EU Risk Management Plan for
Harvoni®
(Ledipasvir/Sofosbuvir Fixed-Dose Combination)

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
11.0	15 July 2025	08 Dec 2025

Rationale for submitting an updated RMP:	Updated the list of safety concerns to remove the important identified risks: "Severe bradycardia and heart block when used with concomitant amiodarone" and "HBV reactivation in HBV/HCV coinfected patients", and to remove targeted follow-up questionnaire related to the important identified risk of severe bradycardia and heart block when used with concomitant amiodarone.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I	Table Part I.1: Product Overview	None
Part II Safety Specification	Section Part II: Module SI: Epidemiology of the indication and target populations(s)	None
	Section Part II: Module SII: Non-clinical part of the safety specification	None
	Section Part II: Module SIII: Clinical Trial exposure	None
	Section Part II: Module SIV: Populations not studied in Clinical Trials	None
	Section Part II: Module SV: Postauthorization experience	Information updated with Postmarketing exposure data.
	Section Part II: Module SVI: Additional EU requirements for the safety specification	None
	Section Part II: Module SVII: Identified and potential risks	Updated to reflect the removal of the important identified risks "Severe bradycardia and heart block when used with concomitant amiodarone" and "HBV reactivation in HBV/HCV coinfected patients".
	Section Part II: Module SVIII: Summary of the safety concerns	Updated to reflect the removal of the important identified risks "Severe bradycardia and heart block when used with concomitant amiodarone"

Part	Module/Annex	Significant changes to RMP
		and "HBV reactivation in HBV/HCV coinfected patients".
Part III Pharmacovigilance Plan		Removal of targeted questionnaire collecting information on bradyarrhythmia.
Part IV Plan for post-authorization efficacy studies		None
Part V Risk Minimization Measures		Updated to reflect the removal of the important identified risks "Severe bradycardia and heart block when used with concomitant amiodarone" and "HBV reactivation in HBV/HCV coinfected patients".
Part VI Summary of RMP		Updated to reflect the removal of the important identified risks "Severe bradycardia and heart block when used with concomitant amiodarone" and "HBV reactivation in HBV/HCV coinfected patients".
Part VII Annexes		Updated Annex 4 to reflect the removal of the targeted questionnaire for bradyarrhythmia. Updated Annex 8 to reflect the changes in this RMP.

Other RMP versions under evaluation:

RMP Version number	Submitted on	Procedure number
None	Not applicable	Not applicable

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
9.0	EMEA/H/C/003850/WS2356/0107	12 January 2023 (CHMP Opinion)

QPPV name:	Rainer Heissing
QPPV signature:	The RMP has been reviewed and approved by the QPPV and the electronic signature is on file.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
AFP	alpha-fetoprotein
aIRR	adjusted incidence rate ratio
ALT	alanine transaminase
ARV	antiretroviral
AST	aspartate transaminase
ATC	anatomical therapeutic chemical classification system
ATR	Atripla®
ATV	atazanavir
ATV/r	ritonavir-boosted atazanavir
AUC	area under the curve
AUC_{inf}	area under the concentration curve verses time curve from time zero to infinity
AUC_{tau}	area under the concentration versus time curve over the dosing interval
$AUC_{0\text{-}inf}$	AUC curve to infinite time
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time “x” to time “xx”
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BOC	boceprevir
BSEP	bile salt export pump
CAD	coronary artery disease
CatA	cathepsin A
CD4	antigenic marker on helper/inducer T cells
CDA	Center for Disease Analysis
CDC	Centers for Disease Control
CES1	carboxylesterase 1
CHC	chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CKD	chronic kidney disease
CLcr	creatinine clearance
C_{max}	maximum concentration
CNS	central nervous system
COBI	cobicistat
CPT	Child-Pugh-Turcotte (score)
CrCl	creatinine clearance

CsA	cyclosporine A
C_{tau}	observed drug concentration at the end of the dosing interval
CYP	cytochrome P450
DAA	direct-acting antiviral
DCV	daclatasvir
DDI	drug-drug interaction
DHPC	Direct Healthcare Professional Communication
DNA	deoxyribonucleic acid
DoT	days of treatment
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
EASL	European Association for the Study of the Liver
EBR	elbasvir
EC	European Commission
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPC	Epclusa®
ESRD	end-stage renal disease
EU	European Union
EU-RMP	EU Risk Management Plan
FDA	Food and Drug Administration
FDC	fixed dose combination
FPFV	First patient first visit
FTC	emtricitabine
GERS	European data collection system for the healthcare market
GI	gastrointestinal
GLE	Glecaprevir
GLP	good laboratory practices
GT	Genotype
GZR	grazoprevir
HBcAB	Hepatitis B core antigen antibody
HBsAB	Hepatitis B surface antigen antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	Healthcare professional
HCV	hepatitis C virus
hERG	human ether-à-go-go related gene
HINT1	histidine triad nucleotide-binding protein 1

HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HVN	Harvoni (ledipasvir/sofosbuvir)
IC_{50}	concentration that results in 50% inhibition
IDU	injection drug use or injection drug user
IFN	Interferon
IMS	Health services vendor of U.S. physician prescribing data
IRB	Institutional Review Board
JNDA	Japan New drug application
LDV	ledipasvir (GS-5885)
LPLV	last patient last visit
MAA	marketing authorization application
MAH	marketing authorization holder
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
mRNA	messenger ribonucleic acid
MRP	multidrug resistance related protein
mtDNA	mitochondrial deoxyribonucleic acid
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NASH	nonalcoholic steatohepatitis
NDP	nucleoside diphosphate
NHANES	national health and nutrition examination survey
NOEL	no observed effect level
NOAEL	no observed adverse effect level
NS5A	nonstructural protein 5A
NS5B	nonstructural protein 5B
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OMB	ombitasvir
PASS	Post-authorization safety study
PBRER	periodic benefit-risk evaluation report
PD	pharmacodynamics
PDCO	pediatric committee
PEG	pegylated Interferon or peg-IFN-alfa-2a
Pgp	p-glycoprotein
PHAC	Public Health Agency of Canada
PI	protease inhibitor
PIB	Pibrentasvir
PIL	patient information leaflet

PIP	pediatric investigation plan
PK	pharmacokinetics
PMR	Postmarketing requirement
PPI	proton pump inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PRF	patient record forms
PSUR	periodic safety update report
PTV	paritaprevir
pTVR	Posttreatment virologic response
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RAL	raltegravir
RAV	resistance-associated variants
RBV	ribavirin
RMP	Risk Management Plan
RNA	ribonucleic acid
RPV	rilpivirine
RTV	ritonavir
SAE	serious adverse event
SmPC	summary of product characteristics
SMQ	Standardized MedDRA query
SMV	simeprevir
SOF	sofosbuvir
SVR	sustained virologic response
SVRxx	sustained virologic response at “xx” weeks following completion of all treatment
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TGV	tegobuvir
TVD	Truvada®
TVR	Telaprevir
UC	Unlimited Company
UGT	uridine diphosphate glucuronosyltransferase
UK	United Kingdom
US	United States
VDV	vedroprevir
VSV	sofosbuvir/velpatasvir/voxilaprevir
VEGF	Vascular endothelial growth factor
VEL	velpatasvir
WHO	World Health Organization
ZDV	zidovudine

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Ledipasvir/Sofosbuvir
Pharmaco-therapeutic group(s) (ATC Code):	Direct-acting antiviral (J05AP51)
Marketing Authorization Holder:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Harvoni
Marketing authorization procedure	Centralized
Brief description of the product	*Chemical class* Ledipasvir: HCV nonstructural protein 5A (NS5A) inhibitor. Sofosbuvir: nucleotide NS5B polymerase inhibitor.
	Summary of mode of action Ledipasvir is a HCV NS5A inhibitor that has demonstrated potent anti-HCV activity. Sofosbuvir is a nucleotide analogue that potently inhibits genotypes 1 to 6 HCV ribonucleic acid (RNA) replicons in vitro and has demonstrated high sustained virological response (SVR) rates when administered with ribavirin (RBV) and with pegylated interferon (Peg-IFN)+RBV.
	Important information about its composition *None*
Hyperlink to the Product Information	Harvoni Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Harvoni is indicated for the treatment of chronic hepatitis C (CHC) infection in adult and pediatric patients aged 3 years and above.
	Proposed: Not applicable

Dosage in the EEA

Current: The recommended dose of Harvoni in adults is one tablet 90 mg/400 mg once daily with or without food.

The recommended dose of Harvoni in paediatric patients aged 3 years and above is based on weight (as detailed in Table 1) and can be taken with or without food.

A granule formulation of Harvoni is available for patients for the treatment of chronic HCV-infection in paediatric patients aged 3 years and above having difficulty swallowing film-coated tablets. Please refer to the Summary of Product Characteristics for Harvoni 33.75 mg/150 mg or 45 mg/200 mg granules.

Table 1. Dosing for pediatric patients aged 3 years and above using Harvoni tablets or oral granules

Body Weight (kg)	Dosing of Harvoni Tablets or Oral Granules	LDV/SOF Daily Dose
≥ 35	one 90/400 mg tablet once daily or two 45/200 mg tablets once daily or two 45/200 mg sachets of granules once daily	90/400 mg/day
17 to < 35	one 45/200 mg tablet once daily or one 45/200 mg sachets of granules once daily	45/200 mg/day
< 17	one 33.75/150 mg sachets of granules once daily	33.75/150 mg/day

Proposed: Not applicable

Pharmaceutical form(s) and strengths

Current**:** Film-coated tablet of 90 mg LDV and 400 mg SOF
Film-coated tablet of 45 mg LDV and 200 mg SOF
Granules sachet of 45 mg LDV and 200 mg SOF
Granules sachet of 33.75 mg LDV and 150 mg SOF

Proposed: Not applicable

Is the product subject to additional monitoring in the EU?

