+RBV±Peg-IFN, with or without cirrhosis, were treated with HARVONI+RBV for 12 weeks (N=45). In Study ION-4, 13 patients who had failed SOVALDI+RBV were treated with HARVONI without ribavirin for 12 weeks.

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

The efficacy of HARVONI in liver transplant recipients and/or patients with decompensated cirrhosis was evaluated in two open-label Phase 2 trials (SOLAR-1 and SOLAR-2) that enrolled 670 patients with genotype 1 and 4 CHC post-liver transplant and/or with decompensated cirrhosis. Patients in the two trials were treated with HARVONI+RBV for 12 or 24 weeks.

Serum HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System in ION-3, ION-1, ION-2, SIRIUS and ION-4 studies or the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) in ELECTRON-2, LEPTON, SOLAR-1, SOLAR-2, Study 1118 and 1119. The COBAS Taqman HCV test (version 2.0) for use with the High Pure System has a lower limit of quantification (LLOQ) of 25 IU per mL and the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) has a LLOQ of 15 IU per mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than LLOQ at 12 weeks after the cessation of treatment.

Clinical Trials in Patients with Genotype 1 CHC

Treatment-Naïve Patients– ION-3 (Study 0108)

ION-3 was a randomised, open-label trial that evaluated 8 weeks of treatment with HARVONI with or without ribavirin and 12 weeks of treatment with HARVONI in treatment naïve non-

cirrhotic patients with genotype 1 CHC. Patients were randomised in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a vs 1b).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 647 treated patients, the median age was 55 years (range: 20 to 75); 58% of the patients were male; 78% were White, 19% were Black; 6% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 18 to 56 kg/m^2); 81% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 80% had genotype 1a HCV infection; 73% had non-CC IL28B alleles (CT or TT).

Table 8 presents the response rates for the treatment groups in the ION-3 trial.

Table 8 Response Rates in Study ION-3

	HARVONI 8 weeks (N=215)	**HARVONI+RBV 8 weeks (N=216)**	**HARVONI 12 weeks (N=216)**
Overall SVR	94% (202/215)	93% (201/216)	96% (208/216)
Outcome for patients without SVR			
On-treatment virologic failure	0/215	0/216	0/216
Relapse[a]	5% (11/215)	4% (9/214)	1% (3/216)
Other[b]	<1% (2/215)	3% (6/216)	2% (5/216)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up)

The 8-week treatment of HARVONI without ribavirin was noninferior to the 8-week treatment of HARVONI with ribavirin (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%) and the 12-week treatment of HARVONI (treatment difference -2.3%; 97.5% confidence interval: -7.2% to 2.5%). Among patients with a baseline HCV RNA < 6 million IU/mL, the SVR was 97% (119/123) with 8-week treatment of HARVONI and 96% (126/131) with 12-week treatment of HARVONI.

Response rates for selected subgroups are presented in Table 9.

Table 9 SVR Rates for Selected Subgroups in ION-3

	HARVONI 8 Weeks (N = 215)	**HARVONI+RBV 8 Weeks (N = 216)**	**HARVONI 12 Weeks (N = 216)**
Genotype			
Genotype 1a	93% (159/171)	92% (159/172)	96% (165/172)
Genotype 1b	98% (42/43)	95% (42/44)	98% (43/44)

Relapse rates by baseline viral load are presented in Table 10.

Table 10 Relapse rates by baseline viral load in study ION-3

	HARVONI 8 weeks (n = 215)	HARVONI+RBV 8 weeks (n = 216)	HARVONI 12 weeks (n = 216)
Number of responders at end of treatment	215	216	216
Baseline HCV RNA[a]			
HCV RNA < 6 million IU/mL	2% (2/123)	2% (3/137)	2% (2/131)
HCV RNA ≥ 6 million IU/mL	10% (9/92)	8% (6/77)	1% (1/85)

a. HCV RNA values were determined using the Roche TaqMan Assay; a patient's HCV RNA may vary from visit to visit.

