PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrHARVONI®

ledipasvir/sofosbuvir tablets

90 mg/400 mg, Oral

Antiviral Agent

Gilead Sciences Canada, Inc.
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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustments in Adults, Special Populations, Pediatrics	01/2020
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustments in Adults, Special Populations, Renal Impairment	01/2020
7 Warnings and Precautions, Renal	01/2020
7 Warnings and Precautions, Special Populations, 7.1.3 Pediatrics	01/2020

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HARVONI (ledipasvir/sofosbuvir) is indicated for the treatment of chronic hepatitis C virus (CHC) infection in adults (≥ 18 years of age).

HARVONI is indicated for the treatment of CHC genotype 1 infection in pediatric patients ≥ 12 years of age, without cirrhosis or with compensated cirrhosis.

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

Efficacy with HARVONI + ribavirin (RBV) regimen has been established in adult CHC genotype 1 or 4 liver transplant recipients without cirrhosis, with compensated cirrhosis (Child-Pugh-Turcotte [CPT] A) and genotype 1 liver transplant recipients with decompensated CPT B and CPT C cirrhosis.

Efficacy with HARVONI + RBV regimen has been established in adult CHC genotype 1 patients with decompensated cirrhosis, irrespective of transplantation status (see **4 DOSAGE AND ADMINISTRATION** and **14 CLINICAL TRIALS**).

Patients Co-infected with Human Immunodeficiency Virus (HIV-1)

Efficacy with HARVONI has been established in adult CHC genotype 1 or 4 patients, with or without cirrhosis, co-infected with HIV-1 (see **4 DOSAGE AND ADMINISTRATION** and **14 CLINICAL TRIALS**).

1.1 Pediatrics (< 18 years of age)

Safety and efficacy with HARVONI have been established in pediatric patients ≥ 12 years of age with genotype 1 CHC (see **14 CLINICAL TRIALS**).

Safety and efficacy in pediatric patients infected with other CHC genotypes or in patients who are < 12 years of age have not been established (see **7 WARNINGS AND PRECAUTIONS**).

1.2 Geriatrics (≥ 65 years of age)

Clinical studies of HARVONI included 200 patients (8.7% of total number of patients in clinical trials) 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. HARVONI can be administered in geriatric patients (see **10 CLINICAL PHARMACOLOGY**).

2 CONTRAINDICATIONS

HARVONI is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the **4 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the Product Monograph.

When HARVONI is administered with RBV, the contraindications to RBV also apply to this combination regimen. Refer to the RBV Product Monograph for a list of contraindications for RBV.

The use of RBV is contraindicated in pregnant women and in men whose female partners are pregnant, may be pregnant, or plan to become pregnant because of the risks for birth defects and fetal death associated with RBV (see **7 WARNINGS AND PRECAUTIONS**, **7.1 Special Populations**, **7.1.1 Pregnant Women**).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Potential for Hepatitis B Virus (HBV) Reactivation**

Screen all patients for evidence of current or prior HBV infection before initiating HARVONI treatment. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct acting antivirals (DAAs) in patients co-infected with HBV (see **7 WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The treatment duration of HARVONI is fixed and is not guided by a patient's HCV RNA levels (ie, no response guided therapy).

4.2 Recommended Dose and Dosage Adjustments in Adults (≥ 18 years of age)

HARVONI is a fixed dose single tablet regimen. No dosage adjustments are possible for HARVONI.

The recommended dose of HARVONI is one tablet of 90 mg/400 mg ledipasvir/sofosbuvir, taken orally, once daily with or without food (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics**).

The recommended treatment duration for HARVONI in adult patients (≥ 18 years of age) is provided in Table 1.

Table 1. Treatment Duration for HARVONI in HCV-infected Adult Patients

	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve[a] with or without cirrhosis[b]	HARVONI 8 or 12 weeks[c]
	Treatment-experienced[d] without cirrhosis[b]	HARVONI 12 weeks
	Treatment-experienced[d] with cirrhosis[b]	HARVONI 24 weeks[e]

	Patient Population	Treatment Regimen and Duration
	Treatment-naïve[a] and treatment-experienced[d] with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + RBV[g] 12 weeks
Genotype 1 or 4	Treatment-naïve[a] and treatment-experienced[d] liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + RBV[f] 12 weeks
Genotype 1 or 4	Treatment-naïve[a] and treatment-experienced[d] HCV/HIV-1 co-infected patients, with or without cirrhosis[b]	HARVONI 12 weeks[h]
Genotype 2, 4, 5 or 6	Treatment-naïve[a] and treatment-experienced[d], with or without cirrhosis[b]	HARVONI 12 weeks
Genotype 3	Treatment-naïve[a] with or without cirrhosis[b]	HARVONI + RBV[f] 12 weeks
	Treatment-experienced[d] with or without cirrhosis[b]	HARVONI + RBV[f] 24 weeks

a. Treatment-naïve is defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct acting antiviral agent at the time of treatment initiation.
b. Cirrhosis is defined as any one of the following: Liver biopsy showing cirrhosis (eg, Metavir score = 4 or Ishak score ≥ 5); or Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa; or FibroTest® score of > 0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of > 2.
c. HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL (see **14 CLINICAL TRIALS**).
d. Treatment-experienced is defined as those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor.
e. HARVONI+RBV[f] for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for RBV.
f. The daily dose of RBV is weight based (<75 kg = 1000 mg; ≥75 kg = 1200 mg) and administered orally in two divided doses with food. Refer to RBV PM for information on dose modification.
g. Administer ribavirin at a starting daily dosage of 600 mg in two divided doses with food. If the starting dosage is well-tolerated, the dosage can be titrated up to a maximum of 1000-1200 mg daily divided (<75 kg = 1000 mg; ≥75 kg = 1200 mg) and administered twice daily with food If the starting dosage is not well-tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels. Refer to RBV PM for information on dose modifications.
h. Refer to Tables 5-7 for dosing recommendations with HIV-1 antiviral agents and for observed drug exposure levels when coadministered with HIV antiviral agents (see **9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions**).

Special Populations

Pediatrics (< 18 Years of age)

In pediatric patients ≥ 12 years of age with genotype 1 CHC without cirrhosis or with compensated cirrhosis, the recommended dose of HARVONI is one tablet of 90 mg/400 mg ledipasvir/sofosbuvir, taken orally once daily with or without food for 12 weeks (see **14 CLINICAL TRIALS** and **10 CLINICAL PHARMACOLOGY**). No data are available to make a dose recommendation for pediatric patients < 12 years or ≥ 12 years of age with other genotypes.

HARVONI is not indicated for use in pediatric patients < 12 years of age.

HARVONI is not indicated for use in pediatric patients with severe renal impairment or end-stage renal disease (ESRD).

Geriatrics (≥ 65 years of age)

HARVONI can be administered in elderly patients (see **10 CLINICAL PHARMACOLOGY**).

Hepatic Impairment

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see **7 WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACOLOGY**). Safety and efficacy of HARVONI have been established in genotype 1 CHC adult patients with decompensated cirrhosis.

Renal Impairment

Renal impairment studies have been conducted with HARVONI or the individual drugs, ledipasvir and sofosbuvir. HARVONI can be administered in patients with all stages of renal impairment, including ESRD requiring dialysis (see **7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, 10 CLINICAL PHARMACOLOGY** and **14 CLINICAL TRIALS**).

4.5 Missed Dose

If a patient misses a dose of HARVONI within 18 hours of the time it is usually taken, the patient should take HARVONI as soon as possible, and then take the next dose of HARVONI at the regularly scheduled time.

If a patient misses a dose of HARVONI and it is after 18 hours of the time it is usually taken, the patient should not take the missed dose, but resume the usual dosing schedule. A double dose of HARVONI must not be taken.

If a patient vomits less than 5 hours after taking a dose of HARVONI, the patient should take another dose of HARVONI. If a patient vomits more than 5 hours after taking a dose of HARVONI, the patient should take the next dose at the regularly scheduled time.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

No specific antidote is available for overdose with HARVONI. If overdose occurs the patient must be monitored for evidence of toxicity. Hemodialysis is unlikely to result in significant removal of ledipasvir since ledipasvir is highly bound to plasma protein. Hemodialysis can efficiently remove (53% extraction ratio) the predominant circulating metabolite GS-331007.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient are recommended.

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 trials, there were no untoward effects observed at this dose level, 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 90 mg ledipasvir/ 400 mg sofosbuvir	Colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

HARVONI is a fixed-dose single tablet regimen containing ledipasvir and sofosbuvir for oral administration.

HARVONI is available as an orange colored, diamond shaped, film-coated tablet debossed with “GSI” on one side and “7985” on the other side of the tablet. Each bottle contains 28 tablets, a silica gel desiccant, polyester coil, and closed with a child resistant closure.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Treatment with HARVONI should be initiated and monitored by a physician experienced in the management of CHC.

The safety and efficacy of HARVONI in combination with other anti-HCV medicines have not been studied. The sustained virologic response (SVR) of HARVONI is reduced in treatment-experienced patients with HCV containing certain NS5A baseline mutations (see **15 MICROBIOLOGY**).

The safety and efficacy of HARVONI have not been studied in patients who have failed previous therapy with HARVONI.

Use with P-gp Inducers

Medicinal products that are P-glycoprotein (P-gp) inducers [eg, rifampin, St. John's wort (*Hypericum perforatum*)] may significantly decrease ledipasvir and sofosbuvir plasma concentration leading to reduced therapeutic effect of HARVONI and potential loss of virologic response. Rifampin and St. John's wort should not be used with HARVONI (see **9 DRUG INTERACTIONS**).

Use with Certain HIV Antiretroviral Regimens

HARVONI has been shown to increase tenofovir exposure when used together with an HIV regimen containing tenofovir disoproxil fumarate (tenofovir DF) (see **9 DRUG INTERACTIONS**). Patients receiving HARVONI concomitantly with tenofovir DF, particularly those at increased risk for renal dysfunction should be monitored for tenofovir-associated adverse reactions. Refer to Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.

Coadministration with Related Products

HARVONI should not be administered concurrently with other medicinal products containing sofosbuvir (SOVALDI®, EPCLUSA®, VOSEVI®).

Cardiovascular

Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Post-marketing 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 (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions** and **9 DRUG INTERACTIONS**).

Gastrointestinal

HARVONI contains lactose. This medicine is not recommended for patients with rare hereditary problems of galactose intolerance (severe lactase deficiency or glucose-galactose malabsorption).

Hepatic/Biliary/Pancreatic

Hepatic impairment studies have been conducted with the individual drugs, ledipasvir, and sofosbuvir. HARVONI can be administered in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see **10 CLINICAL PHARMACOLOGY** and **4 DOSAGE AND ADMINISTRATION**). Safety and efficacy of HARVONI have been established in adult genotype 1 CHC patients with decompensated cirrhosis. Safety and efficacy in liver transplant recipients with decompensated CPT C cirrhosis are based on the results seen in 17 patients.

Liver function monitoring (including direct bilirubin), when clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with HARVONI + RBV (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

Monitoring and Laboratory Tests

Clearance of HCV may lead to increased replication of HBV in patients who are co-infected with HCV and HBV; co-infected patients should be monitored for clinical and laboratory signs (eg, HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **7 WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

As liver function may improve during treatment with HARVONI, monitoring of certain laboratory parameters and/or concomitant medications may be required. For guidance see **9 DRUG INTERACTIONS**, **9.4 Drug-Drug Interactions**, **Other Forms of Interactions**.

Potential for HBV Reactivation

Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV co-infected patients who were undergoing, or completed treatment containing DAAs. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to initiation of HCV

treatment. Patients with positive HBV serology (HBsAg positive) and patients with serologic evidence of resolved HBV infection (ie, HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation (see **7 WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Renal

No dosing adjustment of HARVONI is required for patients with any degree of renal impairment or ESRD. No safety data are available in patients with decompensated cirrhosis and severe renal impairment or ESRD.

When used with RBV, refer to the ribavirin Product Monograph for dose modification for renal impaired patients.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnancy should be avoided while taking HARVONI as there are no data on the use of HARVONI in pregnant women. HARVONI should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Patients should be advised to notify their health-care provider immediately in the event of a pregnancy.

In the rat and rabbit, at ledipasvir AUC exposures 5- and 2-fold higher, respectively, than the human exposure at 90 mg dose, no effects on fetal development were observed (see **16 NON-CLINICAL TOXICOLOGY**).

In the ledipasvir rat pre- and post-natal 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 (see **16 NON-CLINICAL TOXICOLOGY**).

No effects on fetal development were observed in rats and rabbits at the highest doses of sofosbuvir tested. In the rat and rabbit, exposure to the predominant circulating metabolite GS-331007 at the highest dose was approximately 6-fold and 16-fold the exposure in humans at the recommended clinical dose, respectively (see **16 NON-CLINICAL TOXICOLOGY**).

Pregnancy and Concomitant Use with RBV

Ribavirin may cause birth defects and/or death of the exposed fetus (see **2 CONTRAINDICATIONS**). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients when HARVONI is administered in combination with RBV as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to RBV.

HARVONI in combination with RBV should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time (see the RBV Product Monograph).

7.1.2 Breast-feeding

It is not known whether ledipasvir, sofosbuvir, and its metabolites are excreted in human breast milk. A risk to the newborn/infant cannot be excluded; therefore, breast-feeding should be discontinued before treatment with HARVONI.

When administered to lactating rats, ledipasvir was detected in the plasma of suckling rats likely due to excretion of ledipasvir via milk. Ledipasvir plasma AUC ratio in the suckling rats to the lactating female rats was 0.26 on Lactation Day 10. Ledipasvir had no effects on the nursing pups.

Excretion of sofosbuvir in milk was studied in postpartum female rats after a single oral dose. The milk:plasma concentration ratios in the female rats were 0.1 at 1 hour post-dose and 0.8 at 24 hours post-dose. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, and the metabolite had no effect on the nursing pups.

7.1.3 Pediatrics (< 18 years of age)

The safety and efficacy with HARVONI have been established in pediatric patients ≥ 12 years of age with genotype 1 CHC (see **14 CLINICAL TRIALS**).

The safety and efficacy of HARVONI in pediatric patients infected with other CHC genotypes or in patients who are < 12 years of age have not been established.

No data are available regarding the safety of HARVONI in pediatric patients with renal impairment.

