EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2014
EMA/702742/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Harvoni

International non-proprietary name: ledipasvir / sofosbuvir

Procedure No. EMEA/H/C/003850/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma/serum/PBMC concentration versus time curve
AUC_{tau}	AUC over the dosing interval
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
BQL	Below the Quantification Limit
CatA	cathepsin A
CES1	carboxyl esterase 1
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed plasma/serum/PBMC concentration of drug
CsA	cyclosporine (cyclosporin A)
DAA	direct-acting antiviral
DDI	drug-drug interaction
$EC_{50/90}$	half-maximal/90% effective concentration
eGFR	estimated glomerular filtration rate
FMO	flavin monooxygenase
GGT	gamma-glutamyltransferase
GT	genotype
H2RA	H2-receptor antagonist
HINT1	histidine triad nucleotide binding protein 1
IC_{50}	half-maximal inhibitory concentration
IFN	interferon
IL28B	interleukin 28B gene
ka	Absorption rate constant
LDV	ledipasvir
LLOQ	lower limit of quantitation
MATE1	multidrug and toxin extrusion protein 1
mRNA	messenger ribonucleic acid
MRP2	multidrug resistance-associate protein 2
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NS (3/4A/5A/5B)	nonstructural protein (3/4A/5A/5B)
OATP	organic anion transporting polypeptide
OC	Ortho Tri-Cyclen Lo
OCT	organic cation transporter
Peg-IFN	pegylated interferon
P-gp	p-glycoprotein
PI	protease inhibitor
PopPK	Population Pharmacokinetics
PXR	Pregnane X receptor
Q	Quartile
QD	Once Daily
/r	boosted with ritonavir
RAL	raltegravir
RAV	resistance-associated variant
RBV	ribavirin
SOF	sofosbuvir

SVR	sustained virologic response
TE	treatment experienced
TFV	Tenofovir
TGV	Tegobuvir
TN	treatment naive
UGT	uridine disphosphate glucuronosyltransferase
ULN	upper limit of the normal range
Vc	Apparent central volume of distribution
VDV	Vedroprevir, GS-9451
Vp	Apparent peripheral volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 28 February 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Harvoni, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2013.

The applicant applied for the following indication: Harvoni is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 in adults (see sections 4.2, 4.4 and 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ledipasvir was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0248/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0248/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

The application did not contain a critical report pursuant with Article 8 of the Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance ledipasvir contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19/01/2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Gilead Sciences Limited.
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Joseph Emmerich

CHMP Peer reviewer(s): Greg Markey

The EMA Product Team Leader: Sabrina Spinosa Guzman

- The application was received by the EMA on 28 February 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 20 February 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 June 2014 (Annex 2). In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 21-24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2014 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 September 2014.
- The Rapporteurs circulated a list of outstanding issues on 18 September 2014 to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 September 2014.
- During the meeting on 22-25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Harvoni.

2. Scientific discussion

2.1. Introduction

Chronic Hepatitis C virus (HCV) infection is a global health problem with an estimated 170 million individuals infected worldwide. HCV infection is a major European public health challenge, with a prevalence of 0.4-3.5% in different EU member states. It is the most common single cause of liver transplantation in the Union. HCV is divided into six major genotypes and numerous subtypes, which are based on phylogenetic relationship. Genotype 1 is the most common genotype in Europe, comprising approximately 70 % of infections. Genotype 3 is second most common, followed by genotype 2. Genotype 4 is predominant in Egypt, the nation in the world with the highest documented HCV prevalence. Genotypes 5 and -6 are uncommon in Europe and the US, but are more common in South Africa and South-East Asia, respectively (Simmonds et al, Hepatology 2005). HCV genotype does not clearly impact the rate of disease progression. Treatment response, or the required drug pressure (number of drugs, treatment duration) needed to obtain maximal activity with presently approved regimens, differs between genotypes.

The goal of antiviral therapy against HCV is to reach sustained virological response (SVR), which has traditionally been defined as the absence of quantifiable virus in plasma at least 24 weeks after the end of therapy (SVR24). However, most relapses occur within 4 weeks of treatment discontinuation, and a 98-99% concordance has been shown between absence of quantifiable virus 12 weeks after therapy, and SVR24 (Florian et al, AASLD 2011). Therefore the absence of measurable virus 12 weeks post end of treatment (SVR12) is presently considered accepted by European and US regulators as the primary endpoint in clinical trials. Though occasional late relapses occur, in general the durability of SVR has been demonstrated (e.g., Ng and Saab, Clin Gastroenterol Hepatol 2011). Of note, SVR4 (absence of quantifiable virus 4 weeks after treatment discontinuation) has an approximately 90% positive predictive value for SVR24 (Florian et al, AASLD 2011).