Treatment-Naïve Adults with or without Compensated Cirrhosis ─ ION-1 (Study 0102)

ION-1 is an ongoing randomised, open-label trial to evaluate 12 and 24 weeks of treatment with HARVONI with or without ribavirin in 865 treatment naïve patients with genotype 1 CHC including those with cirrhosis. Patients were randomised in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks or HARVONI + ribavirin for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis and HCV genotype (1a vs 1b). The interim primary endpoint analysis for SVR only included all patients enrolled in the 12-week treatment groups (N = 431). SVR rates for all patients enrolled in the 24 week treatment groups (N= 434) were not available at the time of interim analysis.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 865 treated patients, the median age was 54 years (range: 18 to 80); 59% of the patients were male; 85% were White, 12% were Black; 12% were Hispanic or Latino; mean body mass index was 27 kg/m^2 (range: 18 to 48 kg/m^2); 79% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 67% had genotype 1a HCV infection; 70% had non-CC IL28B alleles (CT or TT) and 16% had cirrhosis.

Table 11 presents the response rates for the treatment groups of HARVONI with or without ribavirin for 12 weeks in the ION-1 trial.

Table 11 Response Rates in Study ION-1

	HARVONI 12 Weeks (N = 214)	HARVONI+RBV 12 Weeks (N = 217)
SVR[a]	99% (210/213)	97% (211/217)
Outcome for subjects without SVR		
On-Treatment Virologic Failure	0/213	0/217
Relapse[b]	<1% (1/212)	0/217
Other[c]	<1% (2/213)	3% (6/217)

a. Excluding one patient with genotype 4 infection

b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response groups for selected subgroups are presented in Table 12.

Table 12 SVR Rates for Selected Subgroups in Study ION-1

	HARVONI 12 Weeks (N = 214)	**HARVONI+RBV 12 Weeks (N = 217)**
Genotype		
Genotype 1a	98% (142/145)	97% (143/148)
Genotype 1b	100% (67/67)	99% (67/68)
Cirrhosis[a]		
No	99% (176/177)	97% (177/183)
Yes	94% (32/34)	100% (33/33)

a Patients with missing cirrhosis status were excluded from this subgroup analysis.

Previously-Treated Adults with or without Compensated Cirrhosis – ION-2 (Study 0109)

ION-2 was a randomised, open-label trial that evaluated 12 and 24 weeks of treatment with HARVONI with or without ribavirin in genotype 1 HCV-infected patients with or without cirrhosis who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor. Patients were randomised in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + ribavirin for 12 weeks, HARVONI for 24 weeks or HARVONI + ribavirin for 24 weeks. Randomisation was stratified by the presence or absence of cirrhosis, HCV genotype (1a vs 1b) and response to prior HCV therapy (relapse/breakthrough vs nonresponse).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 440 treated patients, the median age was 57 years (range: 24 to 75); 65% of the patients were male; 81% were White, 18% were Black; 9% were Hispanic or Latino; mean body mass index was 28 kg/m^2 (range: 19 to 50 kg/m^2); 89% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 79% had genotype 1a HCV infection; 88% had non-C/C IL28B alleles (CT or TT) and 20% had cirrhosis. Forty-seven percent (47%) of the patients failed a prior therapy of pegylated interferon and ribavirin. Among these patients, 49% were relapse/breakthrough and 51% were non-responder. Fifty-three percent (53%) of the patients failed a prior therapy of pegylated interferon and ribavirin with an HCV protease inhibitor. Among these patients, 62% were relapse/breakthrough and 38% were non-responder.

Table 13 presents the response rates for the treatment groups in the ION-2 trial.

Table 13 Response Rates in Study ION-2

	HARVONI 12 Weeks (N=109)	HARVONI+RBV 12 Weeks (N=111)	HARVONI 24 Weeks (N=109)	HARVONI+RBV 24 Weeks (N=111)
SVR	94% (102/109)	96% (107/111)	99% (108/109)	99% (110/111)
Outcome for subjects without SVR				
On-Treatment Virologic Failure	0/109	0/111	0/109	<1% (1/111)
Relapse[a]	6% (7/108)	4% (4/111)	0/109	0/110
Other[b]	0/109	0/111	<1% (1/109)	0/111

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Response rates for selected subgroups are presented in Table 14.