7.1.4 Geriatrics (≥ 65 years of age)

Clinical studies of HARVONI included 200 patients (8.7% of total number of patients in clinical trials) 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. HARVONI can be administered in geriatric patients.

7.1.5 Others

HCV/HBV Co-infection

The safety and efficacy of HARVONI have not been established in patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **7 WARNINGS AND PRECAUTIONS**, **Potential for HBV Reactivation**).

Patients Co-infected with HIV-1

In a clinical trial in HIV-1 co-infected adult patients, the relapse rate in Black patients was 9% (10/115), all of whom were IL28B non-CC genotype, and none in non-Black patients (0/220). In 3 clinical trials in HCV mono-infected patients, relapse rates were 3% (10/305) in Black patients and 2% (26/1637) in non-Black patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of HARVONI was established in the following patient populations: adult patients infected with HCV genotypes 1, 2, 3, 4, 5, or 6 who were treatment-naïve or who failed prior treatments (PEG-IFN/RBV or PI + PEG-IFN/RBV), and included a portion of patients with compensated cirrhosis; adult CHC genotype 1 or 4 patients co-infected with HIV-1; adult CHC patients who are post-liver transplant (genotype 1 or 4) and/or who have decompensated cirrhosis (genotype 1); and pediatric patients ≥ 12 years of age with genotype 1 CHC without cirrhosis or with compensated cirrhosis.

The safety assessment of HARVONI in patients with genotype 1 CHC is based on pooled data of 1080 patients 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.

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. The proportion of Grade 3 adverse events considered related to study drug by site investigators was 0% and 0.4% for 8 and 12 weeks, respectively; no Grade 4 adverse events were reported.

No adverse drug reactions specific to HARVONI have been identified.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trials in Adults (≥ 18 years of age)

The adverse reactions (Grades 2 to 4) observed in ≥ 2% of patients receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials are listed in Table 3.

Table 3. Adverse Reactions (Grades 2 – 4) Reported in ≥ 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N = 215	N = 539	N = 326
Headache	3%	4%	4%

	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N = 215	N = 539	N = 326
Fatigue	2%	2%	5%

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Patients with Cirrhosis

The safety assessment of HARVONI with or without RBV was based on a randomized, double-blind and placebo-controlled trial in treatment-experienced genotype 1 patients with compensated cirrhosis and was compared to placebo in the SIRIUS trial. Patients were randomized to receive 24 weeks of HARVONI once daily by mouth without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI once daily by mouth + RBV (see **14 CLINICAL TRIALS** section). Table 4 presents the adverse reactions, as defined above, that occurred with at least 5% greater frequency in patients treated with 24 weeks of HARVONI or 12 weeks of HARVONI+RBV, compared to those reported for 12 weeks of placebo. The majority of the adverse reactions presented in Table 4 were Grade 1 or 2 in severity.

Table 4. Adverse Reactions Reported ≥5% Greater Frequency in Treatment-Experienced Patients with Cirrhosis Receiving HARVONI[a] for 24 Weeks or HARVONI+RBV for 12 Weeks Compared to Placebo for 12 weeks

	HARVONI 24 weeks (N=78)	HARVONI+RBV 12 weeks (N=76)	Placebo 12 weeks (N=77)
Asthenia	31%	34%	23%
Headache	29%	13%	16%
Fatigue	18%	4%	1%
Cough	5%	11%	1%
Myalgia	9%	4%	0
Dyspnea	3%	9%	1%
Irritability	8%	7%	1%
Dizziness	5%	1%	0

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.

Patients with other HCV Genotypes

The safety assessment of HARVONI in genotype 2 patients is based on study GS-US-337-1468 (LEPTON) that included 26 treatment-naïve or treatment-experienced genotype 2 patients who received 12 weeks of HARVONI. For genotype 3 patients, the safety assessment is based on study GS-US-337-0122 (ELECTRON-2) that included 101 treatment-naïve or treatment-experienced patients, with or without cirrhosis. Treatment-naïve patients were treated with HARVONI or HARVONI + RBV for 12 weeks; all treatment-experienced patients

received HARVONI + RBV for 12 weeks. For genotype 4 patients (other than those included in SOLAR-1 or SOLAR-2, below), the safety assessment is based on pooled clinical trial data from studies GS-US-337-1119 (N=44) and GS-US-337-0115 (ION-4, N=8) that included 52 genotype 4 treatment-naïve or treatment-experienced patients who received HARVONI for 12 weeks. For genotype 5 and 6 patients, safety assessments are based on two phase 2 clinical trials [GS-US-337-1119 and GS-US-337-0122 (ELECTRON-2)] that included 41 and 25 patients for genotypes 5 and 6, respectively.

The safety profile associated with the use of HARVONI ± RBV in nongenotype 1 CHC did not differ from the safety profile observed in patients with genotype 1 CHC. 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.

Special Populations

Liver Transplant Recipients and/or Patients with Decompensated Cirrhosis

The safety of HARVONI+RBV was assessed in adult liver transplant recipients and/or patients with decompensated liver disease in two Phase 2 open-label trials in which patients received HARVONI+RBV for 12 (N=336) or 24 weeks (N=334).

The observed adverse events were consistent with expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known toxicity profile of RBV. One adverse event of direct bilirubin increased, where drug induced liver injury (DILI) could not be excluded and which resulted in permanent discontinuation of HARVONI, was reported in a liver transplant recipient with decompensated CPT B cirrhosis. This event, however, occurred at Week 20 of treatment with HARVONI and RBV, which is past the recommended dosing period of 12 weeks (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

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

HIV-1 Co-infected Patients

The safety of HARVONI was assessed in an open-label trial of 335 adult patients with HCV/HIV-1 co-infection who were on stable antiretroviral therapy (see **14 CLINICAL TRIALS**). The safety profile in HCV/HIV-1 co-infected patients was similar to that observed in HCV mono-infected patients. The most common adverse reactions occurring in at least 10% of patients were headache (20%) and fatigue (17%). No adverse reactions specific to HARVONI were identified.

Patients with Renal Impairment

The safety of HARVONI was assessed in an open-label trial (Study GS-US-334-0154) in which adult patients with genotype 1 CHC without cirrhosis or with compensated cirrhosis and severe renal impairment received HARVONI for 12 weeks (N=18). The adverse events observed were consistent with expected clinical sequelae of severe renal impairment. The most common adverse reaction was fatigue (17%).

The safety of HARVONI was assessed in an open-label clinical trial (Study GS-US-337-4063) in which a total of 95 adult patients without cirrhosis or with compensated cirrhosis and ESRD

requiring dialysis received HARVONI for 8 (N=45), 12 (N=31), or 24 (N=19) weeks. The adverse events observed were consistent with expected clinical sequelae of ESRD. The most common adverse reactions were insomnia and headache (4% each).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (≥ 12 years of age)

The safety assessment of HARVONI in pediatric patients ≥ 12 years of age is based on data from an ongoing Phase 2, open-label clinical trial (GS-US-337-1116) 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 **8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions**).

8.3 Less Common Clinical Trial Adverse Reactions (< 2%)

Adverse reactions (Grades 2 to 4) occurring in less than 2% of patients receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials are listed below by body system:

Table 5. Adverse Reactions (Grades 2 – 4) Reported in < 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI[a] from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

Body System	HARVONI 8, 12, or 24 Weeks[b]
Blood And Lymphatic System Disorders	Factor VIII inhibition
Cardiac Disorders	Palpitations
Eye Disorders	Visual impairment
Gastrointestinal Disorders	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhoea, dyspepsia, gastrooesophageal reflux disease, mesenteric vein thrombosis, nausea, oral discomfort, vomiting
General Disorders And Administration Site Conditions	Asthenia, feeling abnormal, irritability, edema
Hepatobiliary Disorders	Hepatitis acute
Infections And Infestations	Conjunctivitis infective, salpingitis, sinusitis
Injury, Poisoning And Procedural Complications	Contusion, ligament sprain, meniscus injury, muscle strain
Metabolism and Nutrition Disorders	Abnormal loss of weight, decreased appetite, gout
Musculoskeletal and Connective Tissue Disorders	Arthralgia, joint effusion, muscle spasms, muscular weakness
Nervous System Disorders	Disturbance in attention, dizziness, memory impairment, migraine, migraine with aura, parosmia, somnolence

Body System	HARVONI 8, 12, or 24 Weeks[b]
Psychiatric Disorders	Affect lability, aggression, anxiety, depressed mood, depression, emotional disorder, insomnia, libido decreased, sleep disorder
Renal And Urinary Disorders	Urinary retention
Reproductive System and Breast Disorders	Erectile dysfunction, metrorrhagia
Respiratory, Thoracic and Mediastinal Disorders	Oropharyngeal pain, sinus congestion
Skin And Subcutaneous Tissue Disorders	Acne, alopecia, hyperhidrosis, prurigo, pruritus, rash
Vascular Disorders	Hemorrhage, hypertension

a. Frequencies of adverse reactions are based on treatment-emergent adverse events, considered related to study drug by site investigators.
b. Note: adverse events have not been distinguished by whether they occurred during 8, 12, or 24 weeks of therapy.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory Abnormalities

The frequency of treatment-emergent laboratory abnormalities (Grades 2-4) occurring in at least 2% of patients receiving 8, 12, or 24 weeks of treatment with HARVONI are described in Table 6.

Table 6. Laboratory Abnormalities (Grades 2-4) Reported in ≥ 2% of Patients Receiving 8, 12, or 24 Weeks of HARVONI from the Pooled Phase 3 Studies (ION-1, ION-2, ION-3)

Laboratory Abnormality Parameters	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N = 215	N = 538[a]	N = 325[a]
Neutrophils (<1.0 x 10^9/L)	< 1%	< 1%	3%
Platelets (< 100 x 10^9/L)	0	2%	5%
Lipase (> 1.5 x ULN)	4%	6%	9%
Serum glucose (Hyperglycemia) (> 160 mg/dL)	9%	10%	12%
Serum glucose (Hypoglycemia) (< 55 mg/dL)	< 1%	2%	2%
Total Bilirubin (> 1.5 x ULN)	3%	< 1%	2%

ULN = Upper Limit of Normal

a. One patient was dosed but did not have any post-baseline lab values and was therefore excluded from the analysis.

All patients with grades 2 to 4 elevations in lipase were asymptomatic, and the elevations were generally transient, with no treatment emergent clinical events of pancreatitis.

All patients with Grade 3 or 4 increased serum glucose had either a medical history of diabetes or glucose intolerance (HbA1c > 6.0%) at screening.

8.5 Post-Market Adverse Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions have been identified during post approval use of HARVONI. Because post-marketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Serious symptomatic bradycardia when amiodarone is coadministered with HARVONI (see 7 **WARNINGS AND PRECAUTIONS, Cardiovascular** and **9 DRUG INTERACTIONS**).

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson Syndrome, angioedema and skin rashes (sometimes with blisters or angioedema-like swelling).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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 result 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.

9.3 Drug-Behavioural Interactions

Interactions of HARVONI with individual behavioural risks have not been established.

9.4 Drug-Drug Interactions

Potential for HARVONI to Affect Other Drugs

Ledipasvir is an inhibitor of intestinal efflux 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 hepatic uptake transporters OATP1B1, OATP1B3, and hepatic efflux transporter BSEP only at concentrations exceeding those achieved in clinic. Ledipasvir is not an inhibitor of renal efflux transporters MRP2, MRP4, MATE1, renal uptake transporters OCT2, OAT1, OAT3, and hepatic uptake transporter 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 efflux transporters drug transporters P-gp, BCRP, renal efflux transporter MRP2, hepatic efflux transporter BSEP, hepatic uptake transporters OATP1B1, OATP1B3, and OCT1 and GS-331007 is not an inhibitor of renal uptake transporters OAT1, OCT2, and renal efflux transporter MATE1.

Ledipasvir inhibits UGT1A1 only at concentrations exceeding those achieved in the clinic.

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 efflux drug transporters P-gp and BCRP while GS-331007 is not. Drugs that are P-gp inducers (eg, rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of HARVONI and potential loss of virologic response, and should not be used with HARVONI (see **7 WARNINGS AND PRECAUTIONS, General, Use with P-gp Inducers**). Coadministration with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir and ledipasvir plasma concentrations without increasing GS-331007 plasma concentration; HARVONI may therefore 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 uptake 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 ledispavir 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.

Based on these data, ledipasvir, sofosbuvir and its metabolites are predicted to have low liability to cause clinically significant drug interactions through human CYP or drug transporters. The fact that ledipasvir and sofosbuvir are substrates of P-gp and BCRP suggests that they may be susceptible to modest changes in PK that can occur via P-gp and/or BCRP transporter-based drug interactions. Clinical studies were conducted to evaluate the effect of drugs that can affect or be affected by ledipasvir, sofosbuvir, and GS-331007 during coadministration.

Table 7 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. The table is not all-inclusive (see **10 CLINICAL PHARMACOLOGY**).

Table 7. Established and Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration[b]**	**Clinical Comment**
Acid Reducing Agents:	↓ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (eg, aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists[c] (eg, famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (eg, omeprazole)		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 serious 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 **7 WARNINGS AND PRECAUTIONS, Cardiovascular** and **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions**).
digoxin	↑ digoxin	Coadministration of HARVONI with digoxin may result in increased plasma concentration of digoxin due to intestinal inhibition of P-gp by LDV. Caution is warranted and therapeutic concentration monitoring of digoxin is recommended to obtain the desired clinical effect when coadministered with HARVONI.
Anticonvulsants: carbamazepine phenytoin phenobarbital	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with carbamazepine, phenytoin or phenobarbital is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifampin[c] rifapentine	↓ ledipasvir ↓ sofosbuvir	HARVONI should not be used with rifampin, a P-gp inducer (see **7 WARNINGS AND PRECAUTIONS, General, Use with P-gp Inducers**). Coadministration of HARVONI with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antiretrovirals: Regimens containing tenofovir disoproxil fumarate (tenofovir DF)[c]	↑ tenofovir	HARVONI has been shown to increase tenofovir exposure. Patients receiving tenofovir DF and HARVONI concomitantly should be monitored for adverse reactions associated with tenofovir DF. Refer to the Product Monographs for tenofovir DF-containing products for recommendations on renal monitoring.
Other HIV Antiretrovirals tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir*[c]	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased significantly when simeprevir is coadministered with ledipasvir. Coadministration is not recommended.