No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. Hepatitis C

SI.1.1. Incidence

The rate of new hepatitis C virus (HCV) infections is difficult to determine due to the asymptomatic nature of acute infections. Worldwide, it is estimated that there were 1.75 million new HCV infections in 2015 {The Polaris Observatory HCV Collaborators 2017, World Health Organization (WHO) 2017}. Unsafe healthcare procedures and injection drug use are the leading causes of new HCV infections globally {World Health Organization (WHO) 2017}.

The World Health Organization (WHO) reports that the Eastern Mediterranean Region and the European region have higher rates of infection compared to other world regions {World Health Organization (WHO) 2017} (Table SI.1). Variation in HCV incidence is largely determined by differences in practices, transmission risk factors, and access to care by region (Table SI.1).

Table SI.1. Incidence estimates of HCV infection by WHO region {World Health Organization (WHO) 2017}

WHO region	Incidence rate per 100,000		Total number (000)	
	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African region	31.0	22.5-54.4	309	222-544
Region of the Americas	6.4	5.9-7.0	63	59-69
Eastern Mediterranean Region	62.5	55.6-65.2	409	363- 426
European Region	61.8	50.3-66.0	565	460-603
South-East Asia Region	14.8	12.5-26.9	287	243-524
Western Pacific Region	6.0	5.6-6.6	111	104-124
Global	23.7	21.3-28.7	1,751	1,572-2,120

SI.1.2. Prevalence

The prevalence of HCV infection worldwide is estimated to be 1% (approximately 71 million people) and varies considerably among different regions {World Health Organization (WHO) 2017}. Estimates of HCV viraemic prevalence through modelling found that, in 2015, the range of prevalence estimates by country spanned from 0.1% in the Netherlands to as high as 7.0% in Gabon {The Polaris Observatory HCV Collaborators 2017}.

The WHO estimates that HCV prevalence in Europe is approximately 1.5%, corresponding to 14 million people living with HCV {World Health Organization (WHO) 2017} (Table SI.1). The highest viraemic prevalence in 2015 was observed in Eastern Europe (3.3%, 95% Uncertainty Interval 2.1-3.4) and the lowest was observed in Western Europe (0.5%, 95% Uncertainty Interval 0.4-0.8) {The Polaris Observatory HCV Collaborators 2017}. In Central Europe, the viraemic prevalence was estimated to be 1.1% in 2015 (95% Uncertainty Interval 0.8-1.0).

The available data from Europe indicate a wide variation in viraemic prevalence between countries, ranging from 0.1% to 3.3% {The Polaris Observatory HCV Collaborators 2017}. The lowest HCV prevalence estimates (0.2% or lower) were observed in the Netherlands and Austria, and the highest (2.0% or higher) were from Romania, Latvia and Russia.

The true prevalence is likely to be higher as general population studies may exclude high-risk subgroups like active injection drug users (IDUs), the homeless, the incarcerated, and veterans. The HCV infection rate is substantially higher in these subgroups as illustrated by a study that showed that HCV prevalence among prisoners in Spain was 22.7% {Saiz de la Hoya 2011}. Studies have shown that the overall prevalence is higher than national estimates when these subgroups are considered {Chak 2011, Gish 2005}.

Injection drug use has become the main risk for HCV transmission in developed countries with well-established HCV screening programs of blood products and lower HCV prevalence. Among 71 million HCV-infected persons, 5.6 million (8%) currently inject drugs {World Health Organization (WHO) 2017}. For example, in Northern European countries such as Norway and Sweden, or in the United Kingdom (UK) or Canada, IDU is the main risk factor for HCV transmission, accounting for more than half of HCV-infected patients (ie, Norway 67%, Sweden 65%, Canada 58% and UK 90%). In some countries with increasing HCV prevalence, the increase may be explained by a dramatic increase in IDU {Cornberg 2011}.

Globally, HCV genotype 1 is the most prevalent, accounting for 44% of all infections, followed by genotype 3 (25% of all infections) and genotype 4 (15% of all infections) {The Polaris Observatory HCV Collaborators 2017}. Infection with HCV genotype1 accounts for the majority (60%) of infections in high-income and upper-middle income countries; in contrast, genotype 3 is common in lower middle-income countries (36%) and genotype 4 is common in low-income countries (45%).

Table SI.2. Prevalence estimates of HCV infection by WHO region {World Health Organization (WHO) 2017}

	Estimates of the prevalence of HCV infection (%)			Estimated number of persons living with HCV (millions)		
	Uncertainty interval			Uncertainty interval		
WHO region	Best	Lower	Higher	Best	Lower	Higher
African region	1.0	0.7	1.6	11	7	16
Region of the Americas	0.7	0.6	0.8	7	6	8
Eastern Mediterranean Region	2.3	1.9	2.4	15	13	15

	Estimates of the prevalence of HCV infection (%)			Estimated number of persons living with HCV (millions)		
	Uncertainty interval			Uncertainty interval		
WHO region	**Best**	**Lower**	**Higher**	**Best**	**Lower**	**Higher**
European Region	1.5	1.2	1.5	14	11	14
South-East Asia Region	0.5	0.4	0.9	10	8	18
Western Pacific Region	0.7	0.6	0.8	14	10	15
Global	1.0	0.8	1.1	71	62	79

SI.1.3. Demographics of the HCV Population

SI.1.3.1. HCV Infection by Gender

The rate of chronicity in HCV infection appears to be lower in women, particularly younger women. Being of the male sex has been associated with accelerated progression of hepatic fibrosis among those infected with HCV {Shepard 2005}.

SI.1.3.2. HCV Infection by Age

Worldwide, prevalence rates tend to increase with age and peak in ages 55-64 years {Alter 2007, Mohd Hanafiah 2013}. In Turkey, Spain, Italy, Japan, and China, people over 50 years of age account for the highest prevalence of infections, indicating a cohort effect in which the risk for HCV infection was higher in the distant past (ie, 40-60 years previously). Young adults (ages 20 to 35 years) are at highest risk for acute infection, with an incidence 6 times higher than those over 40 years of age {Armstrong 2000, Kantar Health 2014, Mohd Hanafiah 2013}.

There are limited data on the prevalence of HCV infection among adolescents 12<18 years of age. It is estimated that approximately 2.1 to 3.5 million individuals 15 years of age or younger are chronically infected with HCV {European Association for the Study of the Liver (EASL) 2018, Nwaohiri 2018}. The prevalence varies by geographic location. The estimated prevalence of HCV infection in children is up to 0.4% in Europe and the United States (US), and up to 6% in resource-limited countries {El-Shabrawi 2013, Khaderi 2014}. The natural history of chronic HCV infection in children differs from that in adults since HCV infection in children is relatively benign. In general, the burden of disease is much lower in this age group than among older persons. A recent meta-analysis of primary national data sources and peer-reviewed papers used mathematical modeling to determine that the HCV antibody seroprevalence rate among subjects 10-19 years of age in 2005 was 1.2-1.3% in Western and Central Europe, 1.4-1.6% in Eastern Europe, and 0.6% in North America {Mohd Hanafiah 2013}. It must be noted that anti-HCV is a sign of previous and current infection that does not differentiate acute from chronic infections. Data from Europe and the United States show that the seroprevalence of anti-HCV among patients aged 10-19 has dropped in several countries since 2005 (Table SI.3) {Kantar Health 2014}. Whether these estimates have been influenced by changes in HCV surveillance and/or availability of highly effective direct acting antiviral (DAA) treatment is unclear.

Table SI.3. Estimated Number of Seroprevalent HCV Cases Among Patients Aged 10-19 in Different European Countries and United States

Country	Number of cases in 2005	Number of cases in 2015
United Kingdom	9,731	945
France	3,658	4,367
Germany	3,544	1,016
Italy	28,491	855
Spain	8,221	8,675
United States	134,554	6,573

SI.1.3.3. HCV Infection by Ethnicity

There are differences in the rate of chronic HCV infection, response to treatment, and development of complications, among different racial and ethnic groups with HCV infection. In particular, African Americans appear to have a higher rate of chronic HCV infection than Caucasians and Hispanic whites, along with higher viral loads, lower clearance rates, and lower responses to anti-HCV therapy {Pyrsopoulos 2005}.

SI.1.3.4. Risk Factors for Hepatitis C

People at increased risk for hepatitis C infection include the following {Centers for Disease Control and Prevention (CDC) 2015}:

- Current injection drug users
- Past injection drug users, including those who injected only one time or many years ago
- Recipients of donated blood, blood products, and organs
- People who received a blood product for clotting problems made before 1987
- Hemodialysis patients or persons who spent many years on dialysis for kidney failure
- People who received body piercing, acupuncture, or tattoos done with non-sterile instruments
- People with known exposures to HCV virus, such as
  - Health care workers injured by needle sticks
  - Recipients of blood or organs from a donor who tested positive for HCV
- Human immunodeficiency virus (HIV)-infected persons
- Children born to mothers infected with HCV

Less common risks include:

- Having sexual contact with a person who is infected with HCV
- Sharing personal care items, such as razors or toothbrushes, that may have come in contact with the blood of an infected person

SI.1.4. Main Existing Treatment Options

Approved direct acting antiviral (DAA) -based treatment regimens are generally well tolerated and result in high sustained virologic response (SVR) at 12 weeks following completion of all treatment (SVR12) rates across most, but not all, patient populations.