Until the European Commission marketing authorisation of sofosbuvir in January 2014, all approved therapeutic regimens for the treatment of chronic HCV infection contained an interferon. For the treatment of genotype 1 infection, the addition of either one of the NS3/4A protease inhibitors telaprevir or boceprevir, authorised in 2011, was considered standard of care. For genotypes other than GT-1, there were no direct-acting antivirals (DAA) authorised, therefore dual therapy with pegIFN/RBV was the standard of care.

Interferon-based therapies have limited efficacy in many patients and are associated with potentially serious side effects that are important in limiting real life effectiveness. These include a risk of hepatic decompensation and septicaemia in patients with advanced liver disease, as well as bone marrow suppression. Also, there are psychiatric side effects such as depression, which considerably limits eligibility to treatment in the target population (e.g., Bini et al, Am J Gastroenterol 2005).

For these reasons, the development of highly effective interferon-free regimens for the treatment of hepatitis C targets addresses an important previously unmet medical need.

SOF/LDV is a fixed-dose combination (FDC) tablet containing sofosbuvir (a previously approved NS5B polymerase inhibitor) and ledipasvir, a new NS5A-inhibitor. HCV NS5A is a multifunctional protein with key functions in HCV replication, virus assembly, and the modulation of cellular signaling pathways (e.g., Sheel and Rice, Nature Medicine, 2013).

The FDC tablet contains 400 mg of SOF and 90 mg of LDV. SOF/LDV has the potential to be a simple and effective all-oral, once-daily treatment regimen for chronic HCV infection.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 90 mg of ledipasvir and 400 mg of sofosbuvir as active substances.

Other ingredients are copovidone, lactose monohydrate, microcrystaline cellulose (E460i), croscarmellose sodium (E468), colloidal silicon dioxide (E551), magnesium stearate (E470b), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b) and Sunset Yellow FCF aluminium lake (E110).

The product is available in high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure, silica gel desiccant and polyester coil.

2.2.2. Active Substance

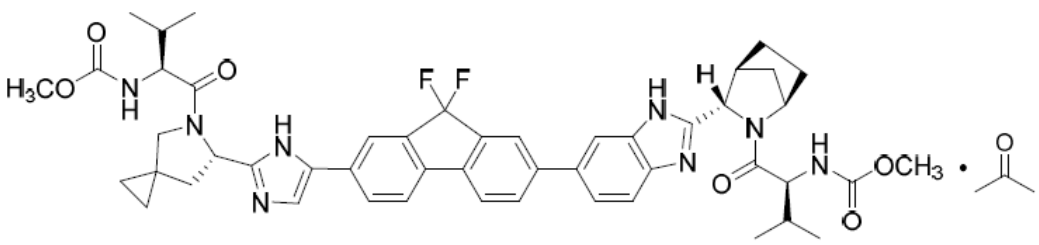
General information

The finished product is a fixed dose combination of two active substances: ledipasvir and sofosbuvir. Ledipasvir has never previously been assessed or marketed in the EU. Sofosbuvir, however, is the active ingredient of the already-authorised product Sovaldi. Information on its quality is essentially the same as in the Sovaldi dossier.

Ledipasvir

General information

The chemical name of ledipasvir acetone solvate (LDV-AS) is methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate propan-2-one (1:1), also known as carbamic acid, *N*-[(1*S*)-1-[[(6*S*)-6-[5-[9,9-difluoro-7-[2-[(1*R*,3*S*,4*S*)-2-[(2*S*)-2-[(methoxycarbonyl)amino]-3-methyl-1-oxobutyl]-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl]-9H-fluoren-2-yl]-1*H*-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl]carbonyl]-2-methylpropyl]-, methyl ester, compd. with 2-propanone (1:1) or methyl {(1*S*)-1-[(1*R*,3*S*,4*S*)-3-{5-[9,9-difluoro-7-(2-{(6*S*)-5-[*N*- (methoxycarbonyl)-l-valyl]-5-azaspiro[2.4]hept-6-yl}-1*H*imidazol-4-yl)-9H-fluoren-2-yl]-1H-benzimidazol-2-yl}-2-azabicyclo[2.2.1]heptane-2-carbonyl]-2-ethylpropyl}carbamate, compound with 2-propanone (1:1) and it has the following structure:



The structure of ledipasvir was unambiguously confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, UV spectroscopy, IR spectroscopy, high resolution mass spectrometry, elemental analysis and X-ray crystallography.