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.
c. These interactions have been studied in healthy adults.
*Drug not marketed in Canada.

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 either been observed or are expected when HARVONI is used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, emtricitabine, efavirenz, lamivudine, methadone, midazolam, oral contraceptives, oxcarbazepine, pravastatin, raltegravir, rifabutin, rilpivirine, tacrolimus (see **9 DRUG INTERACTIONS**, **9.4 Drug-Drug Interactions**, **Other Forms of Interactions**), or verapamil. For use of HARVONI with certain HIV regimens containing tenofovir DF, see **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS**, Table 7.

Other Forms of Interactions

As liver function may improve due to treatment of HCV with DAAs, it is recommended to closely monitor:

- the International Normalized Ratio (INR) in patients taking vitamin K antagonists,
- blood glucose levels in diabetic patients,
- immunosuppressive drug levels (eg, calcineurin inhibitors cyclosporine and tacrolimus) in patients receiving immunosuppressive therapy,
- other relevant laboratory parameters in susceptible patients and/or other concomitant medications significantly affected by changes in hepatic function.

The dose of vitamin K antagonists, anti-diabetic agents, immunosuppressive agents, or other concomitant medications significantly affected by changes in hepatic function should be modified when necessary.

Assessment of Drug Interactions

The drug interaction studies described were conducted with HARVONI, or components of HARVONI (ledipasvir or sofosbuvir).

The effects of coadministered drugs on the exposure of ledipasvir, sofosbuvir, and GS-331007 are shown in Table 8. The effects of ledipasvir or sofosbuvir on the exposure of coadministered drugs are shown in Table 9.

Table 8. Drug Interactions: Changes in Pharmacokinetic Parameters for Ledipasvir, Sofosbuvir, and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir 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}
Anticonvulsants								
Carbamazepine	300 twice daily	ND	400 single dose	24	sofosbuvir	0.52 (0.43, 0.62)	0.52 (0.46, 0.59)	NA
					GS-331007	1.04 (0.97, 1.11)	0.99 (0.94, 1.04)	NA
Anti-HCV Drugs								
Simeprevir*[h]	150 once daily	30 once daily[g]	ND	22	ledipasvir	1.81 (1.69, 2.94)	1.92 (1.77, 2.07)	NA
Anti-HIV Drugs								
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 (1.09, 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	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)
Atazanavir/ ritonavir + emtricitabine/ tenofovir DF	300/100/200/300 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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir 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}
Darunavir/ ritonavir[h]	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 single dose	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 + emtricitabine/ tenofovir disoproxil fumarate	800/100/200/300 once daily simultaneously with HARVONI[b]	90 once daily	400 once daily	23	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 + emtricitabine/ tenofovir DF	50 + 200/300 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)	NA
					GS-331007	0.99 (0.95, 1.03)	1.06 (1.03, 1.09)	1.06 (1.03, 1.10)
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[c]	600/200/300 once daily	90 once daily	400 once daily	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
					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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir 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}
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[e]	200/25/300 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)
Raltegravir[h]	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
Anti-infectives								
Rifabutin	300 once daily	ND	400 single dose	20	sofosbuvir	0.64 (0.53, 0.77)	0.76 (0.63, 0.91)	NA
					GS-331007	1.15 (1.03, 1.27)	1.03 (0.95, 1.12)	NA
Rifampin[h]	600 once daily	90 single dose[f]	ND	31	ledipasvir	0.65 (0.56, 0.76)	0.41 (0.36, 0.48)	NA
		ND	400 single dose	17	sofosbuvir	0.23 (0.19, 0.29)	0.28 (0.24, 0.32)	NA
					GS-331007	1.23 (1.14, 1.34)	0.95 (0.88, 1.03)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir 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}
H2-Receptor Antagonists								
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
Immunosuppressants								
Cyclosporine[h]	600 single dose	ND	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
					GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Tacrolimus[h]	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 (0.83, 1.14)	1.00 (0.87, 1.13)	NA
Opiate Agonist								
Methadone[h]	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

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir Dose (mg)	Sofos-buvir 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}
Proton Pump Inhibitors								
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
	20 once daily 2 hours prior to ledipasvir	30 single dose	ND	17	ledipasvir	0.52 (0.41, 0.66)	0.58 (0.48, 0.71)	NA

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

a. All interaction studies conducted in healthy volunteers.
b. Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricibatine/tenofovir DF and HARVONI provided similar results.
c. Administered as ATRIPLA®.
d. This study was conducted to support the use of STRIBILD.
e. Administered as COMPLERA®.
f. This study was conducted in the presence of two other investigational HCV direct acting agents.
g. Ledipasvir dose administered in this study is 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.
h. These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.

*Drug not marketed in Canada.

Table 9. Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Ledipasvir, Sofosbuvir, or HARVONI[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir 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}
Anti-HCV							
Simeprevir*[f]	150 once daily	30 once daily[e]	ND	28	2.61 (2.39, 2.86)	2.69 (2.44, 2.96)	NA
Anti-HIV							
Abacavir /lamivudine	abacavir 600 once daily	90 once daily	400 once 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[g]	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 + emtricitabine/ tenofovir disoproxil fumarate[g] simultaneously with HARVONI[h]	atazanavir 300 once daily[i]	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[i]				0.98 (0.94, 1.02)	1.00 (0.97, 1.04)	1.04 (0.96, 1.12)
	enofovir disoproxil fumarate 300 once daily[i]				1.47 (1.37, 1.58)	1.35 (1.29, 1.42)	1.47 (1.38, 1.57)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir 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}
Darunavir (boosted by ritonavir[f,g])	800/100 once daily	90 once daily	ND	23	1.02 (0.88, 1.19)	0.96 (0.84, 1.11)	0.97 (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)
Darunavir/ ritonavir + emtricitabine/ tenofovir disoproxil fumarate simultaneously with HARVONI[h]	darunavir 800 once daily[j]	90 once daily	400 once daily	23	1.01 (0.96, 1.06)	1.04 (0.99, 1.08)	1.08 (0.98, 1.20)
	ritonavir 100 once daily				1.17[j] (1.01, 1.35)	1.25[j] (1.15, 1.36)	1.48[j] (1.34, 1.63)
	emtricitabine 200 once daily[j]				1.02 (0.96, 1.08)	1.04 (1.00, 1.08)	1.03 (0.97, 1.10)
	tenofovir disoproxil fumarate 300 once daily[j]				1.64 (1.54, 1.74)	1.50 (1.42, 1.59)	1.59 (1.49, 1.70)
Dolutegravir + emtricitabine/ tenofovir DF[k]	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 DF 300 once daily				1.61 (1.51, 1.72)	1.65 (1.59, 1.71)	2.15 (2.05, 2.26)
Efavirenz/ emtricitabine/ tenofovir disoproxil fumarate[b]	efavirenz 600 once daily	90 once daily	400 once daily	15	0.87 (0.79, 0.97)	0.90 (0.84, 0.96)	0.91 (0.83, 0.99)
	emtricitabine 200 once daily				1.08 (0.97, 1.21)	1.05 (0.98, 1.11)	1.04 (0.98, 1.11)
	tenofovir disoproxil fumarate 300 once daily				1.79 (1.56, 2.04)	1.98 (1.77, 2.23)	2.63 (2.32, 2.97)
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide	elvitegravir 150 once daily	90 once daily	400 once daily	30	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)

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir 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}
	emtricitabine 200 once daily				1.03 (0.96, 1.11)	0.97 (0.93, 1.00)	0.95 (0.91, 0.99)
	tenofovir alafenamide 10 once daily				0.90 (0.73, 1.11)	0.86 (0.78, 0.95)	NA
Emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate[d]	emtricitabine once 200 daily	90 once daily	400 once daily	14	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)
	tenofovir disoproxil fumarate 300 once daily				1.32 (1.25, 1.39)	1.40 (1.31, 1.50)	1.91 (1.74, 2.10)
Raltegravir[f]	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)
Benzodiazepines							
Midazolam	2.5 single dose	90 single dose	ND	30	1.07 (1.00, 1.14)	0.99 (0.95, 1.04)	NA
		90 once daily			0.95 (0.87, 1.04)	0.89 (0.84, 0.95)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Ledi-pasvir dose (mg)	Sofos-buvir 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}
Estrogen-based Contraceptives							
Norelgestromin	Norgestimate 0.180/0.215/0.250/ ethinyl estradiol 0.025 once daily[f]	90 once daily	ND	15	1.02 (0.89, 1.16)	1.03 (0.90, 1.18)	1.09 (0.91, 1.31)
		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)
Immunosuppressants							
Cyclosporine[f]	600 single dose	ND	400 single dose	19	1.06 (0.94, 1.18)	0.98 (0.85, 1.14)	NA
Tacrolimus[f]	5 single dose	ND	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Opiate Agonists							
R-Methadone[f]	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[f]					0.95 (0.79, 1.13)	0.95 (0.77, 1.17)	0.95 (0.74, 1.22)

NA = not available/not applicable, ND = not dosed.
a. All interaction studies conducted in healthy volunteers.
b. Administered as ATRIPLA.
c. This study was conducted to support the use of STRIBILD.
d. Administered as COMPLERA.
e. Ledipasvir dose administered in this study was 30 mg which is lower than the ledipasvir dose of 90 mg when administered as HARVONI.
f. These studies have not been performed with HARVONI; they were conducted with either ledipasvir or sofosbuvir administered as single agents.

g. Ledipasvir leads to moderate increases of ritonavir plasma exposures.
h. Staggered administration (12 hours apart) of atazanavir/ritonavir+emtricitabine/tenofovir DF or darunavir/ritonavir+emtricitabine/tenofovir DF and HARVONI provided similar results.
i. Comparison based on exposures when administered as atazanavir/ritonavir+emtricitabine/tenofovir DF.
j. Comparison based on exposures when administered as darunavir/ritonavir+emtricitabine/tenofovir DF.
k. Comparison based on exposures when administered as dolutegravir + emtricitabine/tenofovir DF.
*Drug not marketed in Canada.

9.5 Drug-Food Interactions

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. 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_{inf}. The exposures of GS-331007 and ledipasvir were not altered in the presence of either meal type. (see **4 DOSAGE AND ADMINISTRATION** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics**).

9.6 Drug-Herb Interactions

St. John's wort should not be used with HARVONI.

Coadministration of St. John's wort, a P-gp inducer, may decrease ledipasvir and sofosbuvir plasma concentrations, which may result in loss of therapeutic effect. See **7 WARNINGS AND PRECAUTIONS**, **General, Use with P-gp Inducers**.

9.7 Drug-Laboratory Test Interactions

Interactions of HARVONI with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

Ledipasvir is an HCV NS5A inhibitor. Sofosbuvir is a nucleotide analog pan-genotypic NS5B polymerase inhibitor.

10.1 Mechanism of Action

HARVONI

HARVONI is a fixed-dose single tablet regimen of ledipasvir and sofosbuvir.

Both sofosbuvir and ledipasvir exhibit high potency and specificity as individual agents against HCV as compounds that target the HCV NS5B and NS5A proteins, respectively. Both compounds display low cytotoxicity in a number of distinct cell lines and display no significant antiviral activity against other viruses tested. *In vitro* combination studies using both sofosbuvir and ledipasvir showed an additive effect as measured by *in vitro* cell based genotype 1a and 1b HCV replicon assays. As individual components, both sofosbuvir and ledispasvir showed additive to synergistic activity with all other anti-HCV agents.

Ledipasvir

Ledipasvir is a DAA that inhibits HCV RNA replication and virion production by targeting the HCV NS5A protein. The NS5A protein is thought to play multiple roles in mediating viral replication, host-cell interactions, and viral pathogenesis. As a nonstructural (NS) protein with no apparent enzymatic activity, NS5A functions through interaction with other viral and cellular proteins. The protein NS5A protein is critical for HCV viability and the rapid viral load (HCV RNA) decline produced by NS5A inhibitors has been postulated to be due to inhibition of viral replication (as with NS3 and NS5B inhibitors) and additional inhibition of virion assembly or secretion from infected cells. The HCV NS5A protein is phosphorylated on multiple sites by host cell kinases and interacts with host cell membranes. While no known enzymatic function has been ascribed to NS5A, it is an essential component of the HCV replicase. *In vitro* resistance selection and cross-resistance studies also indicate ledipasvir targets NS5A as its mode of action.

Sofosbuvir

Sofosbuvir is a pan-genotypic polymerase inhibitor of the HCV NS5B RNA-dependent RNA polymerase (RdRp). HCV NS5B is the essential initiating and catalytic subunit of the membrane-associated multiprotein complex that mediates HCV RNA replication and is critical for the viral replication cycle. There is no human homolog for HCV NS5B RdRp. Sofosbuvir is a monophosphorylated pyrimidine nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). Incorporation of GS-461203 into nascent RNA strongly reduces the efficiency of further RNA elongation by RdRp, resulting in premature termination of RNA synthesis. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

10.2 Pharmacodynamics

Effect on Electrocardiogram

Thorough QT studies have been conducted for ledipasvir and sofosbuvir.

The effect of ledipasvir 120 mg twice daily for 10 days on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) three period crossover thorough QT trial in 59 healthy subjects. The effects of sofosbuvir at the therapeutic dose (400 mg) and 3-fold above therapeutic dose (1200 mg) on QTc interval were evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects.

The results from both studies showed the expected effect of the single dose of moxifloxacin (positive control) on the QTc interval, indicating that the study had appropriate assay sensitivity; the lower bound of the 2-sided 90% confidence interval was > 5 msec at more than 1 time point.

Evaluation of the baseline-adjusted mean differences between ledipasvir 120 mg BID, sofosbuvir 400 mg or 1200-mg doses and placebo and their associated 2-sided 90% confidence intervals demonstrated a lack of effect of ledipasvir or sofosbuvir on prolongation of the QTcF interval (primary PD endpoint). The upper bounds of the 90% confidence intervals were < 10 msec at all time points after dosing. Consistent with the results using the QTcF correction formula, the upper bounds of the 2-sided 90% confidence intervals were < 10 msec for ledipasvir and both doses of sofosbuvir at all time points using other correction methods.