Table 14 SVR Rates for Selected Subgroups in Study ION-2

	HARVONI 12 Weeks (N=109)	HARVONI +RBV 12 Weeks (N=111)	HARVONI 24 Weeks (N=109)	HARVONI +RBV 24 Weeks (N=111)
Genotype				
Genotype 1a	95% (82/86)	95% (84/88)	99% (84/85)	99% (87/88)
Genotype 1b	87% (20/23)	100% (23/23)	100% (24/24)	100% (23/23)
Cirrhosis[a]				
No	95% (83/87)	100% (88/88)	99% (85/86)	99% (88/89)
Yes	86% (19/22)	82% (18/22)	100% (22/22)	100% (22/22)
Response to prior HCV Therapy				
Relapse/Breakthrough	95% (57/60)	97% (63/65)	100% (60/60)	98% (59/60)
Nonresponder	92% (45/49)	96% (44/46)	98% (48/49)	100% (51/51)

[a] Patients with missing cirrhosis status were excluded from this subgroup analysis.

Across the treatment groups, SVR rates of greater than 90% were observed in patients previously treated HCV protease inhibitors with pegylated interferon and ribavirin; and were similar to that observed in patients previously treated with pegylated interferon and ribavirin.

Previously-Treated Adults with Compensated Cirrhosis ─ SIRIUS (Study 0121)

SIRIUS was a randomised, double-blind and placebo-controlled trial that evaluated the efficacy of HARVONI + ribavirin for 12 weeks or HARVONI without ribavirin for 24 weeks in genotype 1 HCV-infected patients with compensated cirrhosis who failed prior therapy with a Peg-IFN + RBV regimen followed by a subsequent Peg-IFN +RBV + an HCV protease inhibitor regimen. Patients were randomised in a 1:1 ratio to receive placebo for 12 weeks followed by HARVONI + ribavirin for 12 weeks or HARVONI for 24 weeks. Randomisation was stratified by HCV genotype (1a vs 1b) and response to prior HCV therapy (never achieved HCV RNA less than LLOQ vs achieved HCV RNA less than LLOQ).

Demographics and baseline characteristics were balanced across the treatment groups. Of the 155 randomised patients, the median age was 56 years (range: 23 to 77); 74% of the patients were male; 97% were White; mean body mass index was 27 kg/m^2 (range: 19 to 47 kg/m^2); 63% had

genotype 1a HCV infection; 94% had non-C/C IL28B alleles (CT or TT). All patients (with the exception of 1) met the protocol defined definition of cirrhosis as defined by biopsy, transient elastography (>12.5 kPa) or FibroTest score >0.75 and an AST:platelet ratio index (APRI) >2. One patient discontinued therapy while on placebo, and was not included in the efficacy analysis.

The SVR rate was 96% (74/77) and 97% (75/77) in patients treated with HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks without ribavirin, respectively. All 5 patients who did not achieve SVR12 relapsed.

Clinical Trials in Patients with Genotype 2, 3 ,4, 5, or 6 CHC

Genotype 2

In the open-label Study LEPTON, HARVONI was administered for 12 weeks to 26 treatment-naive or treatment-experienced patients with genotype 2 HCV infection, with or without compensated cirrhosis. The SVR was 96% (25/26). The patient who did not achieve SVR12 withdrew consent and discontinued from the study after receiving a single dose of HARVONI.

Genotype 3

In the open-label Study ELECTRON-2, HARVONI was administered with or without ribavirin to 51 treatment-naive patients and 50 treatment-experienced patients with genotype 3 HCV infection, with or without compensated cirrhosis. Treatment-naive patients were treated with HARVONI (N=25) or HARVONI + RBV (N=26) for 12 weeks. All treatment-experienced patients were treated with HARVONI + RBV for 12 weeks. The SVR rates in treatment-naive patients were 64% (16/25) and 100% (26/26) for the HARVONI and HARVONI + ribavirin treatment groups, respectively. The SVR rate in treatment-experienced patients was 82% (41/50) with 8 patients relapsed and one patient experienced on-treatment virologic failure.