The following HCV DAAs are currently approved in Europe for treatment of HCV and are recommended in the 2018 EASL guidelines; these can be used in combination and with or without RBV:

- SOF-containing products
  - Sovaldi (sofosbuvir, SOF)
  - Harvoni (ledipasvir/sofosbuvir, HVN)
  - Epclusa (sofosbuvir/velpatasvir, EPC)
  - Vosevi (sofosbuvir/velpatasvir/voxilaprevir, VSV)
- Ombitasvir/paritaprevir/ritonavir + dasabuvir (OMB/PTV/r + DSV)
- Ombitasvir/paritaprevir/ritonavir (OMB/PTV/r)
- Grazoprevir/elbasvir (GZR/EBR)
- Glecaprevir/pibrentasvir (GLE/PIB)

According to the most recent European guidelines {European Association for the Study of the Liver (EASL) 2018}:

- SOF-containing FDCs HVN, EPC and VSV with or without RBV are among the recommended treatment options for patients with genotypes 1-6 including adolescents (Sovaldi and HVN), those with HIV/HCV coinfection, decompensated liver disease (excluding VSV), post-transplant recurrence or those who are DAA failures (VSV).

For patients with decompensated cirrhosis, SOF-containing regimens (HVN and EPC) are the only currently approved DAAs that are recommended. None of the SOF-free regimens are recommended (and some are contraindicated) in patients with decompensated cirrhosis (Child-Pugh B or C).

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

The natural course of HCV infection and disease varies widely. Several factors have been associated with accelerated progression of hepatic fibrosis among those infected with HCV, or with increased incidence of HCV-related complications of chronic liver disease and HCC. These factors are HIV and hepatitis B virus (HBV) coinfections, inflammation, male sex, older age at acquisition of HCV infection, obesity, smoking, and excessive alcohol consumption {Shepard 2005}.

Although HCV-related liver disease is a leading cause of mortality in adults and is the primary reason for liver transplantation in many developed countries {Kim 2005, Kim 2001, World Health Organization (WHO) 2005}, the vast majority of carriers die with, rather than from, this infection. In fact, many patients remain asymptomatic and unaware that they have been infected with the virus. Acute HCV infection usually occurs within the first six months of exposure to HCV and is typically asymptomatic; however, 20-30% of patients may experience malaise, fatigue, weakness, anorexia, or right upper quadrant pain, followed by jaundice.

Following the acute phase, 5-25% of HCV patients spontaneously resolve the infection within 2-12 weeks, while the rest develop chronic HCV disease. Patients with chronic HCV disease tend to be minimally symptomatic over the course of 20-40 years. A subset of patients (approximately 20%) develops nonspecific symptoms, including mild fatigue and malaise, nausea, and right upper quadrant pain. Patients with persistent viremia and years of chronic infection are at risk of fibrosis and cirrhosis, but the extent of liver damage and the time course of disease progression vary among individuals.

Approximately 15-35% of HCV patients will develop cirrhosis after 25-30 years of infection {Thrift 2017}. Although cirrhosis distorts the structure and degrades the function of the liver, it can remain asymptomatic for several years as healthy tissue compensates for diseased tissue. However, once cirrhosis is established, complications such as jaundice, ascites, variceal hemorrhage, and encephalopathy may ensue. The development of these complications defines decompensated cirrhosis, or end-stage liver disease. Decompensated liver disease was estimated to be present in 11.7% of HCV patients with cirrhosis in 2010, and this proportion is expected to rise at least through 2030 {Davis 2010}. In patients with decompensated cirrhosis, the five-year survival rate is 50% {Fattovich 1997}. In addition, approximately 10-25% of patients with cirrhosis may develop HCC {Hezode 2003, Poynard 1997, Seeff 1999}.

Worldwide, more than 500,000 deaths occur from hepatitis C-related diseases, which include cirrhosis and liver cancer, every year. The mortality rate among HCV-infected persons was estimated to be 12 times higher than the mortality rate in the general population in a large US cohort study, suggesting that over 50,000 deaths in the US were related to HCV infection in 2010 {Mahajan 2014}. A Danish cohort study found that the higher risk of death among younger HCV-infected patients compared to an age- and sex-matched comparison cohort was due primarily to unnatural deaths (i.e. deaths related to mental and behavioral disorders, psychoactive substance use, and external causes), whereas excess mortality in older HCV-infected patients was due to liver-related deaths {Omland 2011}.

SI.1.6. Important Co-morbidities

Infection with HCV is associated with numerous extrahepatic clinical manifestations, including autoimmune and lymphoproliferative disorders in addition to diseases of the cardiovascular, renal, metabolic, and central nervous system {Cacoub 2016}. A number of comorbidities in HCV patients have also been associated with antiviral treatment with interferon and/or ribavirin. Below is a list of important conditions that have evidence of higher risk among HCV-infected patients {Cacoub 2016}:

SI.1.6.1. Cardiovascular Disease

Cardiovascular disease risk appears to be elevated among HCV-infected patients compared to the general population. As measured by the Framingham risk score, cardiovascular disease was found to be 2.4% higher in HCV patients from New York based clinics compared to the US general population (NHANES sample) ($p < 0.001$) {Kakinami 2013}. Studies have also shown higher risk of coronary artery disease among HCV-positive patients {Roed 2012}. Recent studies indicate that carotid atherosclerosis is quite common in patients with chronic HCV infection. The prevalence has been reported to range from 42 to 53% {Roed 2012}, and rises to 78% among those with hepatic steatosis {Roed 2012}.

Previous reports have identified significant positive associations between chronic HCV status and any of the following conditions: carotid-artery plaque, intima-media thickness, coronary flow reserve by transthoracic Doppler echocardiography, carotid plaque score, brachial artery endothelium-dependent dilatation, and pulse wave velocity {Roed 2012}.

Further, positive associations have been observed between chronic HCV infection and coronary artery disease (CAD) defined in other ways, including angiographic documentation (> 50% stenosis) and modified Reardon severity score system {Roed 2012}. A recent retrospective cohort study found a positive association with chronic HCV and coronary heart events, defined by CAD onset, chronic stable angina, unstable angina, or acute myocardial infarction {Paydak 2014}. Other studies show positive associations between HCV infection and cardiomyopathy (either dilated or hypertrophic) {Roed 2012}, as well as a study that found HCV positive subjects to have almost twice the risk of stroke compared to HCV negative subjects {Roed 2012}.

SI.1.6.2. Depression

Depressive symptoms are frequently recognized in both untreated and treated HCV patients. The previous standard of care for HCV, PEG plus RBV is associated with a high rate of depression (10 to 40% depending on the screening method used) and other mental and neuropsychiatric syndromes {Hauser 2002, Papafragkakis 2012, Raison 2005}. An estimated 24 to 70 percent of people with chronic hepatitis C were found to be clinically depressed, as compared to 6 to 10% in the general population {Coughlan 2002, Schafer 2007}. In another study, a three-fold risk was observed in HCV seropositive patients when compared to the general US population {Basseri 2010}.

SI.1.6.3. Diabetes Mellitus Type 2

An increased prevalence of insulin resistance {Serfaty 2009} and, subsequently, diabetes mellitus has been observed within HCV patient populations {Allison 1994, Caronia 1999}, {Knobler 1998, Mason 1999, Simo 1996}. HCV infection has been identified as a risk factor for the development of insulin resistance in patients with visceral obesity {Eguchi 2009}, while diabetes also has been identified as a risk factor for rapid progression of fibrosis in HCV infection {Ortiz 2002}. A proposed mechanism for this relationship is hepatocyte dysfunction in severe HCV infection, which may lead to insufficient carbohydrate metabolism and glucose homeostasis {Petrides 1989}. Host cell adaptive mechanisms or viral proteins themselves (ie, in genotype 1 infection) may disrupt the insulin signaling pathway in hepatocytes and liver inflammation may induce cytokines, thus promoting insulin resistance.

Reports from North America, Europe, and the Middle East consistently found an increased prevalence of diabetes among patients with chronic HCV infection (24% to 62%) compared with people with alternate forms of liver disease and other control groups (3% to 13%) {Mehta 2000}. Moreover, HCV was associated with over 40% increased risk of type 2 diabetes mellitus compared with the general US population {Basseri 2010}.

SI.1.6.4. Hepatitis B

Due to overlapping routes of transmission, HBV and HCV coinfection is not uncommon among individuals in HBV endemic areas who also have a high risk of parenteral infections, such as injection drug users {Pallas 1999}, patients on hemodialysis {Reddy 2005}, patients undergoing organ transplantation {Aroldi 2005} and HIV-positive individuals {Zhou 2007}. The prevalence of HBV and HCV coinfection varies from 9% to 30% depending on the geographic region {Liaw 1995, Zarski 1998}. HCV coinfection with HBV also has exhibited higher rates of progression to cirrhosis from liver fibrosis {Chen 2006}.

Although liver disease activity and progression are generally more severe in the presence of HCV/HBV coinfection, an inverse relationship in the replicative levels of the 2 viruses exists, suggesting viral interference. Usually, HCV is the dominant virus, and HBV replication is suppressed in the presence of HCV coinfection, with resultant lower HBV deoxyribonucleic acid (DNA) levels and decreased hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) levels in coinfected patients compared to HBV monoinfected patients {Amin 2006, Biliotti 2008, Bini 2010, Chu 1998, Crockett 2005, Konstantinou 2015, Liaw 2004, Raimondo 2005, Saravanan 2009, Tyson 2013, Wiegand 2015}. The converse has also been observed, with some patients experiencing high HBV DNA levels while others present alternating phases of dominance of one virus over the other {Konstantinou 2015}.

HBV reactivation in HCV/HBV coinfected patients has been observed following effective treatment of HCV, both with older regimens involving PEG+RBV and also with newly approved DAAs (interferon-free regimens):

- *HBV reactivation with PEG+RBV*: HBV reactivation following successful treatment of HCV with PEG+RBV has been reported in HCV/HBV coinfected patients {Liu 2012, Yu 2013} {Hamzaoui 2013, Potthoff 2009, Yalcin 2003}. HBV reactivation has been reported to occur in 14% to 38% of HCV/HBV coinfected patients following PEG+RBV or interferon (IFN) + RBV treatment {Liu 2012, Vigano 2009, Yu 2013}, and the risk of viremia was increased in cases where the virologic response to HCV therapy was sustained (HBV reactivation occurred in 31% of patients who experienced HCV sustained virologic response [SVR] and 11% of patients without HCV SVR) {Liu 2012}.