Ledipasvir AUC_{0-24} and C_{max} were 3.7- fold and 4.2-fold higher, respectively, than the mean exposure (based on population PK exposures) achieved in Phase 2 and 3 studies following administration of HARVONI. The mean exposures of GS-331007 (AUC_{0-24} and C_{max}) and sofosbuvir (AUC_{0-24} and C_{max}) at the supratherapeutic dose (sofosbuvir 1200 mg) were approximately 2.2-, 2.9-, 1.8-, and 3.4-fold higher, respectively, than the mean exposures (based on population PK exposures) achieved following administration of HARVONI.

Safety Pharmacology

The effects of ledipasvir on the central nervous, cardiovascular and respiratory systems were examined in a core battery of safety pharmacology studies. The studies did not reveal any concerns for cardiovascular, respiratory, or CNS effects.

The effects of sofosbuvir (evaluated as GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer) on the central nervous, cardiovascular, and respiratory systems were examined in a core battery of safety pharmacology studies. The studies presented have not identified any undesirable pharmacodynamic effect of sofosbuvir on physiological function at therapeutic dose level.

10.3 Pharmacokinetics

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 1200 mg.

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in patients with chronic hepatitis C following oral administration of HARVONI.

The pharmacokinetics of HARVONI are shown in Table 10.

Table 10. Summary of Once-Daily Administration of HARVONI in Healthy Adult Subjects and HCV-Infected Patients

PK Parameters	Healthy Subjects[a] HARVONI N=192 Geometric Mean (Range)			HCV-Infected Patients[b] HARVONI N=2113 Geometric Mean (Range)		
	LDV[c]	SOF	GS-331007	LDV	SOF[d]	GS-331007
AUC_{0-24} (ng·h/mL)	9600 (1160, 36800)	1170 (505, 2470)	11400 (5660, 21300)	7290 (416, 49100)	1320 (511, 6690)	12000 (1790, 32000)
C_{max} (ng/mL)	476 (56.9, 1590)	563 (156, 1290)	826 (492, 1730)	323 (19.6, 1910)	618 (87.7, 2540)	707 (83.1, 1690)
C_{min} (ng/mL)	283 (33.5, 1180)	ND	ND	211 (13.4, 1550)	ND	ND

a. Population PK analysis from Phase 1 studies.
b. Population PK analysis from Phase 2 and 3 studies.

c. N=191, one subject did not have estimable PK parameters for LDV
d. N=1542; 571 subjects did not have estimable PK parameters for SOF
ND: not determined

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.

Relative to healthy subjects, ledipasvir AUC_{0-24} and C_{max} were 24% lower and 32% lower, respectively in HCV-infected patients. Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and patients with HCV infection.

Based on population PK analyses, age, race, BMI, treatment status (treatment-naïve or treatment-experienced), presence of RBV in the treatment regimen, or the presence or absence of cirrhosis had no clinically relevant effects on the exposure of SOF, GS-331007, or LDV.

Absorption:

The pharmacokinetic properties of ledipasvir, sofosbuvir, and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects 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.

Effects of Food

The response rates in Phase 3 trials were similar in HCV-infected patients who received HARVONI with food or without food.

A study conducted in 28 healthy subjects showed that relative to fasting conditions, for GS-331007, an approximately 18% to 30% lower C_{max} was observed upon administration of HARVONI with food, with no change in AUC (90% CIs of the Geometric Mean Ratios (GMRs) were contained within 80-125%). The decrease in GS-331007 C_{max} was not considered clinically significant. Similar LDV plasma exposures (AUC and C_{max}) were achieved upon administration of HARVONI under fasted or fed conditions (90% CIs of the GMRs were contained within 70-143%).

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 slowed the rate of absorption of SOF (high or moderate fat meal versus fasted; prolonged T_{max}: 2.0-2.25 hours versus 1.0 hours) but did not substantially affect the sofosbuvir C_{max} and AUC_{inf} as evidenced by < 30% higher C_{max} and < 2-fold higher mean AUC.

HARVONI can be administered without regard to food.

Distribution:

Ledipasvir is >99.8% bound to human plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. After a single 90 mg dose of [^{14}C]-ledipasvir in 8 healthy adult male subjects, the blood to plasma ratio of [^{14}C]-radioactivity ranged between 0.51 and 0.66, indicating that total radioactivity was excluded from erythrocytes. [^{14}C]-ledipasvir-derived radioactivity was absorbed and widely distributed to tissues (eg, alimentary canal, liver, kidney, pancreas, adrenal gland, and brown fat) of male mice and rats after a single oral dose. Low levels of [^{14}C]-ledipasvir-derived radioactivity were observed in the CNS, bone, eye and testes. Plasma LDV exposure in nursing pups of postpartum female rats orally administered LDV illustrates transfer into milk.

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 (< 10%) in human plasma. After a single 400 mg dose of [^{14}C]-sofosbuvir in healthy male subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.7.

After a single 400 mg dose of [^{14}C]-sofosbuvir in 7 healthy adult male subjects, derived radioactivity was absorbed and widely distributed to tissues (eg, alimentary canal, lymphatic system, excretory system) of male rats and pregnant, non-pregnant, and postpartum female rats after a single oral dose. Drug-derived radioactivity was transferred through the placenta of females and was found in amniotic fluid and absorbed into fetuses. Low levels of [^{14}C]-sofosbuvir-derived radioactivity were observed in the CNS, bone, eye, testes, and white adipose. Fetal blood and brain levels of drug-related material were higher than those observed in dams. Levels of drug-derived radioactivity were quantifiable in the milk collected from postpartum females. Levels of drug-derived radioactivity were transferred into nursing pups and were detectable in the liver and gastrointestinal (GI)/stomach contents. See **7 WARNINGS AND PRECAUTIONS**, **7.1 Special Populations**, **7.1.2 Breast-feeding.**

Metabolism:

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Following a single dose of 90 mg [^{14}C]-ledipasvir to 8 healthy adult male subjects, the systemic exposure was almost exclusively due to the parent drug (> 98%) with 1.1% and 0.75% attributed to unidentified metabolites (M1 and M12, respectively). Unchanged ledipasvir is the major species present in feces.

Sofosbuvir is extensively metabolized 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 catalyzed 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 biosysthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

In a human mass balance study conducted with sofosbuvir administered as a single agent at a 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

Elimination:

Following a single 90 mg oral dose of [^{14}C]-ledipasvir to 8 healthy adult male subjects, the mean cumulative urinary and fecal recovery of the [^{14}C]-radioactivity was approximately 87%, with most of the radioactive dose recovered in the feces (approximately 86%). The major component excreted in feces was unchanged ledipasvir, accounting for a mean of 70% of the administered dose; 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 following administration of HARVONI was 47 hours.

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir in healthy male subjects (n=7), mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. Renal clearance is the major elimination pathway for GS-331007. Consistent with substantial elimination of GS-331007 in the urine, clinically significant changes in GS-331007 PK were noted with declining renal function. The median terminal half-life of sofosbuvir and GS-331007 following administration of HARVONI were 0.5 and 27 hours respectively.

Special Populations and Conditions

- **Pediatrics (< 18 years of age)**

  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 pediatric patients < 12 years of age.

- **Geriatrics (≥ 65 years of age)**

  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 200 patients (8.7% of total patients in the clinical trials) aged 65 and over. The response rates observed for patients ≥65 years of age were similar to that of patients <65 years of age, across treatment groups.

- **Sex**

  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 male and female patients across the Phase 3 studies. No clinically relevant pharmacokinetic differences have been observed between men and women for sofosbuvir and GS-331007.

- **Ethnic Origin**

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

- **Hepatic Insufficiency**

  Hepatic impairment studies have been conducted with the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have been established in genotype 1 CHC adult patients with decompensated cirrhosis (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

  The pharmacokinetics of ledipasvir was studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with normal hepatic function and 10 HCV negative matched control subjects with severe hepatic impairment (Child Pugh Class C). Similar AUC_{inf}, a modestly lower (approximately 35%) C_{max} and prolonged terminal $t_{1/2}$ (median 84.25 hrs vs 45.72 hrs) observed in subjects with severe hepatic impairment as compared to subjects with normal hepatic function. A reduction in C_{max} in the absence of a change in AUC was not deemed clinically important. Mild and moderate hepatic impairment is not expected to meaningfully alter the pharmacokinetics of ledipasvir. No dose adjustment of ledipasvir is recommended for patients with mild, moderate, or severe hepatic impairment. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of ledipasvir (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

  The pharmacokinetics of sofosbuvir was 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 subjects with normal hepatic function, the sofosbuvir AUC_{0-24} was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} was 18% and 9% higher, respectively. Mild hepatic impairment is not expected to meaningfully alter the pharmacokinetics of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate, or severe hepatic impairment. 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 (see **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

- **Renal Insufficiency**

  Renal impairment studies have been conducted with HARVONI or the individual drugs, ledipasvir and sofosbuvir. Data from these studies support the use of HARVONI in adult patients without cirrhosis or with compensated cirrhosis with any stage of renal impairment, including ESRD requiring dialysis (see **7 WARNINGS AND PRECAUTIONS**, **4 DOSAGE AND ADMINISTRATION**, and **14 CLINICAL TRIALS**).

  The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in 10 HCV negative subjects with severe renal impairment (eGFR < 30 mL/min by Cockcroft-Gault) and 10 matched control subjects with normal renal function (eGFR ≥ 90 mL/min by Cockcroft-Gault). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.

The pharmacokinetics of sofosbuvir were studied in HCV negative subjects 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 subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir (N=6/group). Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir AUC_{inf} was 61%, 107% and 171% higher in mild, moderate, and severe renal impairment, while the GS-331007 AUC_{inf} was 55%, 88% and 451% higher, respectively. In subjects with ESRD, sofosbuvir AUC_{inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when dosed 1 hour after hemodialysis. The AUC_{inf} of GS-331007 in subjects with ESRD administered sofosbuvir 1 hour before or 1 hour after hemodialysis was at least 10-fold and 20-fold higher, respectively, compared to normal subjects. Hemodialysis is required for the elimination of GS-331007 (extraction ratio 53%) in subjects with ESRD; following a single 400 mg dose of sofosbuvir, a 4 hour hemodialysis removed approximately 18% of administered dose.

In HCV-infected adult patients without cirrhosis or with compensated cirrhosis with severe renal impairment treated with HARVONI for 12 weeks (N=18), the pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were consistent with that observed in HCV negative patients with severe renal impairment. The steady-state AUC_{0-24} of sofosbuvir and GS-331007 was approximately 103% and 501% higher, respectively, than that observed in HCV-infected adult patients with normal renal function.

The pharmacokinetics of ledipasvir, sofosbuvir, and GS-331007 were studied in HCV-infected adult patients with ESRD requiring dialysis treated with HARVONI for 8, 12, or 24 weeks. Steady-state AUC_{tau} of ledipasvir, sofosbuvir and GS-331007 were increased by 61%, 89%, and 2180%, respectively, compared to patients without renal impairment in the ledipasvir/sofosbuvir Phase 2/3 trials. No exposure-safety relationships were observed in HCV-infected adult patients with ESRD requiring dialysis treated with HARVONI.

No dose adjustment of HARVONI is required for adult patients with any stage of renal impairment, including ESRD requiring dialysis.

11 STORAGE, STABILITY AND DISPOSAL

Store below 30°C (86°F).

- Dispense only in original container.
- Do not use if seal over bottle opening is broken or missing.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

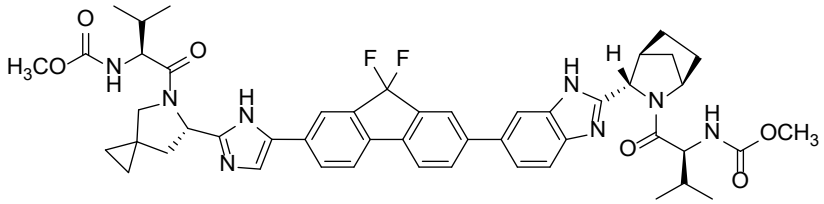
Proper name: **ledipasvir**

Chemical name: Methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Molecular formula: $C_{49}H_{54}F_2N_8O_6$

Molecular mass: 889.00

Structural formula:



Physicochemical properties:

Solubility: Ledipasvir is practically insoluble (<0.1 mg/mL) across the pH range of 3.0-7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).

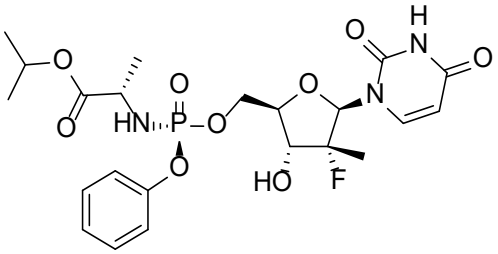
Proper name: **sofosbuvir**

Chemical name: (*S*)-Isopropyl 2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate

Molecular formula: $C_{22}H_{29}FN_3O_9P$

Molecular mass: 529.45

Structural formula:



Physicochemical properties:

Appearance	Sofosbuvir is a white to off-white crystalline solid.
Solubility	Sofosbuvir is slightly soluble in water.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Adults

In clinical trials described in this section, the efficacy of HARVONI (±RBV) was evaluated in a total of 3127 patients with CHC.

The efficacy of HARVONI was evaluated in three Phase 3 trials with data available for a total of 1518 patients with genotype 1 CHC. All three trials evaluated the efficacy of HARVONI with or without RBV. The demographics and baseline characteristics for the patients in studies ION-3, ION-1, and ION-2 were well balanced across the treatment groups as summarized in Table 12, Table 14, and Table 16.

The efficacy of HARVONI in 335 HCV/HIV-1 co-infected patients with genotype 1 (n=327) or 4 (n=8) CHC, with or without cirrhosis, was evaluated in an open-label Phase 3 trial (ION-4). All patients in the trial were treated with HARVONI for 12 weeks.

The efficacy of HARVONI in adult patients with renal impairment was evaluated in two Phase 2 trials (Study GS-US-334-0154 and GS-US-337-4063) where Study 0154 enrolled patients with severe renal impairment and genotype 1 CHC (N=18), and Study 4063 enrolled 95 patients with ESRD requiring dialysis with genotype 1 (N=68, 72%), 2 (N=21, 22%), 4 (N=2, 2%), 5 (N=1, 1%) or 6 (N=3, 3%) CHC.

Patients in all the above trials had compensated liver disease.