Genotype 4

In two open-label studies (Study 1119 and ION-4), HARVONI was administered for 12 weeks to treatment-naïve or treatment-experienced patients with genotype 4 CHC, with or without compensated cirrhosis. Study 1119 enrolled 44 treatment-naïve or treatment-experienced patients with genotype 4 CHC, with or without compensated cirrhosis. Study ION-4 enrolled 8 treatment-naïve or treatment-experienced patients with genotype 4 CHC who are coinfected with HIV-1, none of whom had cirrhosis.

In Study 1119, the SVR was 93% (95% [21/22] in treatment-naïve patients and 91% [20/22] in treatment-experienced patients); All 3 patients who failed to achieve SVR relapsed; SVR was 100% in the 10 patients with cirrhosis. In Study ION-4, 100% (8/8) patients achieved SVR12.

Genotype 5

In the open-label Study 1119, HARVONI was administered for 12 weeks to 41 treatment-naive or treatment-experienced patients with genotype 5 HCV infection, with or without compensated cirrhosis. The SVR was 93% (90% [19/21] in treatment-naïve patients and 95% [19/20] in treatment-experienced patients); of the 3 patients who failed to achieve SVR, 2 patients relapsed and one patient was lost to follow-up. The SVR was 89% (8/9) in patients with cirrhosis.

Genotype 6

In the open-label Study ELECTRON-2, HARVONI was administered for 12 weeks to 25 treatment-naive or treatment-experienced patients with genotype 6 HCV infection, with or without compensated cirrhosis. The SVR rate was 96% (24/25). Two patients had cirrhosis and both achieved SVR. The single patient who relapsed discontinued study treatment early (at approximately Week 8 of 12).

HCV/HIV co-infected patients

ERADICATE

ERADICATE was an open-label study to evaluate 12 weeks of treatment with HARVONI in 50 patients with genotype 1 CHC co-infected with HIV. All patients were treatment naïve to HCV therapy with or without cirrhosis, 26% (13/50) of patients were HIV antiretroviral naïve and 74% (37/50) of patients were receiving concomitant HIV antiretroviral therapy. At the time of the interim analysis, 98% (49/50) patients achieved SVR4. Among the patients who have reached 12 weeks post treatment (n=40), SVR12 was 98% (39/40).

ION-4

ION-4 was an open-label clinical trial that evaluated the safety and efficacy of 12 weeks of treatment with HARVONI without ribavirin in HCV treatment-naïve and treatment-experienced patients with genotype 1 or 4 CHC who were coinfected with HIV-1. Treatment-experienced patients had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + an HCV protease inhibitor or SOVALDI + RBV ± Peg-IFN. Patients were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir, administered with efavirenz, rilpivirine or raltegravir.

Of the 335 treated patients, the median age was 52 years (range: 26 to 72); 82% of the patients were male; 61% were White; 34% were Black; mean body mass index was 27 kg/m^2 (range: 18 to 66 kg/m^2); 75% had genotype 1a HCV infection; 2% had genotype 4 infection; 76% had non-C/C IL28B alleles (CT or TT); and 20% had compensated cirrhosis. Fifty-five percent (55%) of the patients were treatment-experienced.

Table 15 presents the response rates in the ION-4 trial after 12 weeks of HARVONI treatment.

Table 15 Study ION-4: Response Rates after 12 Weeks of Treatment in Patients with Genotype 1 or 4 CHC with or without Cirrhosis Who Are Coinfected with HIV-1

	HARVONI 12 Weeks (N=335)
SVR	96% (321/335)[a]
Outcome for Patients without SVR	
On-Treatment Virologic Failure	<1% (2/335)
Relapse[ab]	3% (10/333)
Other[bc]	<1% (2/335)

a. 8 subjects with genotype 4 HCV infection were enrolled

b The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.

c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

SVR rates were 94% (63/67) in patients with cirrhosis and 98% (46/47) in patients who were previously-treated and had cirrhosis.

No patient had HIV-1 rebound during the study and no clinically meaningful changes in CD4+ cell count from baseline were observed.