LDV-AS is a white to tinted (off-white, tan, yellow, orange, or pink), slightly hygroscopic crystalline solid. It shows pH dependent solubility in aqueous media: it is slightly soluble in pH 2.3 buffer but practically insoluble in pH 4-7.5 buffers. It is freely soluble in ethanol and DMSO and slightly soluble in acetone.

Ledipasvir is chiral and possesses 6 stereogenic centres and enantiomeric purity is controlled in starting material specifications. Three crystalline forms are known and ledipasvir acetone solvate is the designated commercial form. The first step for finished product manufacture involves the dissolution of ledipasvir in ethanol followed by spray-drying and thus precise control of morphology and particle size is not considered important.

Ledipasvir is a chemical substance not previously authorised as a medicinal product in the European Union. Furthermore, it is not a salt, complex, derivative or isomer, (nor mixture of isomers), of a previously authorised substance. Whilst it contains some structural features in common with daclastavir, it is metabolically stable and the applicant presented data indicating that there are no common active metabolites. Therefore, the therapeutic moieties are not the same. Ledipasvir thus meets the definition of a New Active Substance according to the Notice to Applicants (NtA), Vol 2A, Chapter 1, Annex 3.

Manufacture, characterisation and process controls

Ledipasvir is synthesized by multiple manufacturers in five main steps using four well-defined starting materials with acceptable specifications. Manufacturing process design and process controls ensure the consistent quality of ledipasvir AS.

The applicant's original proposal for starting material definition was rejected by the CHMP. The applicant agreed to re-define as requested and was able to do this for two materials before CHMP opinion. Re-definition of a further starting material and implementation of GMP standards for additional steps of the synthetic process will be completed by May 2015. The CHMP agreed to this proposal as no immediate concerns with regard to the quality of the active substance have arisen in relation with the above for these steps. Nevertheless, the re-definition of the starting materials is considered essential in ensuring the continued quality of the active substance throughout the product life-cycle. Adherence to GMP and the associated controls of manufacturing steps will help to prevent a drift in the impurity pattern.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Active substance critical quality attributes were identified based on their ability to impact finished product performance. The proposed control strategy includes raw material specifications, manufacture under GMP, in-process controls and release testing. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered acceptable.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (UV, HPLC, GC (for acetone)), assay (HPLC), acetone content (GC), impurities (HPLC), elemental impurities (ICP-MS), residual solvents (GC), water content (KF) and clarity of solution (in-house method). Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data for 20 batches of the active substance are provided. The batches were manufactured on pilot and commercial scale and were used for clinical trials, stability and toxicology studies and process validation. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on eight batches of LDV-AS manufactured using the proposed commercial process stored in the intended commercial packaging for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability was also tested under stressed conditions. One commercial scale batch was stored at 50, 5 and -20 ºC for up to 4 weeks. Photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. LDV-AS was also exposed to high temperature in the solid state (100 ºC), and in solution (50 ºC). Samples were also exposed to acidic (1.2 M HCl, 60 ºC), basic (1.2 M NH4OH, 60 ºC) and oxidative (H2O2) forced degradation conditions. The following parameters were tested: appearance, impurities (HPLC), assay (HPLC) and water content (KF). The analytical methods used were the same as for release. The analytical methods used were the same as for release and were stability indicating.

No significant changes to any of the measured parameters, other than a minor increase in water content, occurred on storage under long term, accelerated or stressed conditions. A large (up to 3.7%) increase in a highly coloured photo-degradation product was observed in the photostability study. Degradation also occurred under acidic, basic, and oxidative forced degradation conditions. As a result, the active substance is stored protected from light.

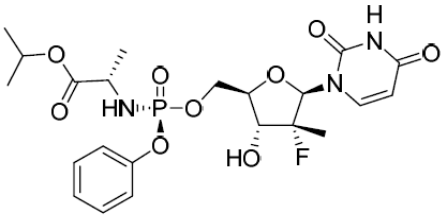
The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

The applicant will complete all on-going stability studies under long term conditions up to at least the 36 month time point. In addition, stability studies will be carried out on the first 3 commercial batches of LDV-AS and at least one commercial batch per year.