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 patients with genotype 1 (N=628) and 4 (N=42) CHC post-liver transplant and/or with decompensated cirrhosis. Patients in the two trials were treated with HARVONI+RBV for 12 or 24 weeks.

Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate which was defined as HCV RNA less than Lower Limit of Quantitation (LLOQ) at 12 weeks after the cessation of treatment.

Clinical Trials in Patients with Genotype 1 CHC

Treatment-Naïve Patients without Cirrhosis (ION-3 [Study 0108])

Trial Design

The trial design of Study ION-3 is described in Table 11.

Table 11. Summary of Trial Design in Treatment Naïve[a] Patients without Cirrhosis (ION-3)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO	HARVONI	8 weeks
		HARVONI + RBV	8 weeks
		HARVONI	12 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct acting antiviral agent at the time of enrollment), non-cirrhotic, with genotype 1 CHC. Patients were randomized in a 1:1:1 ratio to one of the three treatment groups and stratified by HCV genotype (1a vs. 1b).

Demographics and Other Baseline Characteristics

Demographic characteristics for patients in ION-3 are provided in Table 12.

Table 12. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients without Cirrhosis (ION-3)

Characteristics	HARVONI 8 Weeks N= 215 n (%)	HARVONI + RBV 8 Weeks N = 216 n (%)	HARVONI 12 Weeks N = 216 n (%)	Total N = 647 n (%)
Age (years)				
Mean (range)	53 (20-75)	51 (21-75)	53 (20-71)	52 (20-75)
Gender				
Male	130 (60)	117 (54)	128 (59)	375 (58)
Female	85 (40)	99 (46)	88 (41)	272 (42)
Race				
White	164 (76)	176 (82)	167 (77)	507 (78)
Black	45 (21)	36 (17)	42 (19)	123 (19)
Asian	5 (2)	2 (1)	3 (1)	10 (2)
Other	1 (1)	2 (1)	4 (2)	7 (1)
BMI				
< 30 kg/m^2	151 (70)	152 (70)	159 (74)	462 (71)
> 30 kg/m^2	64 (30)	64 (30)	57 (26)	185 (29)

Characteristics	HARVONI 8 Weeks N= 215 n (%)	HARVONI + RBV 8 Weeks N = 216 n (%)	HARVONI 12 Weeks N = 216 n (%)	Total N = 647 n (%)
Viral Load				
HCV RNA Log_{10} IU/mL	6.5 ± 0.8	6.4 ± 0.7	6.4 ± 0.8	6.4 ± 0.7
< 800,000 copies/mL	34 (15)	45 (21)	44 (20)	123 (19)
≥ 800,000 copies/mL	181 (84)	171 (79)	172 (80)	524 (81)
HCV genotype				
1a	171 (80)	172 (80)	172 (80)	515 (80)
1b	43 (20)	44 (20)	44 (20)	131 (20)
1 (no confirmed subtype)	1 (< 1)			1 (< 1)
IL28B				
CC	56 (26)	60 (28)	56 (26)	172 (27)
Non-CC	159 (74)	156 (72)	160 (74)	475 (73)
Interferon Eligible Status				
Eligible	202 (94)	203 (94)	201 (93)	606(94)

Treatment-Naïve Patients with or without Cirrhosis (ION-1 [Study 0102])

Trial Design

The trial design of Study ION-1 is described in Table 13.

Table 13. Summary of Trial Design in Treatment Naïve[a] Patients with or without Cirrhosis (ION-1)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, ongoing, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO +/- RBV 1000 or 1200 mg/day, BID, PO	HARVONI	12 weeks
		HARVONI + RBV	12 weeks
		HARVONI	24 weeks
		HARVONI + RBV	24 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day
a. Patients were treatment naïve (defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct acting antiviral agent at the time of enrollment), with genotype 1 CHC, including those with cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and stratified by the presence or absence of cirrhosis and HCV genotype (1a vs. 1b).

Demographic and Baseline Characteristics

Demographic characteristics for patients in ION-1 are provided in Table 14.

Table 14. Demographic and Other Baseline Characteristics of HCV Treatment-Naïve Patients with or without Cirrhosis (ION-1)

Characteristics	HARVONI 12 Weeks N = 214 n (%)	HARVONI + RBV 12 Weeks N = 217 n (%)	HARVONI 24 Weeks N = 217 n (%)	HARVONI + RBV 24 Weeks N = 217 n (%)	Total N= 865 n (%)
Age (years) Mean (range)	52 (18–75)	52 (18-78)	53 (22-80)	54 (24-77)	52 (18-80)
Gender					
Male	127 (59)	128 (59)	139 (64)	119 (55)	513 (59)
Female	87 (41)	89 (41)	78 (36)	98 (45)	352 (41)
Race					
White	187 (87)	188 (87)	177 (82)	183 (84)	735 (85)
Black	24 (11)	26 (12)	32 (15)	26 (12)	108 (13)
Asian	1 (1)	0	5 (2)	5 (2)	11 (1)
Other	2 (1)	3 (1)	3 (1)	3 (1)	11 (1)
BMI					
< 30 kg/m^2	176 (82)	171 (79)	168 (77)	177 (82)	692 (80)
> 30 kg/m^2	38 (18)	46 (21)	49 (23)	40 (18)	173 (20)
Viral Load					
HCV RNA Log_{10} IU/mL	6.4 ± 0.7	6.4 ± 0.6	6.3 ± 0.7	6.3 ± 0.7	6.4 ± 0.7
< 800,000 copies/mL	45 (21)	44 (20)	49 (23)	44 (20)	182 (21)
≥ 800,000 copies/mL	169 (80)	173 (80)	168 (77)	173 (79)	683 (79)
HCV genotype	144 (67)	148 (68)	146 (67)	143 (66)	581 (67)
1a	66 (31)	68 (31)	68 (31)	71 (33)	273 (32)
1b	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	4 (< 1)
1 (no confirmed subtype)					
IL28B					
CC	55 (26)	76 (35)	52 (24)	73 (34)	256 (30)
Non-CC	159 (74)	141 (65)	165 (76)	144 (66)	609 (70)
Interferon Eligible Status Eligible	200 (93)	197 (91)	198 (91)	203 (94)	798 (92)
Cirrhosis					
Yes	34 (16)	33 (15)	33 (15)	36 (17)	136 (16)
No	178 (83)	182 (84)	184 (85)	181 (83)	726 (84)

Treatment Experienced Patients with or without Cirrhosis (ION-2 [Study 0109])

Trial Design

The trial design of Study ION-2 is described in Table 15.

Table 15. Summary of Trial Design in Treatment Experienced[a] Patients with or without Cirrhosis (ION-2)

Trial Design	Dosage and Route of Administration	Treatment Regimen	Total Duration
Phase 3, randomized, open label, multicentre	HARVONI (90 mg/400 mg), QD, PO RBV 1000 or 1200 mg/day, BID, PO	HARVONI	12 weeks
		HARVONI + RBV	12 weeks
		HARVONI	24 weeks
		HARVONI + RBV	24 weeks

RBV = ribavirin; PO = orally; QD = once a day; BID = twice a day

a. Patients were treatment experienced (those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor) genotype 1 CHC, with or without cirrhosis. Patients were randomized in a 1:1:1:1 ratio to one of the four treatment groups and 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 Other Baseline Characteristics

Demographic characteristics for patients in ION-2 are provided in Table 16.

Table 16. Demographic and Other Baseline Characteristics of HCV Treatment-Experienced Patients with or without Cirrhosis (ION-2)

Characteristics	HARVONI 12 Weeks N = 109 n (%)	HARVONI + RBV 12 Weeks N = 111 n (%)	HARVONI 24 Weeks N = 109 n (%)	HARVONI + RBV 24 Weeks N = 111 n (%)	Total N = 440 n (%)
Age (years)					
Mean (range)	56 (24–67)	57 (27-75)	56 (25-68)	55 (28-70)	56 (24-75)
Gender					
Male	74 (68)	71 (64)	74 (68)	68 (61)	287 (65)
Female	35 (32)	40 (36)	35 (32)	43 (39)	153 (35)
Race					
White	84 (77)	94 (85)	91 (83)	89 (80)	358 (81)
Black	24 (22)	16 (14)	17 (16)	20 (18)	77 (18)
Asian	1 (1)	0	0	0	1 (<1)
Other	0	1 (1)	1 (1)	2 (2)	4 (1)
BMI					
< 30 kg/m^2	66 (61)	74 (67)	75 (69)	82 (74)	297 (68)
> 30 kg/m^2	43 (39)	37 (33)	34 (31)	29 (26)	143 (32)
Viral Load					
HCV RNA Log10 IU/mL	6.5 ± 0.4	6.4 ± 0.5	6.4 ± 0.6	6.5 ± 0.6	6.5 ± 0.5
< 800,000 copies/mL	6 (5)	13 (12)	16 (15)	15 (13)	50 (11)
≥ 800,000 copies/mL	103 (95)	98 (88)	93 (85)	96 (87)	390 (89)
HCV genotype					
1a	86 (79)	88 (79)	85 (78)	88 (79)	347 (79)
1b	23 (21)	23 (21)	24 (22)	23 (21)	93 (21)
IL28B					

Characteristics	HARVONI 12 Weeks N = 109 n (%)	HARVONI + RBV 12 Weeks N = 111 n (%)	HARVONI 24 Weeks N = 109 n (%)	HARVONI + RBV 24 Weeks N = 111 n (%)	Total N = 440 n (%)
CC	10 (9)	11 (10)	16 (15)	18 (16)	55 (13)
Non-CC	99 (91)	100 (90)	93 (85)	93 (84)	385 (88)
Cirrhosis					
Yes	22 (20)	22 (20)	22 (20)	22 (20)	88 (20)
No	87 (80)	88 (79)	86 (79)	89 (80)	350 (80)
Response to Prior HCV Treatment					
Peg-IFN +RBV	43 (39)	47 (42)	58 (53)	59 (53)	207 (47)
Relapse/ Breakthrough[a]	21 (49)	23 (49)	25 (43)	32 (54)	101 (49)
Non-Responder[b]	22 (51)	24 (51)	33 (57)	27 (49)	106 (51)
Null	17 (77)	12 (50)	19 (58)	16 (59)	64 (60)
Partial	5 (23)	12 (50)	14 (42)	11 (41)	42 (40)
PI+ Peg-IFN +RBV	66 (61)	64 (58)	50 (46)	51 (46)	231 (53)
Relapse/ Breakthrough[a]	39 (59)	42 (66)	35 (70)	28 (55)	144 (62)
Non-Responder[b]	27 (41)	22 (34)	15 (30)	23 (45)	87 (38)

a. Relapse/Breakthrough: Patient achieved undetectable HCV RNA levels (HCV RNA < LLOQ [Lower Limit of Quantitation]) during treatment or within 4 weeks of the end of treatment, but did not achieve SVR.

b. Non-Responder: Patient did not achieve undetectable HCV RNA levels (HCV RNA ≥ LLOQ) while on treatment.

Previously-Treated Patients with Compensated Cirrhosis [SIRIUS (Study 0121)]

SIRIUS was a randomized, double-blind and placebo-controlled trial that evaluated the efficacy of HARVONI+RBV for 12 weeks or HARVONI without RBV for 24 weeks in genotype 1 CHC patients with compensated cirrhosis who failed prior therapy with a Peg−IFN+RBV regimen followed by a subsequent failure with a protease inhibitor (PI)-based regimen (Peg-IFN+RBV+ an HCV PI) . Patients were randomized in a 1:1 ratio to receive HARVONI for 24 weeks or placebo for 12 weeks followed by HARVONI+RBV for 12 weeks. Randomization 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 randomized 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 was 96% (74/77, 95% CI: 89.0% to 99.2%) and 97% (75/77, 95% CI: 90.9% to 99.7%) in patients treated with HARVONI+RBV for 12 weeks and HARVONI for 24 weeks without RBV, respectively.

All 5 patients who did not achieve SVR12 relapsed.

Patients with Other HCV Genotypes

Genotype 2

In a Phase 2 open-label trial (LEPTON), the safety and efficacy of HARVONI were evaluated in 26 treatment-naïve or treatment-experienced patients with genotype 2 HCV infection, with or without cirrhosis. The SVR12 rate was 96% (25/26). Two patients had cirrhosis and both achieved SVR. The patient who did not achieve SVR12 withdrew consent and discontinued from the study after receiving a single dose of HARVONI.

Genotype 3

In a Phase 2 open-label trial, the safety and efficacy of HARVONI were evaluated with or without RBV in 51 treatment-naïve patients and 50 treatment-experienced patients, with genotype 3 HCV infection, with or without cirrhosis. Treatment-naïve 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. SVR12 rates in treatment-naïve patients were 64% (16/25) and 100% (26/26) in the HARVONI and HARVONI + RBV treatment groups, respectively. SVR12 rates in treatment-naïve patients with cirrhosis were 25% (1/4) and 100% (6/6) in the HARVONI and HARVONI + RBV treatment groups, respectively. The SVR12 rate in treatment-experienced patients was 82% (41/50). The SVR12 rate in treatment-experienced patients with cirrhosis was 73% (16/22). Eight patients relapsed and one patient experienced on-treatment virologic failure. The safety of HARVONI with or without RBV was comparable to that observed in patients with genotype 1 HCV infection treated with HARVONI with or without RBV in Phase 3 clinical trials.

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 cirrhosis. Study 1119 enrolled 44 treatment-naïve or treatment-experienced patients with genotype 4 CHC, with or without cirrhosis. Study ION-4 enrolled 8 treatment-naïve or treatment-experienced patients with genotype 4 CHC who are co-infected with HIV-1, none of whom had cirrhosis.

In Study 1119, the SVR12 was 93% (95% [21/22] in treatment-naïve patients and 91% [20/22] in treatment-experienced patients). All 3 patients who failed to achieve SVR12 relapsed; SVR12 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 CHC, with or without cirrhosis.

The SVR12 rate was 93% (90% [19/21] in treatment-naïve patients and 95% [19/20] in treatment-experienced patients). The SVR12 was 89% (8/9) in patients with cirrhosis. Of the 3 patients who failed to achieve SVR12, 2 patients relapsed and one patient was lost to follow-up.

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 CHC, with or without cirrhosis. The SVR12 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).