- *HBV reactivation with approved DAAs*: Unlike PEG and RBV, the approved DAAs for HCV treatment do not have any inhibitory effect on HBV; these DAAs can be used without interferon. Literature articles have reported HBV reactivation in HCV/HBV coinfected patients following treatment of HCV with DAAs {Balagopal 2015, Belperio 2017, Chen 2017, Collins 2015, Ende 2015, Hayashi 2016, Kasahara 2017, Londono 2017, Ogawa 2017, Ou 2017, Takayama 2016, Wang 2017}. Many of the reported cases did not involve clinical flares and resolved either spontaneously or following addition of anti-HBV therapy. Severe cases of HBV reactivation are rare, but there have been reports where HBV reactivation has resulted in acute hepatic failure with the need for a liver transplant or a fatal outcome. Class labeling has been issued for DAAs approved in the EU and other territories regarding the risk of HBV reactivation in HBV/HCV coinfected patients. The labeling recommends HBV screening prior to initiation of HCV therapy, monitoring for HBV reactivation while on HCV treatment and appropriate management per current clinical guidelines should HBV reactivation occur.

SI.1.6.5. HIV

HIV coinfection may alter the natural history of HCV infection, and also contribute to the increasing burden of HCV infection, by accelerating liver fibrosis {Eyster 1993, Mohsen 2003, Rockstroh 1996}. Since the advent of highly-active antiretroviral therapy in the mid-90s, there has been a three-to nine-fold increase in HCV-associated mortality, and HCV infection is associated with up to half of all deaths in patients with HIV {Basseri 2010, Bica 2001, Cacoub 2001, Martin-Carbonero 2001, Soriano 1999}.

Globally, an estimated four to five million people are coinfected with HCV and HIV {Operskalski 2011}. In the US and Western Europe, estimates of coinfection rates range from 15% to over 50% of the HIV-positive population {Quaranta 1994, Rockstroh 2003, Rockstroh 2006, Soriano 2002}. The high prevalence of coinfection is attributed to the shared parenteral route of transmission. Consequently, coinfection with HCV and HIV is particularly common among hemophiliacs and injection drug users. Furthermore, individuals with chronic HIV and HCV coinfection have a greatly elevated risk of accelerated liver, kidney, and cardiovascular disease progression {Operskalski 2011}.

SI.1.6.6. Obesity/Hepatic Steatosis

Obesity is associated with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, diseases that could potentially lead to fibrosis and cirrhosis {Angulo 1999}, and has been identified as a risk factor for rapid fibrosis progression in HCV infection {Ortiz 2002}.

Furthermore, fibrosis stage has been associated with hepatic steatosis {Negro 2009} and the degree of necroinflammatory activity in obese patients with HCV {Adinolfi 2001, Clouston 2001}. In addition, genotype 3 infection may induce steatosis and the degree of severity may correlate with viral load {Serfaty 2009}. Slightly increased prevalence rates of obesity within HCV patients in the US and Canada (24 and 29%, respectively) were found as compared with the general population {Basseri 2010, Chen 2008}.

SI.1.6.7. Renal Insufficiency

Hepatitis C virus infection is a persistent public health concern among end stage renal disease patients who receive dialysis. Before testing of blood products for HCV and the availability of erythropoiesis-stimulating agents, patients on dialysis commonly acquired HCV through blood transfusions. Transmission still may occur because of contaminated medical equipment, patient-to-patient exposure, or other nosocomial routes {Martin 2008}. Differences in patient behavior and community exposures may contribute to persistence of HCV in hemodialysis units and also to variation in HCV prevalence and seroconversion among units {Fissell 2004}.

Prevalence rates of HCV infection are higher in dialysis patients compared to the general population worldwide {Fabrizi 2002}. HCV infection has been reported in 6 to 38% of dialysis patients in the US {Basseri 2010, Fissell 2004}. The prevalence of anti-HCV seropositivity among patients undergoing regular dialysis in Western Europe ranges between 3% and 23% {Fissell 2004}. HCV infection was reported in nearly 15% of dialysis patients in Japan, {Fissell 2004}, and as high as 80% in countries with single center samples, such as Egypt and Morocco {Martin 2008}.

Glomerular disease and other kidney diseases are extrahepatic manifestations of HCV infection {Fabrizi 2013, Kamar 2013}. Chronic HCV infection is associated with a higher risk of mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), and other glomerulonephritis diseases {Fabrizi 2013, Kamar 2013}. Renal failure is reported to occur in 11% to 49% of patients with decompensated cirrhosis, particularly in older patients and patients with more advanced liver disease {Carvalho 2012}.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

No additional non-clinical studies are warranted for Harvoni or any of its components.