Sofosbuvir

General information

The chemical name of sofosbuvir is (*S*)-isopropyl-2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate and it has the following structure:



The structure of Sofosbuvir was unambiguously confirmed by ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR, UV spectroscopy, IR spectroscopy, mass spectrometry, elemental analysis and single crystal X-ray crystallography.

Sofosbuvir is a white to off-white non-hygroscopic crystalline solid, slightly soluble in water (pH 1.2-7.7), freely soluble in ethanol and acetone, soluble in 2-propanol, and insoluble in heptane.

Sofosbuvir is chiral and possesses 6 stereogenic centres which are well controlled by the synthetic process and the specifications of raw materials. The absolute and relative configuration of these chiral centres was established by single crystal X-ray crystallography. Eight polymorphic forms of Sofosbuvir have been observed and the manufacturing process consistently produces Sofosbuvir as the most thermodynamically stable polymorphic form, containing a small amount of a metastable form which were determined to be pharmaceutically equivalent as per ICH Q6A (decision tree #4). Other polymorphic forms are excluded by the manufacturing process and their absence is confirmed by DSC.

Manufacture, characterisation and process controls

Sofosbuvir is synthesized in six synthetic steps using three well-defined starting materials with acceptable specifications. Sofosbuvir possesses six stereocentres and its manufacture under GMP occurs at multiple manufacturers.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set based on the manufacturing experience to date. It is recommended that the applicant considers tightening the impurity limits when sufficient commercial scale experience has been gained to fully assess the capability of the manufacturing process.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), clarity of solution, assay (HPLC), impurities (HPLC), residual solvents and volatile organic impurities (GC), metals (ICP), particle size (Ph. Eur.), and polymorphic form (DSC – Ph. Eur.). Rationale for the absence of tests for water content (non-hygroscopic) and microbiological testing (low water content and water activity, isolation from organic solvent) was considered justified. Residue on ignition testing is not suitable as the active substance contains phosphorous: this test is replaced with a combination of clarity of solution test and ICP for elemental impurities. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 33 batches of the active substance ranging from laboratory through pilot to commercial scale, and used for development, stability, toxicology, clinical studies, and validation were provided. Assessment focussed primarily on later pilot commercial scale batches used for development, stability and validation. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on 8 pilot scale batches of active substance from the proposed manufacturers, as well as the applicant itself, in a container closure system representative of that intended for the market, for up to 12 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following ICH guideline Q1B was performed on 1 batch. Stressed studies were carried out on a single

batch between -20 and 50 ºC for up to 4 weeks. Forced degradation was carried out under acidic (0.1 M HCl), alkaline (10 mM Na_2CO_3) and oxidative (3% H_2O_2) conditions and at 105 ºC.

The parameters tested were appearance, assay, impurity content, water content, and polymorphic form. The analytical methods used were the same as for release, except for water content, measured by GVS, and were stability indicating.

Sofosbuvir was shown to be stable under long-term, accelerated and stressed conditions and is not sensitive to light. Forced degradation revealed that the active substance may degrade *via* oxidation or hydrolysis in solution, but remains stable in the solid state even up to 105 ºC after 1 week.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed 24 months retest period in the proposed container.

The applicant will complete all on-going stability studies under long term conditions up to the 60 month time point. In addition, stability studies will be carried out on the first 3 commercial batches of sofosbuvir. Furthermore, at least 1 commercial batch from each proposed manufacturer per year will be placed on a long-term stability study.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The objective was to develop an immediate release orally available formulation containing a fixed dose combination of ledipasvir and sofosbuvir, stable over the shelf-life of the product, and with reliable bioavailability characteristics.

Ledipasvir exhibits low, but pH-dependent, solubility and high apparent permeability (BCS class II). It is susceptible to the influence of gastrointestinal pH and fed state and so an amorphous spray-dried dispersion of LDV (LDV-SDD) was developed in order to mitigate these food effects. LDV-SDD is an amorphous solid powder. It is hygroscopic and photosensitive, but physically and chemically stable for up to 6 months if protected from light and moisture in a sealed container. The physicochemical properties of LDV-SDD are amenable to formulation in a solid oral tablet.