Clinical Trials in Patients with HCV/HIV-1 Co-infection

ION-4 was an open-label clinical trial that evaluated the safety and efficacy of 12 weeks of treatment with HARVONI without RBV in HCV treatment-naïve and treatment-experienced patients with genotype 1 or 4 CHC who were co-infected 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 disoproxil fumarate (TDF), administered with efavirenz, rilpivirine or raltegravir.

Of the 335 treated patients, the mean age was 52 years (range: 26 to 72); 82% of the patients were male; 18% were female; 61% were White; 34% were Black; 5% were classified as “Other” race; mean body mass index was 27 kg/m^2 (range: 18 to 66 kg/m^2); 75%, 23% and 2% had genotype 1a, 1b and 4 HCV infection, respectively; 76% had non-C/C IL28B alleles (CT or TT); 24% had the CC IL28B allele; 89% had a viral load ≥ 800, 000 IU/mL; and 20% had compensated cirrhosis. Fifty-five percent (55%) of the patients were treatment-experienced.

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 RBV in genotype 1 and 4 CHC patients who have undergone liver transplantation and/or who have decompensated liver disease. The two trials were identical in study design and were pooled for analysis. Patients were enrolled in one of the seven groups based on liver transplantation status and severity of hepatic impairment (see Table 24) (Cohort A, Patients without a liver transplant; and Cohort B, Post-transplantation). Patients with a CPT score >12 were excluded. Within each group, patients were randomized 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 mean age was 58 years (range: 21 to 81); 77% of the patients were male; 23% were female; 91% were White; 5% were Black; 3% were classified as “Other” race; mean body mass index was 28 kg/m^2 (range: 18 to 49 kg/m^2); 60%, 34% and 6% had genotype 1a, 1b, and 4 HCV infection, respectively; 81% had non-C/C IL28B alleles (CT or TT); 19% had the IL28B CC allele; 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.

Clinical Trials in Patients with Renal Impairment

Study GS-US-334-0154 was an open-label clinical trial that evaluated 12 weeks of treatment with HARVONI in 18 adult patients without cirrhosis or with compensated cirrhosis, with CHC genotype 1 and severe renal impairment without dialysis. At baseline, two patients (11%) had cirrhosis and the mean eGFR was 24.9 mL/min (range: 9.0-39.6). The SVR rate was 100% (18/18).

Study GS-US-337-4063 was an open-label three-arm clinical trial that evaluated 8, 12, and 24 weeks of treatment with HARVONI in a total of 95 adult patients without cirrhosis or with compensated cirrhosis, with genotype 1 (72%), 2 (22%), 4 (2%), 5 (1%), or 6 (2%) CHC and ESRD requiring dialysis: 45 treatment-naïve genotype 1 HCV-infected patients without cirrhosis received HARVONI for 8 weeks; 31 treatment-experienced genotype 1 HCV-infected patients and treatment-naïve or treatment-experienced patients with genotype 2, 5, and 6 infection without cirrhosis received HARVONI for 12 weeks; and 19 genotype 1, 2, and 4 HCV-infected patients with compensated cirrhosis received HARVONI for 24 weeks. Of the 95 total patients, at baseline, 20% of patients had cirrhosis, 22% were treatment experienced, 21% had received a kidney transplant, 92% were on hemodialysis, and 8% were on peritoneal dialysis; mean duration on dialysis was 11.5 years (range: 0.2 to 43.0 years). The SVR rates for the 8, 12, and 24 week HARVONI treatment groups were 93% (42/45), 100% (31/31), and 79% (15/19), respectively. Of the 7 patients who did not achieve SVR12, none experienced virologic failure or relapsed.

Pediatrics (12 to < 18 years of age)

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

14.2 Study Results

Clinical Trials in Patients with Genotype 1 CHC

Treatment-Naïve Patients without Cirrhosis (ION-3 [Study 0108])

The response rates for the treatment groups in the ION-3 trial are presented in Table 17. All treatment groups met the primary efficacy endpoint. The 8-week treatment of HARVONI without RBV was noninferior to the 8-week treatment of HARVONI with ribavirin (treatment difference 0.9%; 95% confidence interval (CI): -3.9% to 5.7%) and the 12-week treatment of

HARVONI (treatment difference -1.4%; 97.5% CI: -6.4% to 3.6%). Among patients with a baseline HCV RNA <6 million IU/mL, the SVR rates were similar between 8-week and 12-week treatments of HARVONI. Among patients with a baseline HCV RNA ≥6 million IU/mL, patients treated for 8 weeks had a numerically lower SVR rate compared to those treated for 12 weeks.

Table 17. Virologic Outcome in HCV Treatment-Naïve Patients without Cirrhosis (ION-3)

	HARVONI 8 Weeks N = 215 % (n/N)	HARVONI+ RBV 8 Weeks N = 216 % (n/N)	HARVONI 12 Weeks N = 216 % (n/N)
Overall SVR12[a]	94 (202/215)	93 (201/216)	95 (206/216)
95% CI[b]	89.9 to 96.7	88.8 to 96.1	91.7 to 97.8
HCV RNA <6 million IU/mL at BL	97 (119/123)	96 (133/138)	96 (126/131)
HCV RNA ≥ 6 million IU/mL at BL	90 (83/92)	87 (68/78)	94 (80/85)
HCV RNA <LLOQ[c] by Visits			
HCV RNA < LLOQ at treatment week 4	100 (215/215)	99 (211/213)	100 (216/216)
HCV RNA < LLOQ at treatment week 12 (end of treatment)	N/A	N/A	99 (210/211)
Outcome for patients without SVR			
Overall Virologic Failure	5 (11/215)	4 (9/214)	1 (3/216)
On-Treatment Virologic Failure	0/215	0/216	0/216
Overall Relapse[d]	5 (11/215)	4 (9/214)	1 (3/216)
HCV RNA <6 million IU/mL at BL	2 (2/123)	2 (3/137)	2 (2/131)
HCV RNA ≥ 6 million IU/mL at BL	10 (9/92)	8 (6/77)	1 (1/85)
Lost to Follow Up	<1 (1/215)	2 (5/216)	2 (5/216)
Other[e]	<1 (1/215)	<1 (1/216)	1 (2/216)
Death	0	0	0
Discontinuation			
Due to AE	0	<1 (1/216)	1 (2/216)
Due to Other[f]	0	1 (2/216)	1 (3/216)

BL = baseline; N/A = not applicable

a. SVR12= Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.

b. The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.

c. Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected). 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. The assay had a LLOQ of 25 IU per mL.

d. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
e. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).
f. Other includes patients who did not complete study treatment due to lost to follow up and non-compliance with study drug.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 18.

Table 18. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients without Cirrhosis (ION-3)

Study Outcomes	HARVONI 8-Weeks N=215 % (n/N)	HARVONI + RBV 8-Weeks N=216 % (n/N)	HARVONI 12-Weeks N=216 % (n/N)
Genotype[a]			
1a	93 (159/171)	92 (159/172)	95 (163/172)
1b	98 (42/43)	95 (42/44)	98 (43/44)
Viral Load[a] (HCV RNA Log_{10} IU/ml)			
< 800,000	97 (33/34)	96 (43/45)	96 (42/44)
≥ 800,000	93 (169/181)	92 (158/171)	95 (164/172)
IL28B[a]			
CC	96 (54/56)	95 (57/60)	96 (54/56)
Non-CC	93 (148/159)	92 (144/156)	95 (152/160)
BMI[a]			
< 30 Kg/m^2	93 (141/151)	91 (139/152)	95 (151/159)
≥ 30 Kg/m^2	95 (61/64)	97 (62/64)	97 (55/57)
Interferon eligible patients[a]			
Eligible	94 (190/202)	93 (188/203)	96 (192/201)

a. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, non-CC IL28B allele) had no impact on SVR12 rates.

Treatment-Naïve Patients with or without Cirrhosis (ION-1 [Study 0102])

The response rates for the treatment groups of HARVONI with or without ribavirin for 12 weeks in the ION-1 trial are presented in Table 19. The interim primary endpoint analysis for SVR included all patients enrolled in the 12-week treatment groups (N = 431). The 12-week treatment groups met the primary efficacy endpoint. SVR rates for all patients enrolled in the 24 week treatment groups (N= 434) were not available at the time of interim analysis. However, a total of 197 patients had both post-treatment Week 12 and 24 data available for a concordance analysis (47 patients in the HARVONI 12 Week treatment group, 51 patients in the HARVONI+RBV 12 Week treatment group, 49 patients in the HARVONI 24 Week treatment group, and 50 patients in the HARVONI+RBV 24 Week treatment group). Each of the 197 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% for all groups.

Table 19. Virologic Outcome in HCV Adult Treatment-Naïve Patients with or without Cirrhosis (ION-1)

	HARVONI 12 Weeks N = 214 % (n/N)	HARVONI + RBV 12 Weeks N = 217 % (n/N)
SVR12[a]	98 (209/214)	97 (211/217)
95% CI[b]	94.6 to 99.2	94.1 to 99.0
HCV RNA < LLOQ[c] by visit		
HCV RNA <LLOQ[c] at treatment week 4	100 (213/213)	99 (215/217)
HCV RNA <LLOQ[c] at treatment week 12 (end of treatment for 12 week group)	100 (213/213)	100 (214/214)
Outcome for patients without SVR		
Overall Virologic Failure	<1 (1/214)	0/217
On-Treatment Virologic Failure	0/214	0/217
Relapse[d]	<1 (1/213)	0/217
Lost to Follow Up	1 (2/214)	1 (2/217)
Other[e]	1 (2/214)	1 (3/217)
Death	0	0
Discontinuation		
Due to AE	0	0
Due to Other[f]	1 (2/214)	2 (4/217)

N/A = Not Applicable

a. SVR12 = Sustained virologic response, defined as HCV RNA less than LLOQ at 12 weeks (Lower Limit of Quantitation, 25 IU/mL) after the cessation of treatment.
b. The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.
c. Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).
d. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
e. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).
f. Other includes patients who did not complete study treatment due to lost to follow up, withdrew consent, protocol violation, lack of efficacy and pregnancy.

Subgroup analyses were performed for the primary efficacy endpoint (SVR12) for selected subgroups. Response rates for some of these subgroups are presented in Table 20.

Table 20. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Naïve Patients with or without Cirrhosis (ION-1)

Study Outcomes	HARVONI 12-Weeks N=214 % (n/N)	HARVONI + RBV 12-Weeks N=217 % (n/N)
Genotype[a],		
1a	97 (139/144)	97 (143/148)
1b	100 (66/66)	99 (67/68)
Viral Load[a] (HCV RNA Log_{10} IU/ml)		
< 800,000	98 (44/45)	93 (41/44)
≥ 800,000	98 (165/169)	98 (170/173)
IL28B[a]		
CC	100 (55/55)	97 (74/76)
Non-CC	97 (154/159)	97 (137/141)
Cirrhosis		
Yes	94 (32/34)	100 (33/33)
No	98 (177/180)	97 (178/184)
BMI		
< 30 Kg/m^2	98 (172/176)	97 (166/171)
≥ 30 Kg/m^2	97 (37/38)	98 (45/46)

a. The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, cirrhosis, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates.

Treatment Experienced Patients with or without Cirrhosis (ION-2 [Study 0109])

The response rates for the treatment groups in study ION-2 are presented in Table 21. All treatment groups met the primary efficacy endpoint. A total of 98 patients in the HARVONI 12 Week treatment arm and 107 patients in the HARVONI+RBV 12 Week treatment arm had both post-treatment Week 12 and 24 data available for a concordance analysis. Each of the 205 patients who achieved SVR12 also achieved SVR24, resulting in a positive predictive value of 100.0% in both groups.

Table 21. Virologic Outcome in Treatment-Experienced HCV Patients with or without Cirrhosis (ION-2)

	HARVONI 12 Weeks N=109 % (n/N)	HARVONI +RBV 12 Weeks N=111 % (n/N)	HARVONI 24 Weeks N=109 % (n/N)	HARVONI +RBV 24 Weeks N=111 % (n/N)
SVR12[a]	94 (102/109)	96 (107/111)	99 (108/109)	99 (110/111)
95% CI[b]	87.2 to 97.4	91.0 to 99.0	95.0 to 100.0	95.1 to 100.0
SVR24[c]	94 (102/109)	96 (107/111)	99 (108/109)	99 (110/111)
HCV RNA <LLOQ[d] by Visit				

	HARVONI 12 Weeks N=109 % (n/N)	HARVONI +RBV 12 Weeks N=111 % (n/N)	HARVONI 24 Weeks N=109 % (n/N)	HARVONI +RBV 24 Weeks N=111 % (n/N)
HCV RNA <LLOQ[d] at treatment week 4	100 (109/109)	99 (110/111)	99 (108/109)	99 (110/111)
HCV RNA <LLOQ[d] at treatment week 12 (end of treatment for 12 week group)	99 (108/109)[e]	100 (111/111)	100 (109/109)	100 (110/110)
HCV RNA <LLOQ[d] at treatment week 24 (end of treatment)	N/A	N/A	100 (107/107)	100 (110/110)
Outcome for patients without SVR				
Overall Virologic Failure	6 (7/109)	4 (4/111)	0/109	1 (1/111)
On-Treatment Virologic Failure	0/109	0/111	0/109	1 (1/111)[f]
Relapse[g]	6 (7/108)	4 (4/111)	0/109	0/110
Lost to Follow Up	0/109	0/111	0/109	0/111
Other[h]	0/109	0/111	1 (1/109)	0/111
Death	0	0	0	0
Discontinuation				
Due to AE	0	0	0	0
Due to Other[i]	0	0	2 (2/109)	1 (1/111)

N/A = not available

a. SVR12, Sustained virologic response, defined as HCV RNA less than LLOQ (Lower Limit of Quantitation, 25 IU/mL) at 12 weeks after the cessation of treatment.
b. The exact 95% CI for the proportion of within treatment group was based on the Clopper-Pearson method.
c. SVR24, defined as HCV RNA less than LLOQ (25 IU/mL) at 24 weeks after cessation of treatment.
d. Number of patients reporting HCV RNA less than LLOQ detected + the number of patients with HCV RNA less than LLOQ TND (target not detected).
e. The one patient who did not achieve HCV RNA <LLOQ at the last on treatment visit achieved SVR12.
f. This patient was discontinued after 6 weeks of treatment due to lack of efficacy (rebound) and never achieved HCV RNA <LLOQ. Plasma concentrations of GS-331007 and LDV at weeks 2, 4 and 6 were indicative of noncompliance with the study drug at or around these study visits.
g. The denominator for relapse is the number of patients with HCV RNA < LLOQ at their last on-treatment assessment.
h. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (excluding lost to follow-up).
i. Other includes patients who did not complete study treatment due to protocol violation and lack of efficacy.