SII.1. Ledipasvir

Table SII.1. Table of Key Safety Findings from Non-Clinical Studies (Ledipasvir)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Toxicity	
Single-dose studies	
No formal single dose toxicity studies with LDV have been conducted. Single doses up to 600 mg/kg, at an AUC exposure approximately 4-fold versus the LDV/SOF FDC, were well tolerated in PK studies in rats (AD-256-2116). In a micronucleus study in rats, single oral doses up to 450 mg/kg were well tolerated with clinical signs limited to clear oral discharge and rough hair coat at dose levels ≥ 225 mg/kg.	Within LDV/SOF, the dose of LDV is 90 mg. The data for LDV nonclinical single doses up to 4-fold the exposure compared to the LDV/SOF FDC indicate a low potential for toxicity in humans.
Repeat-dose studies	
Short term repeat dose studies up to 2 weeks (TX-256-2003, TX-256-2004, in rats and dogs respectively), 4 weeks in mice (TX-256-2018), and chronic toxicity studies up to 26 weeks in rats (TX-256-2008) and 39 weeks in dogs (TX-256-2009) via oral gavage did not reveal any LDV-target organ toxicities. The NOAEL in mice was 300 mg/kg/day. The NOAELs in the chronic toxicity studies were 100 mg/kg/day in rats (Week 26 C_{max} of 3.2 µg/mL and AUC_{0-24} of 56.0 µg·h/mL; sexes combined) and 30 mg/kg/day in dogs (Week 39 C_{max} of 4.2 µg/mL and AUC_{0-24} of 62.6 µg·h/mL; sexes combined), the highest dose tested in the respective species.	The exposures based on plasma LDV AUC values at the NOAEL doses in the longest duration studies were approximately 25-fold (mice), 7-fold (rats), and 7-fold (dogs) higher than the systemic exposure in subjects treated once daily with 90 mg LDV in the FDC (mean human AUC_{tau} 8.53 µg•h/mL).
Reproductive & Developmental Toxicity	
In rats, daily oral doses of LDV when administered for 14 days (females) or 28 days (males) prior to cohabitation and during cohabitation had transient effects on body weight and food consumption leading to the paternal and maternal NOAEL of 100 mg/kg/day (TX-256-2017). Ledipasvir had no effects on mating and fertility of the male rats and the male reproductive NOEL was 100 mg/kg/day. There were no effects on the mating and fertility of the female rats as there were no effects on estrous stages, and no differences in the number of pregnant females in the LDV-treated groups when compared to the controls. However, the numbers of corpora lutea and implantation sites were reduced in	Animal data do not indicate direct or indirect harmful effects of LDV with respect to pregnancy or embryonal/fetal development. Ledipasvir does not cause fetal toxicity and, while the average number of corpora lutea and implantations were reduced in the 100 mg/kg/day group, there were no effects on estrous stages and no differences in the percent of pre-implantation loss and the number of pregnant females in the LDV-treated groups compared to controls. The clinical significance of the decrease in corpora lutea and implantation sites with no effect on rat fertility in humans is not known.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
females given 100 mg/kg/day; therefore, the female reproductive no observed effect level (NOEL) was 30 mg/kg/day. Based on toxicokinetic data from the chronic rat study during Week 26 (TX-256-2008), exposure margins at the male and female reproductive NOELs were 7-fold and 3-fold, respectively, when compared to the clinical LDV exposure with the LDV/SOF FDC.	Because there are no clinical data with LDV in pregnant women, as a precaution, it is preferable to avoid use of LDV within LDV/SOF during pregnancy.
Developmental toxicity studies were conducted in the rat (TX-256-2012) and rabbit (TX-256-2013). In the rat, daily oral administration of LDV to pregnant rats during organogenesis had no adverse effects on embryo/fetal viability and growth, or on the incidence of fetal visceral or skeletal abnormalities. The NOAEL for developmental toxicity was 100 mg/kg/day, the highest dose tested. The NOEL for maternal toxicity is 30 mg/kg/day based on significantly decreased maternal body weight gain and food consumption at 100 mg/kg/day. In the rabbit, daily oral administration of LDV to pregnant rabbits during organogenesis had no adverse effects on maternal or embryo/fetal viability and growth, or on the incidence of fetal anomalies. The NOAEL for maternal toxicity and NOEL for developmental toxicity was 180 mg/kg/day, the highest dose tested. At the developmental NOAEL/NOEL, the exposures in the rat and rabbit were 5- and 2-fold above the clinical LDV exposure with the LDV/SOF FDC. In the pre/postnatal developmental toxicity study (TX-256-2020), maternal toxicity was observed at 100 mg/kg/day, and the NOAEL for maternal systemic toxicity was 30 mg/kg/day. Decreased F_1 offspring body weights and body weight gains were noted at 100 mg/kg/day generally throughout the postnatal period. There were no effects on F_1 survival, physical and behavioral development, reproductive performance, and survival of F_2 pups. Based on these results, the NOAEL for F_1 neonatal/developmental toxicity was considered to be 30 mg/kg/day, and the NOAEL for effects on F_1 neurobehavior, F_1 reproductive toxicity, and F_2 neonatal toxicity was considered to be 100 mg/kg/day. At the NOAELs in the study, the margins of exposure for LDV are 1.3-fold (for F_0 maternal systemic toxicity and F_1 neonatal/developmental toxicity) and 4-fold (for F_1 neurobehavior, F_1 reproductive toxicity, and F_2 neonatal toxicity) compared to the mean LDV AUC with the LDV/SOF FDC. Notably, fertility was normal in the offspring of rats exposed daily from before birth (in utero) through weaning. In the repeat dose toxicity studies in mice, rats and dogs, there were no changes in female	Because it is not known if LDV is excreted in human breast milk, nursing should be discontinued prior to initiation of treatment with LDV/SOF.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
reproductive tissues, and there was no notable off-target binding in radioligand binding assays with LDV to suggest a direct effect of LDV on female reproduction. The plasma exposure of LDV in nursing pups was determined as part of a study on the effect of LDV on prenatal and postnatal development in rats (TX-256-2020). Although LDV was not directly measured in rat milk, low levels of LDV were detected in nursing pups presumably exposed via the maternal milk.	
Target Organ Toxicity	
No adverse target organ toxicity has been identified with LDV in mice, rats, and dogs. Ledipasvir exposures at the NOAELs from the chronic repeat dose toxicity studies in rats and dogs were approximately 7-fold higher than clinical exposures at LDV 90 mg within LDV/SOF. In the 2-week rat and dog studies, and the chronic studies, the only notable test article related changes were transient decreases in body weight gain and/or food consumption. In the 26-week chronic rat study, minor changes in organ weights (adrenal, liver) did not have microscopic correlates. Potential test article related microscopic findings were noted only at the interim sacrifice (Week 13) for males given 100 mg/kg/day and were limited to minimal paracortical lymphocyte hyperplasia in the mesenteric lymph nodes and an increased incidence of prostatic inflammation. These findings were not considered adverse due to the frequent occurrence of prostatic inflammation in rats and the absence of similar findings at Week 26. In the 39-week chronic repeat dose dog study, there were no LDV-related findings in body weight, food consumption, ophthalmic, ECG, blood pressure, or clinical or anatomic pathology.	The LDV nonclinical data indicate a low potential for toxicity in humans.
Genotoxicity	
Ledipasvir was negative for mutagenicity in the Ames assay (TX-256-2005) and negative for inducing chromosomal aberrations (TX-256-2006). Ledipasvir, when administered orally up to 450 mg/kg was negative in the in vivo rat bone marrow micronucleus assay (TX-256-2007).	LDV is considered nongenotoxic.
Carcinogenicity	
The carcinogenicity potential of LDV was evaluated in a 6-month RasH2 transgenic mouse study (TX-256-2019) and a 2-year rat carcinogenicity study (TX-256-2016). Ledipasvir was not considered carcinogenic at doses up to 300 mg/kg/day in RasH2	LDV is considered non-carcinogenic.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
mice and 100/30 (males/females) mg/kg/day in rats. Exposure margins at these doses were 26 and 8/3 (male/female) above LDV clinical exposure at 90 mg within LDV/SOF.	
Safety Pharmacology	
Ledipasvir was evaluated in the standard battery of good laboratory practice (GLP) safety pharmacology studies, including the in vitro human ether-à-go-go related gene (hERG) assay and in vivo cardiovascular, respiratory, and CNS studies. A single oral administration of 100 mg/kg did not result in any effects on the respiratory system (PC-256-2006) and did not have any treatment related effects on the CNS of male Sprague Dawley rats (PC-256-2007). The LDV concentration that results in 50% inhibition (IC_{50}) for the inhibitory effect on the hERG potassium current was estimated to be greater than 0.5 µM (PC-256-2008). The acute cardiovascular effects of LDV were studied following a single oral administration to conscious, radio-telemetry-implanted male dogs. There were no LDV-related effects on any ECG or hemodynamic parameters, and the high dose of 30 mg/kg was considered to be the no observed effect level (NOEL; C_{max} was 4.6 µg/mL and AUC_{0-24} was 59.1 µg•h/mL [sexes combined] based on Day 1 values in TX-256-2004) (PC-256-2005). Exposure at the NOEL was 13-fold higher than in HCV infected subjects administered the LDV/SOF FDC (clinical C_{max} = 0.364 µg/mL).	The nonclinical data indicate a low likelihood for neurological, cardiovascular, or respiratory effects in humans.
Mechanisms for Drug Interactions	
<u>Cytochrome P450 and UGT1A1 Inhibition</u>	
Ledipasvir did not inhibit the activity of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 (IC_{50} > 25 µM; AD-256-2096, AD-256-2133). Ledipasvir had an IC_{50} of 9.9 µM for CYP3A catalyzed testosterone metabolism but did not inhibit midazolam metabolism (IC_{50} > 25 µM; AD-256-2096). Ledipasvir had an inhibitory effect on the activity of uridine diphosphate glucuronosyltransferase (UGT)1A1, with an IC_{50} value of 7.95 µM in vitro (AD-256-2132).	In vitro LDV inhibits intestinal CYP3A4 and UGT1A1. Medicinal products that have a narrow therapeutic range and that are metabolised by these isoenzymes should be used with caution and carefully monitored.
<u>Assessment of Induction Liability</u>	
Ledipasvir caused little or no induction of CYP, UGT1A1, and Pgp messenger (m)RNA or CYP activities when assessed in cultured human hepatocytes from 3 separate donors (AD-256-2146). Small increases in CYP2B6 and 3A4 activity and mRNA levels observed at the highest concentration tested (10 µM) were less than 15% of those caused by the positive controls. No concentration dependent	In vitro data indicate that LDV may be a weak inducer of metabolising enzymes such as CYP3A4, CYP2C and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with LDV/SOF. Ledipasvir may inhibit the efflux transport of Pgp and BCRP substrates during intestinal absorption but has a limited potential to cause clinically relevant transport

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
increases in CYP2C9 mRNA, Pgp mRNA, or UGT1A1 mRNA were observed. Results in human hepatocytes are consistent with the lack of induction through the aryl hydrocarbon receptor and weak induction through the pregnane X receptor detected in reporter cell lines (AD-256-2097).	inhibition in the systemic circulation. In agreement with these data, increases of 2.2- to 2.3-fold in SOF exposure, a substrate for Pgp and BCRP, were noted with LDV (GS-US-334-0101). GS-331007 PK was not altered.
Interaction with Transporters Ledipasvir did not inhibit multidrug resistance related protein (MRP)2 but was found to inhibit Pgp and BCRP mediated transport (approximately 50% inhibition at 1 µM; AD-256-2109). Ledipasvir did not inhibit the hepatic uptake transporter OCT1 (AD-256-2143) but showed moderate dose dependent inhibition of OATP1B1 and OATP1B3 with IC_{50} values of 3.5 µM and 6.5 µM, respectively (AD-256-2134). No inhibition of the renal transporters MRP4, OCT2, OAT1, OAT3, and MATE1 was detected (AD-256-2140). Ledipasvir showed minimal potential to inhibit the hepatic efflux pump for endogenous bile acids, BSEP with an IC_{50} of approximately 6 µM. LDV was found to be a substrate for Pgp and BCRP in vitro (AD 256 2144, AD-256-2150).	As LDV is a substrate for Pgp and BCRP, its absorption may be increased by inhibitors or decreased by inducers of these transporters. Consistent with in vitro data, administration of LDV with inhibitors of intestinal efflux transporters, such as SMV or darunavir boosted with ritonavir (DRV/r), resulted in modest (< 2-fold) increases in LDV plasma exposures (GS-US-256-0129, GS-US-344-0102). LDV/SOF may be coadministered with Pgp and/or BCRP inhibitors. Medicinal products that are potent Pgp inducers (eg, rifampicin, carbamazepine, and phenytoin) may significantly decrease ledipasvir plasma concentration, which may lead to reduced therapeutic effect of LDV/SOF. Such medicinal products should not be used with LDV/SOF. Use of herbal medicine St. John's wort (*Hypericum perforatum*), a potent Pgp inducer, is contraindicated in the SmPC.