Clinical Trials in SOVALDI+RBV±Peg-IFN Treatment Failures

The efficacy of HARVONI in patients who had previously failed treatment with SOVALDI+RBV±Peg-IFN is supported by two clinical trials. In Study 1118, 44 patients with genotype 1 infection who had previously failed a SOVALDI+Peg-IFN+RBV or a SOVALDI+RBV regimen were treated with HARVONI + RBV for 12 weeks; the SVR was 100% (44/44). In Study ION-4, 13 HCV/HIV-1 coinfected patients with genotype 1 HCV infection who had failed a SOVALDI+RBV regimen were enrolled; the SVR was 100% (13/13) after 12 weeks of treatment with HARVONI without ribavirin.

Clinical Trials in Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

SOLAR-1 and SOLAR-2 were two open-label clinical trials that evaluated 12 and 24 weeks of treatment with HARVONI in combination with ribavirin in genotype 1 and 4 HCV-infected patients who have undergone liver transplantation and/or who have decompensated liver disease. The two trials were identical in study design. Patients were enrolled in one of the seven groups based on liver transplantation status and severity of hepatic impairment (see Table 11). Patients with a CPT score >12 were excluded. Within each group, patients were randomised in a 1:1 ratio to receive HARVONI + RBV for 12 weeks or HARVONI + RBV for 24 weeks.

Demographics and baseline characteristics were balanced across the treatment groups. Of the 670 treated patients, the median age was 59 years (range: 21 to 81); 77% of the patients were male; 91% were White; mean body mass index was 28 kg/m^2 (range: 18 to 49 kg/m^2); 94% and 6% had genotype 1 and 4 HCV infection, respectively; 78% of the patients failed a prior HCV therapy. Among the patients who had decompensated cirrhosis (pre- or post-transplant), 64% and 36% were CPT class B and C at screening, respectively, and 24% had a baseline Model for End Stage Liver Disease (MELD) score greater than 15.97.

Table 16 presents the pooled response rates of SOLAR-1 and SOLAR-2 in patients with genotype 1 CHC.

Table 16 Pooled Response Rates in Study SOLAR-1 and SOLAR-2 in Patients with Genotype 1 CHC

	HARVONI+RBV 12 Weeks (N = 307)[a,b]	HARVONI+RBV 24 Weeks (N = 307)[a,b]
Pre-transplant		
CPT B	87% (45/52)	92% (46/50)
CPT C	88% (35/40)	83% (38/46)
Post-transplant		
Metavir score F0-F3	95% (94/99)	99% (99/100)
CPT A	98% (55/56)	96% (51/53)
CPT B	89% (41/46)	96% (43/45)
CPT C	57% (4/7)	78% (7/9)
Fibrosis cholestatic hepatitis	100% (7/7)	100% (4/4)

a. Twelve patients transplanted prior to post-treatment Week 12 with HCV RNA<LLOQ at last measurement prior to transplant were excluded.
b. Two patients who did not have decompensated cirrhosis and had also not received a liver transplant were excluded due to failure to meet the inclusion criteria for any of the treatment groups.

Among the 26 patients with genotype 1 CHC who did not achieve SVR12 after 12 weeks of treatment, 14 patients relapsed and the other 12 subjects were considered treatment failure due to death (N=11) or withdrawal of consent (N=1). Among the 19 patients with genotype 1 CHC who did not achieve SVR12 after 24 weeks of treatment, 6 patients relapsed and the other 13 patients were considered treatment failure due to death (N=11), withdrawal of consent (N=1) or early discontinuation after 8 days on treatment (N=1).

Among 40 patients with genotype 4 CHC enrolled in SOLAR-1 and SOLAR-2 studies, SVR12 were 92% (11/12) and 100% (10/10) in post-transplant patients without decompensated cirrhosis treated for 12 or 24 weeks, respectively. No subjects relapsed. SVR12 were 60% (6/10) and 75% (6/8) in patients with decompensated cirrhosis (pre- and post-liver transplantation) treated for 12 or 24 weeks, respectively. Of the 7 patients who failed to achieve SVR12, 3 relapsed, all of whom had decompensated cirrhosis and were treated with HARVONI+ribavirin for 12 weeks.