Response rates for selected subgroups are presented in Table 22.

Table 22. Sustained Virologic Response (SVR) for Selected Baseline Subgroups of Treatment-Experienced Patients with or without Cirrhosis (ION-2)

Study Outcomes	HARVONI 12 Weeks N=109 % (n/N)	HARVONI +RBV 12 Weeks N=111 % (n/N)	HARVONI 24 Weeks N=109 % (n/N)	HARVONI +RBV 24 Weeks N=111 % (n/N)
Genotype[a]				
1a	95 (82/86)	95 (84/88)	99 (84/85)	99 (87/88)
1b	87 (20/23)	100 (23/23)	100 (24/24)	100 (23/23)
Viral Load[a] (HCV RNA Log_{10} IU/ml)				
< 800,000	83 (5/6)	100 (13/13)	100 (16/16)	100 (15/15)
≥ 800,000	94 (97/103)	96 (94/98)	99 (92/93)	99 (95/96)
Cirrhosis[a]				
Yes	86 (19/22)	82 (18/22)	100 (22/22)	100 (22/22)
No	95 (83/87)	100 (89/89)	99 (86/87)	99 (88/89)
IL28B[a]				
CC	100 (10/10)	100 (11/11)	100 (16/16)	94 (17/18)
Non-CC	93 (92/99)	96 (96/100)	99 (92/93)	100 (93/93)
BMI[a]				
< 30 Kg/m^2	92 (61/66)	96 (71/74)	99 (74/75)	99 (81/82)
≥ 30 Kg/m^2	95 (41/43)	97 (36/37)	100 (34/34)	100 (29/29)
Response to Prior HCV Therapy[a]				
Relapse/ Breakthrough	95 (57/60)	97 (63/65)	100 (60/60)	98 (59/60)
Non-Responder	92 (45/49)	96 (44/46)	98 (48/49)	100 (51/51)
Prior HCV Therapy[a]				
PI + PEG-IFN + RBV	94 (62/66)	97 (62/64)	98 (49/50)	100 (51/51)
PEG-IFN + RBV	93 (40/43)	96 (45/47)	100 (58/58)	98 (58/59)
Cirrhosis by Prior HCV Therapy[a]				
PI + PEG-IFN + RBV				
Yes	86 (12/14)	85 (11/13)	100 (14/14)	100 (13/13)
No	96 (50/52)	100 (51/51)	97 (35/36)	100 (38/38)
PEG-IFN + RBV				
Yes	88 (7/8)	78 (7/9)	100 (8/8)	100 (9/9)
No	94 (33/35)	100 (38/38)	100 (50/50)	98 (49/50)

a. The exact 95% confidence interval (CI) for the proportion within treatment group and subgroup is based on the Clopper-Pearson method. The results were within the 90% CI for all treatment groups.

Host and viral factors that have been traditionally predictive of or associated with lower rates of SVR (eg, African-American race, high BMI, genotype 1a, high viral load, non-CC IL28B allele) had no impact on SVR12 rates. Treatment-experienced patients with cirrhosis who received 12 weeks of treatment showed numerically lower SVR rates compared with treatment-experienced patients with cirrhosis who received 24 weeks of treatment (±RBV).

Clinical Trials in Patients with HCV/HIV-1 Co-infection

Table 23 presents the response rates in the ION-4 trial after 12 weeks of HARVONI treatment.

Table 23. Virologic Outcome in Patients with HCV/HIV-1 Co-infection (ION-4)

	HARVONI 12 Weeks Genotype 1 N = 327 (%)	HARVONI 12 Weeks Genotype 4 N = 8 (%)
SVR	313 (96)	8 (100)
Outcome for patients without SVR		
On-Treatment Virologic Failure	2 (<1)	0
Relapse[a]	10 (3)	0
Other[b]	2 (<1)	0
Cirrhosis		
Yes	250/260 (96)	0
No	63/67 (94)	8/8 (100)
Prior HCV Treatment		
Treatment-Naïve	138/146 (95)	4/4 (100)
Treatment-Experienced	175/181 (97)	4/4 (100)
Treatment-Experienced patients with cirrhosis	46/47 (98)	0

a. The denominator for relapse is the number of patients with HCV RNA < LLOQ (Lower Limit of Quantitation) at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (eg, lost to follow-up).

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

The relapse rate in the ION-4 trial in Black patients was 9% (10/115), all of whom were IL28B non-CC genotype, and none in non-Black patients (0/220). In the ION-1, ION-2, and ION-3 HCV mono-infection studies, relapse rates were 3% (10/305) in Black patients and 2% (26/1637) in non-Black patients.

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

Table 24 presents the SVR rates in patients with genotype 1 CHC (pooled results for SOLAR-1 and SOLAR-2). Overall, 92.7% (569 of 614) patients with genotype 1 CHC achieved the primary endpoint, SVR12.

No patients experienced on-treatment virologic failure. Of the 45 genotype 1 patients who did not achieve SVR12, 20 relapsed, 22 died, and 3 could not be assessed for SVR12 due to withdrawal of consent (n=2) or never had HCV RNA < LLOQ prior to obtaining a post-treatment Week 12 HCV RNA result (n=1).

Table 24. Sustained Virologic Response and Relapse Rates in Genotype 1 CHC patients (pooled SOLAR-1 and SOLAR-2)[a, b, c]

	HARVONI+RBV 12 weeks N=307[d, e]		HARVONI+RBV 24 weeks N=307[d, e]	
	SVR12 (%[n/N])	**Relapse (%[n/N])**	**SVR12 (%[n/N])**	**Relapse (%[n/N])**
Pretransplant[f] (Cohort A)				
CPT B (Group 1)	87% (45/52)	12% (6/51)	92% (46/50)	4% (2/48)
CPT C (Group 2)	88% (35/40)	5% (2/37)	83% (38/46)	7% (3/41)
Post-transplant[g] (Cohort B)				
Metavir score F0-F3 (Group 3)	95% (94/99)	3% (3/97)	99% (99/100)	0/99
CPT A (Group 4)	98% (55/56)	0/55	96% (51/53)	0/51
CPT B (Group 5)	89% (41/46)	2% (1/42)	96% (43/45)	0/43
CPT C (Group 6)	57% (4/7)	33% (2/6)	78% (7/9)	13% (1/8)
Fibrosing cholestatic hepatitis (Group 7)	100% (7/7)	0/7	100% (4/4)	0/4

a. Deaths and those patients with “other” virologic outcome were considered treatment failures. For relapse rates, deaths and those patients with 'Other' virologic outcome (ie, who did not achieve SVR12 or meet virologic failure criteria) are excluded from the analysis.
b. Relapse to post-treatment Week 12 = confirmed HCV RNA ≥ LLOQ (Lower Limit of Quantitation) during the post-treatment period up to post-treatment Day 146 having achieved HCV RNA < LLOQ at last on-treatment visit.
c. Patients who did not achieve SVR12 and did not have virologic failure prior to post-treatment Day 146; and patients transplanted while on treatment or prior to post-treatment Day 70 with HCV RNA < LLOQ at last HCV RNA prior to transplant were excluded from analysis.
d. Twelve patients transplanted prior to post-treatment Week 12 with HCV RNA<LLOQ at last measurement prior to transplant were excluded.
e. 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.
f. Pretransplantation means patients who have never undergone transplantation and includes those who are on the waitlist to receive liver transplant (were expected to be at least 12 weeks from transplantation).
g. Post-transplantation includes patients who have undergone at least one liver transplant

In genotype 4 CHC post-liver transplant patients without cirrhosis or with compensated cirrhosis treated for 12 weeks (N=12) or 24 weeks (N=10), respectively, the SVR12 rates were similar to that seen to rates reported with genotype 1 CHC. No patients relapsed. There is limited data in patients with genotype 4 CHC and decompensated cirrhosis (pre- and post-liver transplantation). Therefore, the safety and efficacy in patients with genotype 4 CHC and decompensated cirrhosis (pre- and post-liver transplantation) could not be established.

A total of 123 patients with HCV and decompensated cirrhosis (pre- or post-transplant), who achieved SVR12 and had post-treatment Week 12 laboratory data available, were assessed for changes from baseline in their MELD and CPT scores.

Change in MELD score: 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 ≥ 15 at baseline, 59% (19/32) had a MELD score < 15 at post-treatment Week 12. Improvement in MELD scores was driven largely by improvement in bilirubin.

Change in CPT: 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 patients 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 scores was driven largely by improvement in bilirubin.

15 MICROBIOLOGY

Antiviral Activity in Cell Culture

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). Ledipasvir has EC_{50} values of 21 nM in genotype 2a and 16 nM against the genotype 2b replicons that have leucine at amino acid position 31 (L31) in NS5A, but has a significantly reduced activity against the genotype 2a replicon (EC_{50} = 249 nM) and the genotype 2b replicon (EC_{50} = 530 nM) that both have methionine at position 31 (M31) as well as genotype 3 replicons (EC_{50} = 168 nM). In addition, ledipasvir is active against genotypes 4a, 5a, and 6a, with EC_{50} values of 0.39 nM, 0.15 nM, and 1.1 nM, respectively. Ledipasvir has substantially lower activity against genotypes 2a, 2b, 3a, and 6e with EC_{50} values of 21-249 nM, 168 nM, and 264 nM, respectively. The presence of 40% human serum reduced anti-HCV activity of ledipasvir by 12-fold against genotype 1a HCV replicon.

Sofosbuvir exhibits pan-genotypic anti-HCV activity. 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 14 to 110 nM. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 62 nM for genotype 1a (range 29-128 nM; N=67), 102 nM for genotype 1b (range 45-170 nM; N=29), 29 nM for genotype 2 (range 14-81 nM; N=15), and 81nM for genotype 3a (range 24-181 nM; N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 30 and 20 nM, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir.

Since there is about 65% homology of the HCV NS5B polymerase across HCV genotypes, and since GS-461203 binds to a highly conserved region of RdRp, sofosbuvir is a pan-genotypic inhibitor of the HCV NS5B polymerase with a high barrier to resistance. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0.7 to 2.6 μM. GS-461203 is not an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

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

Antiviral Activity *in vivo*

In patients taking HARVONI, an average HCV RNA viral load decline of -4.5 (log_{10} IU/ml) was observed by Week 1 of treatment.

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 1000-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 conferred 2- to 18-fold reduced susceptibility to sofosbuvir and reduced the replication viral 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 Trials

Genotype 1

In a pooled analysis of patients who received HARVONI in Phase 3 trials (ION-3, ION-1, and ION-2), 37 (2.3%) 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, M28, 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 (36.4%), Y93H (27.3%) L31M (22.7%), Y93N (18.2%), Q30H (13.6%), and M28T (9.1%). 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 (85.7%). 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 + RBV) 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.

There were 24 virologic failures (20 relapses and 4 discontinuation prior to achieving HCV RNA <LLOQ). Among post-transplant patients with compensated liver disease or patients with decompensated liver disease (pre- and post-transplant) in 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/E, L31V, H58D, and/or Y93H/C in 13/15 genotype 1a patients, and L31M, Y93H/N in 6/6 genotype 1b patients. No NS5A sequencing data was available from the remaining 3 patients who had low viral load (<1000IU/ml) at the last time point before discontinuation.

The NS5B nucleoside inhibitor resistance associated variants (NS5B NI RAVs) L159F and V321A were each detected in one patient in the Phase 3 trials. The single L159F and V321A variants demonstrated 1.2- and 1.2-fold change in EC_{50} to sofosbuvir in genotype 1a replicon, respectively. A NS5B substitution E237G 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 SOLAR-1 and SOLAR-2 trials 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 the Phase 3 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 a Phase 2 trial (LONESTAR). This patient was subsequently retreated with HARVONI + RBV 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 **14 CLINICAL TRIALS**).

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 the SOLAR-2 study, 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 Resistance Associated Variants on Treatment Outcome

Adults

Genotype 1

Analyses were conducted to explore the association between pre-existing baseline NS5A RAVs and treatment outcome. In the pooled analysis of the Phase 3 trials, 256/1618 (16%) patients had baseline NS5A RAVs identified by population or deep sequencing irrespective of subtype. Of the 256 patients with NS5A RAVs, 235 (91.5%) achieved SVR12 following 8, 12, or 24 weeks of treatment with HARVONI (± RBV). The overall SVR12 rates in patients with baseline NS5A RAVs were 90.6% (174 of 192) for genotype 1a and 95.0% (57 of 60) for genotype 1b.

In genotype 1a treatment-naïve patients with NS5A RAVs (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C), SVR12 rates of 89% (34/38) after 8 weeks and 96% (69/72) after 12 weeks of therapy were observed with HARVONI. All genotype 1b treatment-naïve patients with baseline NS5A RAVs (Y93H) achieved SVR12, regardless of treatment duration. Following HARVONI 12-week treatment, one of the 4 treatment-naïve patients who relapsed had L31M mutation at baseline while 11 other patients with L31M at baseline achieved SVR12.

In treatment-experienced patients in ION 2, a lower SVR rate of 69% (9 of 13) was observed among the small group of patients (n = 13) with NS5A RAVs conferring > 100-fold resistance to ledipasvir and who were treated with HARVONI for 12 weeks compared to 97% (93/96) in those without any baseline RAVs or RAVs conferring a fold-change of ≤100. All treatment-experienced patients with NS5A RAVs conferring ≤ 100-fold resistance had SVR12.

In HCV/HIV-1 co-infected patients in ION-4, 31 of the 34 patients (91.2%) with NS5A RAVs achieved SVR12, while 282 of 291 patients (96.9%) without NS5A RAVs achieved SVR12. For treatment-naïve patients, 33 of 34 patients (97.1%) with NS5A resistance-associated polymorphisms (RAPs) achieved SVR12, while 105 of 110 patients (95.5%) without NS5A RAPs achieved SVR12. For treatment-experienced patients, 45 of 49 patients (91.8%) with NS5A RAPs achieved SVR12, and 130 of 132 patients (98.5%) without NS5A RAPs achieved SVR12. In another study in treatment-experienced patients with compensated cirrhosis (SIRIUS, N=77), 8/8 (100%) patients with baseline N5SA RAVs conferring >100-fold reduced susceptibility to ledipasvir achieved SVR following 12 weeks of treatment with HARVONI + RBV.