SII.2. Sofosbuvir

Table SII.2. Table of Key Safety Findings from Non-Clinical Studies (Sofosbuvir)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Toxicity	
Single-dose toxicity	
SOF (administered as GS-9851) has minimal toxicity after oral dosing to rats (no observed adverse effect level [NOAEL] at 1800 mg/kg; SA-PSI-7851-09-0001).	Within LDV/SOF, the dose of SOF is 400 mg. The GS-331007 exposure at the NOAEL is approximately 15-fold higher when compared with the clinical exposure at 400 mg within LDV/SOF.
Repeat-dose toxicity	
Exploratory and definitive repeat dose toxicity studies have been conducted in mice, rats, and dogs (0515-09260; SA-PSI-7851-08-001; SA-PSI-7851-08-002; SA-PSI-7851-09-0002; SA-PSI-7851-09-0003; SA-PSI-7977-09-0006; SA-PSI-7977-09-0007; SA-PSI-7977-09-0008; SA-PSI-7977-10-0003; SA-PSI-7977-10-0004; TX-334-2012). The target organs identified were gastrointestinal (GI) tract (dog), heart (rat and dog), and liver (dog). Slight (< 10%) hematological changes	To date, manifestations of these target organ toxicities have not been observed in clinical studies with SOF.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
in red cell indices/erythropoiesis were also noted in the dogs. These target organs were identified at adverse (dog) or lethal doses (rat) of GS-9851 in the nonclinical species.	
Reproductive & Developmental Toxicity	
SOF did not have any adverse effects in reproductive and developmental toxicity studies (SA-PSI-7977-10-0005; SA-PSI-7977-10-0008; SA-PSI-7977-11-0008; TX-334-2003). Animal data indicate that SOF has no effect on fertility, does not cause reproductive or fetal toxicity, and has no effects on behavior, reproduction, or development of offspring. The predominant circulating metabolite GS-331007 was a predominant component observed in the milk of lactating rats at a milk to plasma ratio of 0.1 at 1 hour post-dose (SA-PSI-7977-11-0008).	Animal data indicate that SOF does not cause reproductive or fetal toxicity. Because there are no clinical data with SOF in pregnant women, as a precaution, it is preferable to avoid use of SOF (as a component of LDV/SOF) during pregnancy. The predominant circulating metabolite GS-331007 is excreted in rat milk. It is not known whether SOF and its metabolites are excreted in human breast milk. Mothers should be instructed not to breast-feed if they are taking LDV/SOF.
Nephrotoxicity	
SOF and GS-331007 showed little potential for DDIs mediated by renal transporters. GS-331007, cleared renally, was not a substrate, and showed little or no inhibition of the renally expressed transporters such as organic anion transporter (OAT)1, OAT3, OCT2, and multidrug and toxin extrusion 1 (MATE1) transporter (AD-334-2005).	The nonclinical data indicate a low likelihood for nephrotoxicity in humans. Based on clinical data, no dose adjustment of LDV/SOF is required for patients with mild or moderate renal impairment.
Hepatotoxicity	
SOF and GS-331007 showed little potential for DDIs mediated by hepatic transporters. Sofosbuvir is not a meaningful substrate, inhibitor, or inducer of CYP enzymes and does not inhibit UGT1A1 (AD-334-2013). Sofosbuvir and GS-331007 were not substrates or inhibitors of studied hepatic transporters (eg, OCT1, OATP1B1, OATP1B3, and bile salt export pump [BSEP]; AD-334-2004; AD-334-2005; PC-PSI-7977-11-0007). In dogs, dosing with GS-9851 (nucleotide prodrug; isomeric mixture containing GS-7977 [SOF; S diastereomer] and GS-491241 [R diastereomer])at 1500 mg/kg/day for 7 days (SA-PSI-7851-08-002) resulted in alterations in serum chemistry that were suggestive of liver injury (increased mean serum alanine transaminase [ALT], aspartate transaminase [AST], and bilirubin levels in both sexes) with associated histopathologic findings (hepatocellular hypertrophy, glycogen depletion, microvesiculation, and apoptosis). The serum chemistry changes and histopathologic findings were not observed at the end of the 14-day recovery period. In all other studies with SOF or GS-9851, liver related serum chemistry and	It should be noted that the alterations in serum chemistry with the associated histopathologic findings were only observed at 1500 mg/kg/day, a dose that was not tolerated in dogs; Day 7 GS-331007 exposure (area under the curve [AUC]) at 1500 mg/kg/day (sexes combined) is 71-fold higher when compared with the mean clinical exposure at 400 mg within LDV/SOF. No alterations were found at doses up to 500 mg/kg/day for 9 months. Additionally, Phase 2 and 3 clinical safety data with SOF do not indicate a clinically relevant adverse effect on the liver. No dose adjustment of SOF (as a component of LDV/SOF) is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B, or C).

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
histopathologic findings were not observed after daily oral doses up to 500 mg/kg/day for 9 months.	
Genotoxicity	
SOF was negative for mutagenic potential in a bacterial reverse mutation test, negative in a chromosome aberration test using human peripheral blood lymphocytes, and negative in an in vivo mouse micronucleus assay (SA-PSI-7851-08-003; SA-PSI-7851-08-004; SA-PSI-7851-08-005).	SOF is considered nongenotoxic.
Carcinogenicity	
Two-year oral gavage carcinogenicity studies with SOF were conducted in rats (TX-334-2001) and mice (TX-334-2002). In rats (TX-334-2001), SOF administered at 75, 250, and 750 mg/kg/day did not have any carcinogenic effect and did not affect the survivability of the animals. In mice (TX-334-2002), SOF administered at 20, 60, and 200 mg/kg/day for males and 60, 200, and 600 mg/kg/day for females did not affect the survivability or induce neoplastic/non-neoplastic changes at any dose level. No evidence of carcinogenic potential was observed in this study.	Carcinogenicity studies in rats and mice do not indicate any carcinogenicity potential for SOF administered at doses up to 600 mg/kg/day in mouse and 750 mg/kg/day in rat. Exposure to GS-331007 in these studies was at least 7 times (mouse) and 15 times (rat).
Safety Pharmacology	
General Safety Pharmacology	
In a battery of safety pharmacology studies, the effects of GS-9851 on the central nervous, cardiovascular, and respiratory systems were examined. There were no findings in the nonclinical safety pharmacology studies to suggest clinically relevant adverse neurological, cardiovascular, or respiratory effects (SA-PSI-7851-08-006; SA-PSI-7851-08-007; SA-PSI-7851-08-008; SA-PSI-7851-08-009; PC-PSI-7851-08-0023; PC-PSI-7851-08-0028; PC-PSI-7851-09-0001).	The nonclinical data indicate a low likelihood for neurological, cardiovascular, or respiratory effects in humans.
Cardiovascular	
In a 7-day repeat dose dog study, an increase (19%) in QT/QT interval corrected for heart rate (QTc) interval was observed in male but not female dogs at the high dose of 1500 mg/kg/day (SA-PSI-7851-08-002). There were no other waveform changes or electrocardiogram (ECG) findings. The changes in the QT/QTc intervals may be related to the poor condition of the 1500 mg/kg/day high dose animals. There were no cardiovascular findings in the single dose study in telemetry monitored animals up to 1000 mg/kg, nor in	At the adverse dose of 1500 mg/kg/day in dogs in the 7-day study, systemic exposure (C_{max}) to the predominant metabolite GS-331007 was approximately 90-fold greater than the plasma concentration measured in HCV infected subjects at the SOF therapeutic dose of 400 mg once daily within LDV/SOF (human GS-331007 C_{max} of 0.582 µg/mL). While the 7-day repeat dose rat study with GS-9851 indicated a potential toxicity, subsequent 7-day rat study with SOF at the same doses and exposures was well tolerated. In the 4-week repeat dose rat study with

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
dogs given daily oral doses of SOF up to 500 mg/kg/day for 9 months. In rats, high doses of GS-9851 at 2000 mg/kg/day caused multifocal cardiac myofiber degeneration that may have led to the death of several rats by Day 5 in the 7-day range-finding study (SA-PSI-7851-08-001). The myocardial findings were not associated with hematologic evidence of inflammation or higher serum AST concentration. Other biomarkers of myocardial damage (eg, troponins) were not evaluated in this initial toxicity study. Myocardial degeneration was also observed in a few rats at the same high dose 3 and 17 days after cessation of dosing, suggesting no or a slow resolution/recovery. In a 7-day rat toxicity study (Study TX-334-2012) using SOF alone, no early mortalities and no evidence of cardiac toxicity was observed at the high dose of 2000 mg/kg/day. GS-331007 exposure (AUC) at 2000 mg/kg/day SOF was also 29-fold (sexes combined) higher than the mean clinical exposure at 400 mg.	GS-9851 (SA-PSI-7851-09-0003), these myocardial findings were not observed at the highest tested dose (500 mg/kg/day) and there were no changes in the levels of creatine kinase and troponin I when compared to controls. Longer duration studies (up to 26 weeks; SA-PSI-7977-09-0007; SA-PSI-7977-10-0004) with SOF in rats did not show evidence of cardiac toxicity suggesting the effect observed in the 7-day study in rats was related to the very high systemic exposure achieved at lethal dose level. At the lethal dose of 2000 mg/kg/day GS-9851 in the 7-day study, systemic exposures to the predominant metabolite GS-331007 was approximately 29-fold (sexes combined) greater than the exposure in HCV-infected subjects at the therapeutic dose of 400 mg. In the 26-week chronic study (SA-PSI-7977-10-0004), there were no cardiac changes at exposure margins up to 9-fold (sexes combined). Taken together, the data suggest that the observed mortalities and cardiac toxicity in Study SA-PSI-7851-08-001 were the result of GS-491241 and that SOF, at similar exposures, does not produce the same effect. Furthermore, the thorough QT study conducted in healthy subjects at the supratherapeutic dose of 1200 mg did not reveal any effect of SOF on the QTc interval, and there were no clinically significant changes in ECG or wave morphology (P7977-0613). Taken together, the potential for SOF and its metabolites to induce clinically meaningful QT prolongation is considered low.
<u>Cardiovascular Effects with Amiodarone</u>	
Nonclinical studies (7 in vitro studies and 1 ex vivo study) have been conducted to evaluate a potential pharmacodynamic and/or pharmacokinetic mechanistic interaction between amiodarone and SOF in combination with another DAA. In the ex vivo guinea pig heart study, prolongation of the A-H interval was observed when amiodarone was combined with DCV, SMV or SOF compared to amiodarone alone. The triple combination of amiodarone, SOF and DCV resulted in the largest prolongation of the A-H interval, reflecting the observed clinical phenomenon (PC-334-2029 Addendum 1). Results from electrophysiology studies suggest that the human L-type calcium channel 3.2 (hCav3.2) and human hyperpolarization-activated, cyclic nucleotide-gated channel 4 (hHCN4) channels were not involved. Contradictory to the ex vivo guinea pig heart data, hCav1.2 channel may be indirectly inhibited by	The nonclinical data indicate that multiple pharmacodynamic and pharmacokinetic processes may contribute to the observed clinical phenomenon of symptomatic bradycardia in patients treated with amiodarone, SOF and another HCV DAA. The potential of amiodarone and DA to be victims or perpetrators of drug interactions mediated by these transporters is low. Amiodarone and the HCV DAAs are unlikely to cause drug-drug interactions through efflux and hepatic uptake transporters, and plasma or atrial tissue binding displacement.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
amiodarone with SOF or LDV (PC-334-2030, PC-334-2031, PC-334-2032). Data from in vitro studies show that amiodarone and its metabolite *N*-desethylamiodarone (DA) were neither inhibitors nor substrates of efflux transporters P-gp and BCRP, and hepatic uptake transporters OATP1B1 and OATP1B3 (AD-334-2028, AD-334-2029). Both amiodarone and DA appeared to be tightly bound (> 99%) to plasma and atrial tissue and all the tested anti-HCV agents including SOF and its nucleoside metabolite GS-331007 did not affect free fractions of both compounds (AD-334-2030, AD-334-2033).	
Other Toxicity-Related Information	
Secondary Pharmacodynamics	
Sofosbuvir has shown a low potential for toxicity in in vitro studies, since no significant cytotoxicity was observed when a panel of cell lines was treated with SOF. Specifically, SOF shows a low potential for mitochondrial toxicity, since no significant effects were observed on mitochondrial deoxyribonucleic acid levels or mitochondrial biogenesis in SOF-treated cells (PC-334-2012; PC-334-2013; PC-334-2015; PC-PSI-7851-08-0009; PC-PSI-7977-09-0007). Furthermore, no measurable inhibition of human deoxyribonucleic acid (DNA), RNA, or mitochondrial polymerases was observed with the triphosphate form of SOF in vitro, indicating a low likelihood for off-target effects (PC-334-2013; PC-PSI-7851-08-0029; PC-PSI-7851-09-0015).	The nonclinical data indicate a low likelihood for cytotoxicity in humans.
Mechanisms for Drug Interactions	
Transporter Drug Interactions	
Nonclinical data show that SOF is a substrate for the intestinal efflux transporters Pgp and BCRP (8215026; PC-PSI-7977-11-0006). Coadministration with inhibitors or inducers of these intestinal efflux transporters may affect the absorption of SOF from the GI tract (AD-334-2002).	Clinical data also show that SOF is a substrate for Pgp and that its intestinal absorption is limited by efflux transport by these transporters (P7977-1819). For example, the known Pgp and BCRP inhibitor, cyclosporine, was noted to increase A-B permeability through Caco-2 cells, corresponding to complete inhibition of efflux transport, and caused an increase in SOF levels in a clinical drug-drug interaction study. Therefore, administration with potent inducers of intestinal Pgp may decrease the absorption of SOF and lead to reduced delivery of the pharmacologically active triphosphate into the liver. However, coadministration with less potent inducers or those that do not markedly affect intestinal Pgp induction are unlikely to affect SOF levels.