By contrast, sofosbuvir is highly soluble but has low apparent intestinal permeability (BCS class III). It exhibits pH-independent solubility across a pH range from 1.2-7.7. Sofosbuvir is a crystalline solid, routinely manufactured as the most stable polymorphic form containing small quanitites of an equivalent polymorphic form. It is neither hygroscopic nor photosensitive and is stable to oxidation and hydrolytic degradation at neutral pH. Sofosbuvir particle size was found to be critical for dissolution rate, so the active substance is sieved or screen milled and particle size is controlled by specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Compatibility studies of both active substances with the chosen excipients, and with each other, demonstrated that both are stable in the proposed formulation.

Phase I and II clinical trials were carried out with ledipasvir as a single agent. The phase I formulation used ledipasvir amorphous free base in film-coated tablets. The crystalline D-tartrate salt of ledipasvir was used for early phase II trials, and LDV-SDD introduced for later phase II trials to mitigate against food effects. An improvement in *in vivo* performance was demonstrated LDV-SDD as compared to the other ledipasvir forms. Phase III trials used film-coated tablets with a fixed-dose combination of both active substances. The combination tablet showed equivalent pharmacokinetic performance to co-administered

single agent tablets. The only other changes made during phase III trials involved tablet debossing and changing the colour of the film coating.

A dissolution method was developed to distinguish between physiologically relevant properties of the active substances and was demonstrated to be discriminatory.

The primary packaging is high density polyethylene (HDPE) bottles with a polypropylene child-resistant closure, a silica gel desiccant and a polyester coil. The materials comply with Ph. Eur. and EU regulation requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two separate parts.

The LDV spray drying process process is controlled by set-points and normal operating ranges (NORs) during the process. The resultant LDV-AS is considered an intermediate and its quality is controlled by a specification with tests for appearance, appearance (visual inspection), identification (HPLC, IR, NIR), water content (Ph. Eur.), assay (HPLC), degradants (HPLC), amorphous form (XRPD) and particle size (laser light scattering).

The tablet manufacturing process consists of 4 main steps: blending of LDV-SDD and sofosbuvir with intra-granular excipients followed by granulation; blending of granules with extra-granular excipients followed by compression to form tablet cores; film-coating; packaging. The process is considered to be a standard manufacturing process. In-process controls are carried out for critical steps of the manufacturing process.

The applicant will perform a formal validation of the manufacturing process with the first three commercial batches manufactured at each proposed manufacturing site prior to commercial distribution. A validation protocol has been provided and is considered acceptable, given the standard manufacturing process. The in-process controls are adequate for the production of film-coated tablets.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise tests for appearance (visual inspection), identification (HPLC, UV), water content (Ph. Eur.), strength (HPLC), degradants (HPLC), uniformity of dosage units (Ph. Eur.) and dissolution (Ph. Eur.). Studies showed that the finished product tablets exhibit low water activity indicating unfavourable conditions for microbial growth. As stated in ICH Q6A, Decision Tree 8, the absence of microorganism growth at tablet release testing justify excluding routine microbiological limit testing for a non-sterile drug product. Nonetheless, a non-routine microbial examination test (Ph. Eur.) will be included in the product specification.

Batch analysis results are provided for fourteen pilot to commercial scale batches from the two proposed manufacturers confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of eight production scale batches of finished product from the proposed manufacturers stored under long term conditions (25 ºC / 60% RH) for up to 12 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary

packaging proposed for marketing. Samples were tested for appearance (visual inspection), water content (Ph. Eur.), strength (HPLC), degradants (HPLC), dissolution (Ph. Eur.) and microbiological contamination (Ph. Eur.). No relevant change or trend to any of the measured parameters was observed under the three storage conditions. The analytical procedures used are stability indicating.

In addition, stressed stability studies were carried out on one production scale batch. The finished product was exposed for 45 days to the following conditions: 5 ºC; 25 ºC / 80% RH; 25 ºC / 60% RH open container; 30 ºC / 75% RH open container; 50 ºC / ambient humidity. No significant trends were observed apart from an increase in water in the open container studies. However, this had no impact on any of the other tested parameters.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant trends were observed which demonstrates that the finished product tablets are not susceptible to photo-degradation.