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+RBV. 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 group of NS5A RAVs that conferred >100-fold shift and were observed in patients were the following substitutions in genotype 1a (M28A, Q30H/R/E, L31M/V/I, H58D, Y93H/N/C) or in genotype 1b (Y93H). Among treatment-experienced patients who relapsed, the following resistance associated variants were detected at baseline: Q30H/R, L31M, and/or Y93H/N.

The NS5B NI RAV S282T was not detected in the baseline NS5B sequence of any patient in Phase 3 trials 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 (12 to < 18 years of age)

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 resistance-associated substitution S282T in NS5B while all ledipasvir resistance-associated substitutions in NS5A were fully susceptible to sofosbuvir. Sofosbuvir retained activity against the NS5B substitutions L159F and L320F associated with resistance to other nucleoside inhibitors. *In vitro* studies demonstrated no cross resistance between sofosbuvir and ledipasvir when tested individually against HCV mutations resistant to other classes of HCV inhibitors. Both sofosbuvir and ledipasvir have been tested against an extensive panel of known resistance-associated variants (RAVs) to other classes of DAAs with different mechanisms of actions. These included NS3 RAVs affecting HCV protease inhibitors (ie, Q80K, R155K, A156T, and D168E/G/ V in genotype 1a; A156T and D168E/G/V in genotype 1b), and NS5B RAVs known to affect NNIs (ie. L419M/S, R422K, and M423I/T in genotypes 1a and 1b) and RBV (T390I and F415Y). No cross-resistance has been observed in these studies, and sofosbuvir and ledipasvir remain highly potent against RAVs affecting inhibitor classes other than their own. NS5A substitutions conferring resistance to ledipasvir may reduce the antiviral activity of other NS5A inhibitors. The efficacy of ledipasvir/sofosbuvir has not been established in patients who have previously failed treatment with other regimens

that include an NS5A inhibitor.

Cytotoxicity

Sofosbuvir showed little or no cytotoxicity at the highest concentration tested (89 – 100 µM) in human cell lines derived from liver, prostate, lymphoid, or endothelial tissues or primary human cells isolated from the liver, circulating lymphoid cells, or bone marrow, except for Huh-7 cells where 50% cytotoxicity (CC50) was observed at 66 µM.

Ledipasvir showed little or no cytotoxicity in multiple cell lines derived from liver, lymphoid or endothelial tissue. The CC50 values ranged from 2791 nM to > 50,000 nM in 1b-Rluc 2, Huh luc, 1a-HRlucP, HepG2, MT4, and SL3 cell lines. Ledipasvir is therefore highly selective in cell-based replicon assays (Selectivity Index [SI] > 837,000 fold).

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-Dose Toxicity

Ledipasvir

No target organs of toxicity were identified with ledipasvir. Ledipasvir was well tolerated in studies for up to 4 weeks in the mouse, 6 months in the rat and 9 months in the dog. At the respective NOAELs, ledipasvir systemic exposure levels (sexes combined) were approximately 25-, 7-, and 7-fold greater in mice, rats, and dogs, respectively, than those in subjects treated with HARVONI. The only notable changes in the repeat dose toxicity studies were transient decreases in body weight gain and/or food consumption.

Sofosbuvir

Sofosbuvir or GS-9851, a 1:1 diastereomeric mixture of sofosbuvir and its stereoisomer, was evaluated in repeat-dose oral toxicity studies up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The primary target organs identified were the cardiovascular, hepatobiliary, gastrointestinal (GI) and hematopoietic (erythroid) systems. In 7-day toxicity studies with GS-9851, doses of 2000 mg/kg/day in the rat and 1500 mg/kg/day in the dog resulted in (but were not limited to) increased mucus secretions in the stomach, glycogen depletion, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, with associated histopathologic liver findings in dogs; and heart adverse effects in both rats (eg, multifocal cardiac myofiber degeneration) and dogs (eg, increased QT/QTc intervals). At the adverse dose, exposure levels (based on GS-331007 AUC) in the GS-9851 7-day toxicity studies were at least 28-fold higher than human exposure at 400 mg sofosbuvir. In a second 7-day toxicity study conducted with sofosbuvir alone in rats at doses up to 2000 mg/kg/day, no early mortalities or signs of cardiac toxicity were observed. GS-331007 exposure was 29-fold higher than human exposure at 400 mg sofosbuvir, a margin similar to that observed in the previous 7-day rat study with the stereomeric mixture (GS-9851). Findings in the liver and heart were not observed in long-term studies with GS-9851 or sofosbuvir. In chronic toxicity studies in rats (26 weeks) and dogs (39 weeks), sofosbuvir effects included (but were not limited to) GI-related clinical signs (eg, soft feces and emesis) and a decrease (eg, approximately 10%) in mean red cell indices that were observed mainly in the high-dose group of dogs. One male dog was euthanized moribund with intestinal hemorrhage. The relationship to sofosbuvir was undetermined. In general, exposure levels in the chronic toxicity studies at the no observed

adverse effect level were at least 9-fold (based on an AUC of GS-331007) higher than human exposure at 400 mg sofosbuvir.

Carcinogenicity:

Ledipasvir

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.

Sofosbuvir

Sofosbuvir was not carcinogenic in the 2-year mouse and rat carcinogenicity studies at doses resulting in GS-331007 exposures up to 17-times in mice and 9-times in rats~~,~~ higher than human exposure at 400 mg dose.

Genotoxicity:

Ledipasvir

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

Sofosbuvir, when administered as the diastereomeric mixture GS-9851, was not genotoxic in a bacterial mutagenicity assay, in an *in vitro* chromosome aberration test using human peripheral blood lymphocytes and in an *in vivo* mouse micronucleus assay.

Reproductive and Developmental Toxicology:

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.

No teratogenic effects were observed in rat and rabbit developmental toxicity studies with ledipasvir.

In a rat pre- and post-natal 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

Sofosbuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats. No teratogenic effects were observed in rat and rabbit developmental toxicity studies with

sofosbuvir. Sofosbuvir had no adverse effects on behaviour, reproduction, or development of the offspring in the rat pre- and post-natal development study. At the highest dose tested where no adverse effects were observed, exposure to the predominant circulating metabolite GS-331007 was at least 5-fold the exposure in humans at the recommended clinical dose.

Fertility was normal in the offspring of rats exposed daily from before birth (*in utero*) through lactation day 20 at daily GS-331007 exposures of approximately 7-fold higher than human exposures at the recommended clinical dose.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Sovaldi (tablet, 400 mg sofosbuvir), submission control number 202358, Product Monograph, Gilead Sciences Canada, Inc. April 28, 2017

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

HARVONI®

ledipasvir and sofosbuvir tablets

Read this carefully before you start taking **Harvoni** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Harvoni**.

Serious Warnings and Precautions

- Hepatitis B activity (eg, inflamed liver) may increase when taking antiviral drugs like **Harvoni**, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is Harvoni used for?

- **Harvoni** treats chronic (lasting longer than 6 months) hepatitis C infection in adults and children 12 years of age and older.
- **Harvoni** may be used with ribavirin, but not always. Read the ribavirin patient medication information if your doctor says you should also take ribavirin.

How does Harvoni work?

Harvoni contains two medicines, ledipasvir and sofosbuvir, that have been combined together into one tablet (pill). This type of treatment course (regimen) is also known as a single tablet regimen. It provides a complete treatment for hepatitis C. For most patients, **Harvoni** does not need to be taken with either interferon or ribavirin.

- Ledipasvir and sofosbuvir block the virus from making more copies of itself in the body.
- **Harvoni** cures chronic hepatitis C in most patients. Cure means hepatitis C virus is cleared from your blood 3 months after finishing the medicine.

What are the ingredients in Harvoni?

Each tablet has the following medicines: ledipasvir, sofosbuvir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and FD&C Yellow #6/sunset yellow FCF aluminum lake.

Harvoni comes in the following dosage forms:

Harvoni comes in orange tablets. Each tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir.

Do not use Harvoni if:

- you are allergic to ledipasvir, sofosbuvir or any of the other ingredients in this product. (Read also "**What are the ingredients in Harvoni**?" above.)
- your doctor says you should use ribavirin with **Harvoni** and you are pregnant or may become pregnant (or if your partner is pregnant or may become pregnant). Ribavirin may cause birth defects or the death of your unborn baby.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Harvoni. Talk about any health conditions or problems you may have, including if you:

- have liver problems other than hepatitis C infection.
- have had a liver transplant.
- have HIV.
- are pregnant or plan to become pregnant (see "***Pregnancy and Birth Control***" below).
- are breastfeeding or plan to breastfeed. Do NOT breastfeed while taking **Harvoni**.
- are taking anything listed in the section "**The following may interact with Harvoni**".
- if you were born with one of the rare problems of galactose intolerance (severe lactase deficiency or glucose/galactose malabsorption). **Harvoni** contains lactose.

Your doctor may monitor your blood test results during **Harvoni** treatment if you have some conditions, for example, to check:

- how well your blood can clot if you take warfarin (Coumadin®) or other similar medicines called vitamin K antagonists, to thin the blood.
- blood sugar levels if you have diabetes.
- immunosuppressant drug levels if you receive immunosuppressive therapy.

Other warnings you should know about:

Hepatitis B Reactivation:

Taking antiviral drugs such as **Harvoni** may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B.
- you know you have a current hepatitis B infection.
- you have had a previous hepatitis B infection.

Your healthcare provider may do blood tests:

- before hepatitis C treatment.
- to see the hepatitis B levels in your blood.
- and may order hepatitis B treatment.

Ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy and Birth Control:

- If you are pregnant or plan to become pregnant, ask your doctor for advice before taking this medicine. It is NOT known if **Harvoni** will harm your unborn baby.

Harvoni may be used with ribavirin. Ribavirin may cause birth defects and death of the unborn baby. Extreme care must be taken to avoid becoming pregnant.

- Females must have a negative pregnancy test before starting **Harvoni** and ribavirin, every month while on these medicines, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking **Harvoni** with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking **Harvoni** and ribavirin and for 6 months after you have stopped taking them.
- Talk to your doctor about the kind of birth control you can use.
- If you or your partner becomes pregnant while taking **Harvoni** with ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Products containing sofosbuvir:

Because **Harvoni** already contains sofosbuvir, do not take **Harvoni** with any other medicines containing sofosbuvir (eg, SOVALDI®, EPCLUSA®, VOSEVI®).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Harvoni:

- antacids (like Tums®, Rolaids® or Alka-Seltzer®) or medicines that have an ingredient to protect the stomach, used for heartburn and indigestion.
- amiodarone (Cordarone®), a drug used to treat certain irregular heartbeats (see "**What are possible side effects from using Harvoni?**").
- carbamazepine (Tegretol®), a drug used to treat seizures, nerve pain and bipolar disorder.
- digoxin (Lanoxin®, Toloxin®), a drug used to treat congestive heart failure.
- tenofovir disoproxil fumarate (ATRIPLA®, COMPLERA®, STRIBILD®, TRUVADA®, VIREAD®), to treat HIV.
- medicines for indigestion, heartburn or ulcers. Examples are nizatidine (Axid®), famotidine (Pepcid AC®, Peptic Guard®, Ulcidine®), cimetidine (Tagamet®), ranitidine (Zantac®), esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (Losec®), rabeprazole (Aciphex®) and pantoprazole (Pantoloc®).
- phenobarbital, a drug used to treat anxiety and to control seizures.
- phenytoin (Dilantin®), a drug used to control seizures.
- rifampin (Rifadin®, Rifater®, Rofact®), a drug used to treat tuberculosis.
- rifapentine, a drug used to treat tuberculosis.
- rosuvastatin (Crestor®), a drug used to treat high cholesterol and to help prevent heart attacks and strokes.
- simeprevir* (Galexos®), a drug used to treat hepatitis C.
- St. John's wort (*Hypericum perforatum*), an herbal product used for anxiety or depression.
- tipranavir (Aptivus®) or tipranavir/ritonavir (Aptivus® and Norvir®), drugs used to treat HIV.

*Drug not marketed in Canada.

How to take Harvoni:

- Take this medicine with or without food.
- Your doctor will determine how long you need to take this medicine. It can be for 8, 12 or 24 weeks.
- If you are taking an antacid, you may need to take **Harvoni** at a different time than the antacid. Talk to your doctor.
- Do NOT stop taking **Harvoni** without first talking with your doctor.

Usual dose: Adults and children 12 years of age and older

- Take one tablet once each day.

Overdose:

If you think you, or a person you are caring for, have taken too much **Harvoni**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important to take **Harvoni** each day.

- **If you miss a dose** of **Harvoni** and you notice within 18 hours, take a tablet as soon as you can. Then take the next dose at your usual time.
- **If you miss a dose** of **Harvoni** and you notice after 18 hours**,** wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What to do if you vomit (throw up):

- If you vomit **less than 5 hours** after taking **Harvoni**, take another tablet.
- If you vomit **more than 5 hours** after taking **Harvoni**, wait. Do NOT take another tablet until you are scheduled to take the next tablet.

What are possible side effects from using Harvoni?

These are not all the possible side effects you may have when taking **Harvoni**. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of **Harvoni** are: feeling tired and headache.

When **Harvoni** is used with amiodarone (a heart drug), side effects may be:

- slow heartbeat leading to a need for a pacemaker or death. (see the "**Serious side effects and what to do about them**" table below for symptoms)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Slow heartbeat (bradycardia) when taken with amiodarone (Cordarone®) with symptoms such as: • near fainting or fainting • dizziness or lightheadedness • not feeling well • feeling weak or very tired • shortness of breath • chest pains • confusion or memory problems		✓ ✓ ✓ ✓ ✓ ✓ ✓	
Serious Allergic Reactions: skin rashes with or without blisters, swelling of the face, lips, tongue or throat, trouble breathing		✓	
FREQUENCY UNKNOWN			
Stevens-Johnson Syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store **Harvoni** below 30°C (86°F).
- Keep **Harvoni** in its original container.
- Do NOT use **Harvoni** if the seal over the bottle opening is broken or missing.
- Keep this medication where children cannot reach it or see it.

If you want more information about Harvoni:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.gilead.ca), or by calling 1-800-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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