SII.3. Ledipasvir/ Sofosbuvir

Table SII.3. Key Safety Findings from Non-Clinical Studies (LDV/SOF)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Toxicity	
Based on the well-defined toxicity profiles of the single agents, the combination of LDV and SOF is not anticipated to exacerbate known toxicities or lead to new toxicities. Therefore, combination toxicity studies with LDV and SOF are not required and were not conducted, in accordance with the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005, January 2008). The reader is referred to the toxicology profiles for the single agents (Sections SII.2 and SII.1).	At the proposed doses of 90 mg LDV and 400 mg SOF in the FDC, the clinical safety profiles of both compounds when administered as single agents, or as the LDV/SOF FDC, indicate no safety or tolerability issues to date. None of the toxicities observed in the nonclinical studies with the individual agents have been observed in the clinic.
Safety Pharmacology	
Ledipasvir and SOF when tested alone have no clinically meaningful off-target binding activity and both agents have no relevant effects on vital organ systems in safety pharmacology studies. Given the lack of effects for LDV and SOF on the vital organ systems, no additional safety pharmacology studies using the combination of LDV/SOF FDC are considered warranted.	Since there are no overlapping safety considerations and as single agents, LDV and SOF have no adverse effects in the safety pharmacology studies, the combination is unlikely to have significant effects on the respiratory, central nervous system (CNS), or cardiovascular system.
Mechanisms for Drug Interactions	
The FDC of LDV and SOF is primarily supported by nonclinical studies completed with the individual agents, as described above. Ledipasvir and SOF may be involved in transporter related drug-drug interactions (DDIs) during the process of intestinal absorption. Ledipasvir and SOF are substrates for intestinal efflux transporters and their intestinal absorption may be increased by coadministration with inhibitors of intestinal efflux transporters or reduced by inducers. Sofosbuvir is a substrate but not an inhibitor of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). Ledipasvir is a substrate and inhibitor of Pgp and BCRP at concentrations achievable during intestinal absorption. Nonclinical studies suggest that SOF is not an inhibitor or inducer of major drug metabolizing enzyme systems. In vitro data indicate that LDV may be a weak inducer of metabolising enzymes such as CYP3A4, CYP2C and UGT1A1. In vitro LDV inhibits intestinal CYP3A4 and UGT1A1.	Potent Pgp inducers (such as rifampicin) decrease LDV/SOF plasma concentrations, which could lead to reduced therapeutic effect of LDV/ SOF. Potent Pgp inducers should not be used with LDV/SOF. This interaction is included in the SmPC as a Warning and Precaution and is an important potential risk for LDV/SOF. Use of herbal medicine St. John's wort is contraindicated in the SmPC. When LDV/SOF is administered with TDF + a PK enhancer (COBI or ritonavir), TFV concentrations increase; the mechanism for this increase is currently unknown. This interaction is included in the SmPC as a Warning and Precaution and is an important potential risk for LDV/SOF.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Ledipasvir and SOF have more limited potential for transporter related drug-drug interactions in the liver or systemic circulation. Neither SOF nor LDV are substrates for hepatic uptake transporters (organic cation transporter [OCT]1, organic anion transporting polypeptide [OATP]1B1, and OATP1B3). Ledipasvir is an inhibitor of the hepatic transporters OATP1B1 and OATP1B3 (IC_{50} of 3.5 and 6.5 µM, respectively) at concentrations greatly exceeding plasma maximum observed plasma concentration of drug (C_{max}) (409 nM total; < 1 nM unbound). Sofosbuvir, GS-331007, and LDV do not inhibit other tested hepatic and renal transporters at clinically relevant concentrations. The active tubular secretion component of the renal elimination of GS-331007 is not mediated by transporters implicated in renal drug-drug interactions.	

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The following tables in this section present clinical study exposure data to Harvoni up to 05 December 2018 from the following studies in subjects with HCV infection:

- Completed studies: GS-US-334-0111, GS-US-337-0101, GS-US-337-0127, GS-US-337-0128, GS-US-337-1115, GS-US-337-1306, GS-US-337-1501, GS-US-337-1603, GS-US-337-1624, GS-US-337-2091, GS-US-338-1130, GS-US-344-0102, GS-US-366-1689, GS-US-380-1761, GS-US-334-1274, GS-US-337-0102, GS-US-337-0108, GS-US-337-0109, GS-US-337-0113, GS-US-337-0115, GS-US-337-0118, GS-US-337-0121, GS-US-337-0122, GS-US-337-0123, GS-US-337-0124, GS-US-337-0125, GS-US-337-0131, GS-US-337-0133, GS-US-337-1116, GS-US-337-1118, GS-US-337-1119, GS-US-337-1405, GS-US-337-1406, GS-US-337-1428, GS-US-337-1445, GS-US-337-1463, GS-US-337-1468, GS-US-337-1512, GS-US-337-1612, GS-US-337-1643, GS-US-337-1701, GS-US-337-1746, GS-US-337-1903, P7977-0523 (part 6), GS-US-366-1992, GS-US-334-0154.

- Ongoing Open-Label/Unblinded studies: GS-US-337-1655, GS-US-337-1904, GS-US-337-4063

Table SIII.1. Duration of Harvoni Exposure in Subjects with HCV Infection

Duration Of Exposure	Persons	Person-Days
≥ 1 Day	6904	618279
>30 Days	6227	608926
>90 Days	1259	215758
>180 Days	82	19694
>365 Days	0	0

Table SIII.2. Harvoni Exposure by Age Group and Gender in Subjects with HCV Infection

Age Group (Years)	Persons		Person-Days	
	Male	Female	Male	Female
3-<6	10	24	846	1948
6-<12	54	38	4666	3408
12-<18	53	66	4477	5542
18-24	108	54	4133	2939
25-34	380	245	20178	14026
35-44	587	322	40893	21402
45-54	1112	642	107809	59884
55-64	1582	867	167546	84036
65-74	379	306	38638	28719
75-84	39	36	3816	3373
≥85	0	0	0	0

Table SIII.3. Exposure by Ethnic origin in Subjects with HCV Infection

Ethnic origin	Persons	Person-Days
White	4751	439872
Black or African American	854	68008
Asian	1179	98852
American Indian or Alaska Native	18	1611
Native Hawaiian or Other Pacific Islander	35	3442
Other	61	5900
Not Permitted	6	594

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Pregnant females	Limited information on the use in this patient population	No Rationale: SOF and LDV have not been shown to be teratogenic in nonclinical studies. Safety in pregnancy is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of HVN in pregnancy have been identified.
Females who are breast feeding	Limited information on the use in this patient population	No Rationale: Safety in breastfeeding women is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of HVN in breastfeeding have been identified.
Medicinal products excluded from concurrent use, identified as drug-drug interaction (DDIs): Potent intestinal Pgp inducers, Proton pump inhibitors (PPIs) rosuvastatin, digoxin	Pgp inducers and PPIs excluded due to potential decreases in exposure of LDV/SOF. Rosuvastatin excluded as LDV is an inhibitor of BCRP and coadministration would result in increased exposure of rosuvastatin, possibly resulting in an increased risk of myopathy/rhabdomyolysis Digoxin excluded as LDV is a Pgp inhibitor and coadministration would result in increased exposure of digoxin, which has a narrow therapeutic index and could possibly result in digoxin toxicity.	No Rationale: Cases of DDIs are reviewed on an ongoing basis as part of routine pharmacovigilance and are presented in PSURs/PBRERs. No safety signals have been identified following review of these cases regarding DDIs and current labeling is considered sufficient.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	Approximately 6900 subjects have been exposed to LDV/SOF in the LDV/SOF clinical study program.	The clinical study population is large enough to detect at least uncommon adverse drug reactions (ADRs).
Due to prolonged exposure	There is no experience with prolonged exposure (ie, over 1 year) to LDV/SOF in the LDV/SOF clinical study program.	The duration of LDV/SOF treatment is no more than 24 weeks; prolonged exposure (ie, over 1 year) is not applicable.
Due to cumulative effects	Safety data from clinical studies is available for the proposed durations of treatment.	No cumulative effects of LDV/SOF have been identified in the LDV/SOF clinical study program.
Which have a long latency	Safety data was collected for up to 30 days after the last dose was administered.	No ADRs to LDV/SOF with a long latency have been identified in the LDV/SOF clinical study program.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV.3. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure	Considered to be Missing Information
Safety in children (<3 years of age)	No subjects aged < 3 years of age have been exposed to HVN in clinical studies	No Rationale: LDV/SOF is not indicated in patients < 3 years of age. No specific risks in pediatric patients are anticipated and ongoing review of pediatric data presented in PSURs/PBRERs has not identified any safety concerns regarding off-label pediatric use
Pregnant women	Not included in the clinical development program	No Rationale: LDV and SOF have not been shown to be teratogenic in nonclinical studies. Safety in pregnancy is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of HVN in pregnancy have been identified.