Changes in MELD and CPT score from baseline to post-treatment Week 12 were analysed for all patients with decompensated cirrhosis (pre- or post-transplant) who achieved SVR12 and for whom data were available (N=123) to assess the effect of SVR12 on hepatic function:

Change in MELD score: Among those who achieved SVR12 with 12 weeks treatment with HARVONI+RBV, 57% (70/123) and 19% (23/123) had an improvement or no change in MELD score from baseline to post-treatment week 12, respectively; of the 32 patients whose MELD score was $\geq$ 15 at baseline, 59% (19/32) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD score was driven largely by improvement in bilirubin.

Change in CPT: Among those who achieved SVR12 with 12 weeks treatment with HARVONI+RBV, 60% (74/123) and 34% (42/123) had an improvement or no change of CPT scores from baseline to post-treatment week 12, respectively; of the 32 subjects who had CPT C cirrhosis at baseline, 53% (17/32) had CPT B cirrhosis at post-treatment Week 12; of the 88 patients who had CPT B cirrhosis at baseline, 25% (22/88) had CPT A cirrhosis at post-treatment Week 12. Improvement in CPT score was driven largely by improvement in albumin and bilirubin.

Pediatrics

The efficacy of HARVONI in HCV infected patients ≥ 12 years of age was evaluated in a Phase 2, open label clinical trial that enrolled 100 patients 12 to < 18 years with genotype 1 CHC. A total of 80 patients (80%) were treatment-naïve and 20 patients (20%) were treatment-experienced. All patients 12 to < 18 years were treated with HARVONI for 12 weeks.

Demographics and baseline characteristics were balanced across treatment-naïve and treatment-experienced patients. Of the 100 treated subjects, the median age was 15 years (range: 12 to 17); 63% of the patients were female; 90% were White, 7% were Black, and 2% were Asian; 13% were Hispanic/Latino; mean body mass index was 23 kg/m^2 (range: 13.1 to 36.6 kg/m^2); 55% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 81% had genotype 1a HCV infection; 76% had non-CC IL28B alleles (CT or TT); 1 patient had known cirrhosis. The majority of patients (84%) had been infected through vertical transmission.

The SVR12 rate was 98% overall (98% [78/80] in treatment-naïve patients and 100% [20/20] in treatment-experienced patients). No patient experienced on-treatment virologic failure or relapse. Two out of 100 patients were lost to follow-up.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of ledipasvir, sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult patients and in patients with chronic hepatitis C. Following oral administration of HARVONI, ledipasvir median peak concentrations were observed 4.0 to 4.5 hours post-dose. Sofosbuvir was absorbed quickly and the peak median plasma concentration was observed ~ 0.8 to 1 hour post-dose. Median peak plasma concentration of GS-331007 was observed between 3.5 to 4 hours post-dose.

Based on the population pharmacokinetic analysis in HCV-infected patients, geometric mean steady-state AUC_{0-24} for ledipasvir (N=2113), sofosbuvir (N=1542), and GS-331007 (N=2113) were 7290, 1320 and 12,000 ng•hr/ml, respectively. Steady-state C_{max} for ledipasvir, sofosbuvir and GS-331007 were 323, 618 and 707 ng/ml, respectively. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult patients and patients with HCV infection. Relative to healthy subjects (N=191), ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively in HCV-infected patients.

Ledipasvir AUC is dose proportional over the dose range of 3 to 100 mg. Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200 mg to 1,200 mg.

Distribution

Ledipasvir is >99.8% bound to human plasma proteins. After a single 90 mg dose of [^{14}C]-ledipasvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity ranged between 0.51 and 0.66.

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 µg/mL to 20 µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP 2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-LDV, systemic exposure was almost exclusively to the parent drug (>98%). Unchanged ledipasvir is the major species present in faeces.

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [^{14}C]-sofosbuvir, GS-331007 accounted for approximately >90% of total systemic exposure.