The applicant proposes that the date of manufacture of the finished product should be independent of the date of production of LDV-SDD for which 6 months of stability data are available. Two of the eight reported stability batches were manufactured using LDV-SDD stored for 6 months prior to finished product manufacture. This is considered acceptable.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

The applicant will complete all on-going stability studies under intermediate and long term conditions up to the 60 month time point. In addition, stability studies will be carried out on the first 3 commercial batches of finished product under long-term and accelerated conditions. Furthermore, at least 1 commercial batch from each proposed manufacturer per year will be placed on a long-term stability study.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP notes that the applicant has agreed with the Committee's recommendation to re-define starting materials and implement GMP for additional steps of the synthetic process by May 2015.

2.3. Non-clinical aspects

2.3.1. Introduction

Sofosbuvir is a novel HCV nonstructural protein (NS)5B polymerase nucleotide inhibitor that demonstrates potent in vitro inhibition of HCV replicon ribonucleic acid (RNA) replication.

Ledipasvir (methyl [(2S)-1-{(6S)-6-[5-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1Hbenzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate) is a novel compound designed to inhibit HCV replication and virion production by targeting the HCV NS5A protein.

The applicant provided a dossier in support of a marketing authorisation application for a fixed-dose combination (FDC) tablet of sofosbuvir (SOF) and ledipasvir (LDV) for the treatment of hepatitis C (HCV) infection.

Comprehensive programs of nonclinical studies with SOF and LDV as individual agents have been conducted; the nonclinical data are provided in m2.6 of this submission. To facilitate the evaluation of SOF, LDV, and the SOF/LDV FDC, nonclinical virology studies with the individual agents and SOF/LDV FDC were provided.

2.3.2. Pharmacology

Sofosbuvir

Sofosbuvir is a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that is phosphorylated intracellularly to the active triphosphate form (GS-461203). The nucleoside triphosphate is a non-obligate chain-terminating analog of UTP that competes for incorporation at the HCV NS5B polymerase active site. Viral RNA synthesis is inhibited secondary to incorporation of the phosphorylated metabolite into nascent viral RNA by the HCV dependent RNA-dependent RNA polymerase resulting in pangenotypic activity. In biochemical assays direct inhibition of NS5B polymerase was shown and characterised by IC_{50} values ranging from 0.7 to 2.6 µM.

Sofosbuvir and the diasteromeric mixture GS-9851 appeared to have a low potential for mitochondrial toxicity in cell based assays as determined by measuring mitochondrial DNA (mtDNA) depletion or selective cytochrome c oxidase protein depletion. The triphosphate metabolite had no significant inhibitory activity on human DNA polymerases α, β, and γ or RNA polymerase II as reflected in IC_{50}>200 µM.

In studies to determine potential for off target activity of GS-9851 no inhibition or induction greater than 50% at 10 µM was recorded in a panel of 171 receptors, enzymes, and ion channels, including cytochrome P450 (CYP) enzymes. These test systems used various cell types, platelets and tissue systems and incubation times ranging from 10 min to hours. Furthermore, the major metabolite GS-331007 at concentrations of 10 µM had no significant (defined as ≥50% inhibition or stimulation) effect on a panel of receptors, enzymes, and ion channels. The data are consistent with GS-331007 having a limited potential for secondary pharmacological effects.

Sofosbuvir and GS-9851 had no significant activity (EC_{50}>100 µM) against other viruses such as HIV-1 and HBV. At 100 µM GS-9851 showed an 18% inhibition of HBV.

Single oral doses of GS-9851 up to 1000 mg/kg in rat and dog had no major effects on parameters monitored to determine potential for interference with the central nervous, respiratory and cardiovascular

systems. *In vitro*, no significant inhibition of hERG current by GS-9851, GS-566500, GS-606965 and GS-331007 was reported at the highest concentrations used (100-300 µM).

From the non-clinical point of view the data has overall provided adequate characterisation of the pharmacology of sofosbuvir and its major metabolites.

Ledipasvir

The mode of action of ledipasvir has not been directly established but indirect evidence is consistent with the compound targeting the NS5A molecule. *In vitro* resistance selection and cross-resistance studies, and the lack of HCV enzyme or kinase inhibition was taken to support the conclusion that ledipasvir targets NS5A as its mode of action. Ledipasvir has shown antiviral activity against HCV genotypes 1a and 1b with mean EC_{50} values of 0.031 and 0.004 nM, respectively. Antiviral activity determined as EC_{50} against genotypes 2 to 6 ranged from 0.15 to 530 nM.