Type of Special Population	Exposure	Considered to be Missing Information
Breastfeeding women	Not included in the clinical development program	No Rationale: Safety in breastfeeding women is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. No safety concerns regarding use of HVN in breastfeeding have been identified.
Patients with End Stage Renal Failure or Severe Renal Insufficiency	Twenty (20) subjects with HCV and severe renal impairment were exposed to SOF+RBV for 24 weeks (Cohorts 1 and 2) and 18 subjects with HCV and severe renal impairment were exposed to LDV/SOF for 12 weeks in study GS-US-334-0154 (Cohort 3); 95 subjects with HCV on dialysis for ESRD were exposed to LDV/SOF for 8-24 weeks in study GS-US-337-4063; 59 subjects with HCV on dialysis for ESRD were exposed to SOF/VEL for 12 weeks in study GS-US-342-4062.	No Rationale: No safety signals or toxicities were identified in subjects with severe renal impairment or ESRD in studies GS-US-334-0154, GS-US-337-4063, and GS-US-342-4062. No dosage adjustment of LDV/SOF is required for patients with renal impairment, including ESRD requiring dialysis. Given that there are now clinical study data regarding the use of LDV/SOF, SOF/VEL, and SOF+RBV in subjects with HCV infection and severe renal impairment or ESRD which indicates that treatment with SOF or SOF-combination products is safe and well tolerated and there are no additional pharmacovigilance activities ongoing to provide further information on this safety concern, safety in patients with end stage renal failure or severe renal insufficiency is not considered as a category of 'Missing information' in this EU-RMP.
Subpopulations with IL-28B polymorphisms	356 subjects with IL28B CC genotype were exposed to LDV/SOF monotherapy for 8-24 weeks in pivotal studies (ION-1, ION-2, and ION-3); 835 subjects with IL28B non-CC genotype were exposed to LDV/SOF monotherapy for 8-24 weeks in pivotal studies (ION-1, ION-2, and ION-3)	No Rationale: In the pivotal studies SVR 12 rates in subjects with, IL28B polymorphisms, were generally consistent with the overall SVR12 results between treatment groups.

Type of Special Population	Exposure	Considered to be Missing Information
Patients with previous HCC	Not included in the clinical development program	No A study has been conducted jointly between Gilead and other marketing authorization holders (MAHs) of DAAs, to assess the impact of DAA treatment on the incidence of HCC recurrence in patients with previous HCC. Following the completion of the study, the conclusion was that DAA treatment had no impact on the safety of patients with a previous HCC, and this topic was no longer considered an area of missing information.
Development of resistance	Long term follow-up of NS5A resistance in patients who failed therapy with LDV/SOF was not available during the Phase 2 and Phase 3 clinical studies.	No Rationale: Given that there are no outstanding additional pharmacovigilance activities (other than routine pharmacovigilance) ongoing to provide further information on development of resistance, no safety issues regarding resistance have been identified during clinical studies and extensive postmarketing experience with HVN, development of resistance is not considered as a category of 'missing information' in this EU-RMP.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Sales Data

The number of bottles sold during the period of this PSUR/PBRER was multiplied by 28 to provide the number of tablets sold. As Harvoni is taken once daily, this figure was divided by 365.25 to provide patient-years of treatment. Given the various treatment durations for which Harvoni can be administered (i.e., 8 or 12 weeks), patient exposure has been standardized to patient-years.

It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors and wastage.

Prescription Data

Estimates of the demographics of HCV infected patients exposed to Harvoni in the EU (in 5 EU countries: UK, France, Germany, Italy, and Spain) were obtained from prescription data from the following source:

- IMS/GERS by country converted to DoT (Days of Treatment)
- DoT consolidated to provide EU5 aggregate
- Using a patient calculation estimate regarding treatment duration DoT are converted to patient numbers by brand

Therapy Watch HCV EU5 is a quarterly tracking study of the hepatitis C market for Gilead. Data have been collected on a continuous basis, with sample launched in batches to ensure coverage across each month in the quarter. Per wave, 250 HCV treaters are surveyed across EU5 and HCV patient record forms (PRFs) from recently seen patients are completed online, including the following:

- 7 dynamic PRFs (Treatment naïve/experienced who were initiated on treatment in last 12 weeks) each wave
- 7 total PRFs collected each wave (last 7 HCV patients seen, irrespective of treatment status)

SV.1.2. Exposure

SV.1.2.1. Exposure Based on Sales Data

Cumulative patient exposure to Harvoni since first marketing approval in the US on 10 October 2014 to 30 June 2025 is estimated to be 270,837 patient-years, including 48,145 patient-years in the EU.

SV.1.2.2. Exposure Based on Prescription Data

Based on prescription data from UK, France, Germany, Italy and Spain, most patients exposed to HVN were Caucasian males and 46 years of age or older.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for LDV/SOF to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new important identified, important potential risks or missing information have been identified for HVN since the submission of the last RMP.

Risks previously classified as important removed from the list of safety concerns, along with the reasons for their removal, are presented in Table SVII.1.

Table SVII.1 Reason for Removing an Important Identified or Potential Risk or Missing Information from the List of Safety Concerns in the RMP

Safety Concern Removed	Reason for Removal From the List of Safety Concerns
Identified risk	
Severe bradycardia and heart block when used with concomitant amiodarone	Recommended by PRAC to remove the important identified risk of Severe bradycardia and heart block when used with concomitant amiodarone from the list of safety concerns. There are no outstanding additional risk minimization measures or additional PV activities for this risk. Given that the management of this risk is fully integrated into standard clinical practice, the risk is considered fully characterized and appropriately managed. The risk will continue to be monitored through routine pharmacovigilance.
HBV reactivation in HBV/HCV coinfected patients	Recommended by PRAC to remove the important identified risk of HBV reactivation in HBV/HCV coinfected patients from the list of safety concerns. There are no outstanding additional risk minimization measures or additional PV activities for this risk. Given that the management of this risk is fully integrated into standard clinical practice, the risk is considered fully characterized and appropriately managed. The risk will continue to be monitored through routine pharmacovigilance.

Following removal of these safety concerns by the MAH, there will be no safety concerns for Harvoni in the EU-RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for Harvoni.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for Harvoni.

SVII.3.2. Presentation of the Missing Information

There is no missing information for Harvoni.

PART II: MODULE SVIII- SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires in Annex 4.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. Additional Pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities for any of the safety concerns.

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

III.3. Summary table of additional pharmacovigilance activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV:
PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies for HVN.

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. Routine risk minimization measures

The routine risk minimization measures for HVN in the EU comprises the SmPC, the package leaflet (PL), and the legal status of the product. HVN is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HCV infection (SmPC Section 4.2). There are no individual safety concerns for HVN.

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
None	
Important Potential Risks	
None	
Missing information	
None	

V.2. Additional Risk minimization measures

Routine risk minimization activities are described in Part V Section V.1. No additional risk minimization measures are warranted as there are no safety concerns for the medicinal product.

V.3. Summary risk minimization measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. Summary of risk management plan for Harvoni (Ledipasvir/Sofosbuvir)

This is a summary of the risk management plan (RMP) for Harvoni. The RMP details important risks of Harvoni, how these risks can be minimized, and how more information will be obtained about Harvoni's risks and uncertainties (missing information).

Harvoni's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Harvoni should be used.

This summary of the RMP for Harvoni should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Harvoni's RMP.

II. The Medicine and What is it Used for

Harvoni is authorized for the treatment of chronic hepatitis C (CHC) in adults and in pediatric patients aged 3 years and above (see SmPCs for the full indication). It contains sofosbuvir (SOF) and ledipasvir (LDV) as active substances and it is given orally.

Further information about the evaluation of Harvoni's benefits can be found in Harvoni's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/harvoni.

III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Harvoni, together with measures to minimize such risks and the proposed studies for learning more about Harvoni's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Harvoni is not yet available, it is listed under 'missing information' below.

III.A. List of important risks and missing information

Important risks of Harvoni are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Harvoni. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

III.B. Summary of Important Risks

Harvoni has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby Harvoni therapy should be initiated by a doctor experienced in the management of HCV infection (as described in section 4.2 of the SmPC).

There are no important risks or missing information for Harvoni.

III.C. Post-authorization Development Plan

III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or a specific obligation of Harvoni.

III.C.2. Other Studies in Post-Authorization Development Plan

There are no studies required for Harvoni.

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

Not applicable

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material

Annex 8. Summary of Changes to the Risk Management Plan over Time

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