Excretion

Following a single 90 mg oral dose of [^{14}C]-ledipasvir, mean total recovery of the [^{14}C]-radioactivity in faeces and urine was approximately 87%, with most of the radioactive dose recovered from faeces (approximately 86%). Unchanged ledipasvir excreted in faeces accounted for a mean of 70% of the administered dose and the oxidative metabolite M19 accounted for 2.2% of the dose. These data suggest that biliary excretion of unchanged ledipasvir is a major route of elimination with renal excretion being a minor pathway (approximately 1%). The median terminal half-life of ledipasvir was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

Effect of food

Relative to fasting conditions, the administration of a single dose of HARVONI with a moderate fat (~600 kcal, 25% to 30% fat) or high fat (~1000 kcal, 50% fat) meal did not substantially affect the sofosbuvir C_{max} and $AUC_{0\text{-}inf}$. The exposures of GS-331007 and ledipasvir were not altered in

the presence of either meal type. The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food. HARVONI can be administered without regard to food.

Special Populations

Age, Gender and Ethnicity

No clinically relevant pharmacokinetic differences due to race have been identified for ledipasvir, sofosbuvir or GS-331007. No clinically relevant pharmacokinetic differences due to gender have been identified for sofosbuvir or GS-331007.

AUC and C_{max} of ledipasvir were 77% and 58% higher respectively in females than males; however, the relationship between gender and ledipasvir exposures was not considered clinically relevant as high response rates (SVR >90%) were achieved in males across the Phase 3 studies.

Population pharmacokinetic analysis in HCV-infected patients showed that within the age range (18 to 80 years) analyzed, age did not have a clinically relevant effect on the exposure to ledipasvir, sofosbuvir or GS-331007. Clinical studies of HARVONI included 351 patients aged 65 and over. The response rates observed for patients ≥65 years of age were similar to that of subjects <65 years of age, across treatment groups.

Ledipasvir, sofosbuvir, and GS-331007 exposures in pediatric patients ≥ 12 years of age were similar to those in adults from Phase 2/3 studies, following administration of HARVONI (90/400 mg). The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 have not been established in paediatric patients <12 years of age.

Patients with Impaired Renal Function

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy patients and patients with severe renal impairment. No dose adjustment of ledipasvir is required for patients with mild, moderate or severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative patients with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥ 30 and < 50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and patients with end stage renal disease (ESRD) requiring haemodialysis following a single 400 mg dose of sofosbuvir. Relative to patients with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In patients with ESRD, relative to patients with normal renal function, sofosbuvir and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after haemodialysis. Haemodialysis is required for the elimination of GS-331007 in patients with ESRD, with a 4 hour haemodialysis removing approximately 18% of administered dose. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been assessed in patients with severe renal impairment or ESRD.

Patients with Hepatic Impairment

The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe hepatic impairment (Child Pugh Class C). Ledipasvir plasma exposure ($AUC_{0\text{-}inf}$) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate or severe hepatic impairment.

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected patients with moderate and severe hepatic impairment (Child Pugh Class B and C). Relative to patients with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment.

5.3 Preclinical safety data

Ledipasvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Sofosbuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

Ledipasvir was not carcinogenic in the 6-month rasH2 transgenic mouse and the 2-year rat carcinogenicity studies at exposures up to 26-times in mice and 8-times in rats higher than human exposure.

Carcinogenicity studies in mice and rats do not indicate any carcinogenicity potential of sofosbuvir administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was up to 17 times (mouse) and 9 times (rat) higher than the clinical exposure at 400 mg sofosbuvir.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

Silicon dioxide
Copovidone
Croscarmellose sodium
Lactose monohydrate

Magnesium stearate
Microcrystalline cellulose

Film-coating:

Polyvinyl alcohol
Macrogol 3350
Titanium dioxide
Talc-purified
Sunset yellow FCF aluminium lake

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

HARVONI should be stored below 30 °C.

6.5 Nature and Contents of Container

HARVONI is supplied in high density polyethylene (HDPE) bottles containing 28 tablets and is closed with a child resistant closure.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Gilead Sciences (NZ)
c/- Grant Thornton New Zealand Limited
L4, 152 Fanshawe Street,
Auckland 1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

6 November 2014

10 DATE OF REVISION OF THE TEXT

13 August 2019

Summary table of changes

Section changed	Summary of new information
4.5	Include language regarding improvement in liver function and monitoring of relevant laboratory parameters in certain patients and the metabolism of other drugs significantly affected by changes in hepatic function.