Ledipasvir showed no relevant antiviral activity at the highest concentration tested, or the highest concentration without cytotoxicity, against other virus such as bovine viral diarrhea virus (BVDV), RSV, HBV, HIV-1, HRV, influenza A and B, and a panel of flaviviruses (including West Nile virus, yellow fever virus, dengue virus, and banzai virus).

Cytotoxicity of ledipasvir was characterised by CC_{50} of 4029 to >50000 nM using different cell lines (1b-Rluc-2, Huh-luc, 1a-HRlucp, Hep G2, SL3, Huh7, Hep-2, AD-38 and MT4 cells).

Ledipasvir at 10 µM showed significant binding to 3 ion channels and 1 receptor in a radioligand binding assay screen against a panel of 68 mammalian ion channels and receptors. The IC_{50}s of ledipasvir were 0.210 and 3.47 µM against sodium channel site 2 and calcium channel L-type (dihydropyridine), respectively. A 50% inhibition of androgen receptor was noted at 10 µM. Ledipasvir activity against 442 kinases was assessed using a quantitative polymerase chain reaction (qPCR)-based competition assay. Results showed weak competition for binding of 2 kinases, Bruton's tyrosine kinase (BTK) and homeodomain-interacting protein kinase 1 (HIPK1) at 0.1 and 1 µM, respectively. Taking into account the high protein binding, >99.5%, of ledipasvir the large margin between unbound maximum clinical plasma levels (0.8 nM) and potential ion channel/receptor inhibition indicates limited clinical relevance.

In safety pharmacology studies ledipasvir was investigated at doses up to 100 mg/kg in rat and 30 mg/kg in dog corresponding to systemic exposures and C_{max} levels approximately x3 and x9-10, respectively, the expected clinical values. In the rat central nervous system study occasional occurrences of low locomotor activity was observed in one or more groups, including control, but due to the overall low incidence and the lack of dose-related pattern, a relationship to treatment seemed unlikely. No significant findings were noted for other open-field observations. No statistically significant findings were noted for forelimb grip strength, hindlimb grip strength, nociceptive reflex, or body temperature in animals given 10, 30, or 100 mg/kg.

In the rat respiratory study animals given 10 or 30 mg/kg displayed statistically significant overall increases in covariate-adjusted mean minute volume compared with controls across the measured timepoints. The low magnitude of the effect and lack of statistically significant effect at 100 mg/kg suggested that the response was incidental and not related to treatment with the test article.

Occasional intermittent and statistically significant effects were observed in the dog cardiovascular study, but as no dose-response was evident and the changes were minor, these were likely biologically unimportant. Ledipasvir had no effect on the qualitative or quantitative ECG data. The data overall suggest lack of any relevant cardiovascular toxicity of ledipasvir.

The IC_{50} was >0.50 µM, the highest dose tested, in the in vitro hERG study. The dose was based on the limit of solubility in the hERG vehicle (HB-PS+0.3% DMSO). Considering the maximum clinical unbound level a sufficiently high concentration was tested.

Ledipasvir / sofosbuvir

In vitro studies of the combination sofosbuvir and ledipasvir were performed in genotype 1b, 2a, 3a, and 4a replicon cell lines. No significant change in cell viability was reported at sofosbuvir concentrations of 320 nM in combination with ledipasvir ranging from 0.014 nM to 1760 nM. No other studies with the combination are available.

The primary pharmacology of ledipasvir/sofosbuvir has been sufficiently described from the non-clinical point of view. Considering data from secondary pharmacology screening and safety pharmacology studies that addressed potential for unwanted effects with respect to the respiratory, cardiovascular and central nervous systems there were no evident or clinically relevant indications of untoward effects of the compounds alone also suggesting that the combination would not produce any significant synergistic changes.

2.3.3. Pharmacokinetics

The disposition of sofosbuvir and ledipasvir has been investigated in mouse, rat, dog and monkey. Pharmacokinetic/toxicokinetic data to support toxicology studies are available and considered in the sections below.

Sofosbuvir

Pharmacokinetic parameters of sofosbuvir were determined in mouse, rat, dog and monkey. The oral bioavailability following administration to portal vein cannulated dogs was determined to approximately 10% while in pentagastrin treated dogs bioavailability was reported to 18.7%. The hepatic extraction ratio was estimated to 74%. *In vitro* sofosbuvir was found to have a partially saturable efflux and low forward permeability as assessed in Caco-2 cell monolayers.

The stability of sofosbuvir (S-diasteromer at phosphorous), GS-9851 (isomeric mixture at phosphorous containing sofosbuvir, the S-diastereomer and GS-491241, the R-diastereomer) was investigated *in vitro*. The compounds were found to be stable in simulated gastric and intestinal fluids. GS-9851 was degraded rapidly in blood of mouse and rat, but was stable in non-rodent blood. Additional studies showed that sofosbuvir and GS-9851 were unstable in mouse and rat plasma due to esterase activity. Sofosbuvir, its diastereomer and the isomeric mixture GS-9851 were stable in human plasma.

Protein binding was low both for sofosbuvir and its major metabolite GS-331007 in dog and human. Due to instability protein binding for sofosbuvir could not be determined in mouse, rat and rabbit plasma, but protein binding of GS-331007 was minimal in mouse, rat, rabbit, dog and human.

Tissue distribution was studied using whole body quantitative autoradiography and data indicated a similar pattern of distribution in albino and pigmented animals with levels generally higher in tissues of albino animals at 1 hour post dose, but lower than in pigmented animals at 24 hours. After single oral doses of 20 mg/kg in partially pigmented rats highest levels of radiolabel were generally determined at 4 to 6 hours post-dose. Tissues with highest radioactivity included liver, alimentary canal, renal cortex, lymph node, spleen, thymus, bone marrow and lung. Levels in brain were low, but quantifiable up to 24 hours. There was no specific association of radioactive material with melanin. Studies in pregnant rats showed that sofosbuvir crossed the placenta. Foetal blood and brain sofosbuvir derived radioactivity was higher than in dams, but foetal liver and kidney had lower levels than corresponding organs in dams. Sofosbuvir derived radioactivity was also quantifiable in milk from day 2 postpartum rats, but nursing pups did not appear to be extensively exposed to drug-derived radioactivity. Milk to plasma ratios were 0.1 at 1 hour and 0.8 at 24 hours.

In vitro studies in human liver microsomes showed that sofosbuvir was an efficient substrate for Cathepsin A (Cat A) and carboxyesterase 1 (CES1). There were no indications of metabolism via UGTs or

flavin-containing monooxygenase (FMO). Sofosbuvir was cleaved by CatA and CES1 and subsequent activation steps included amino acid removal by HINT1 and phosphorylation by UMP-CMP kinase and NDP kinase. *In vitro* data indicated that Cat A preferentially hydrolysed sofosbuvir the S-diastereomer while CES 1 did not exhibit stereoselectivity. This would be consistent with studies using GS-9851 showing a less efficient metabolism to the triphosphate in the hepatically derived cell line containing the Clone A replicon and shown to exhibit low CES 1 activity, but high Cat A activity compared with primary human hepatocytes. Following incubation of hepatocytes from rat, dog, monkey and human GS-9851 was converted to the triphosphate GS-461203 in all species, most efficiently in human. Sofosbuvir was also readily converted to the triphosphate in dog liver after oral doses and was the dominant metabolite at all time-points assessed with a long half-life of approx. 18 hours. The active metabolite GS-461203 could not be detected in monkey. Further while GS-461203 was detected in rat liver, it could not be measured in liver from mouse.

Isomeric conversion was not evident in rat, dog and human plasma and human urine.

After single oral doses in mouse and rat GS-9851 was not detected in plasma, but the nucleoside metabolite GS-331007 could be determined in plasma and liver. Overall no marked differences in pharmacokinetics between male and female animals were evident and no accumulation appeared to take place after repeated doses.

In male mouse given a single oral dose of 20 mg/kg of sofosbuvir**,** two metabolites GS-331007 and GS-566500, were found in plasma, accounting for 86.5% and 13.5%, respectively, of total plasma radioactivity. These two metabolites were also detected in urine with GS-331007, accounting for 55.2% of radioactivity in 0-168 hours. In mouse feces, only, GS-331007 was observed and amounted to 14.1% of total radioactivity in 0-168 hours.

In rats given a single oral dose of 20 mg/kg of sofosbuvir**,** the major metabolite in plasma was GS-331007 (M1) accounting for 84.2% of AUC of total plasma radioactivity. GS-566500 (M2) was observed in plasma at levels of 10.6%. In urine GS-331007 and GS-566500 were major components. In another study using female rats, plasma M1 was 53.9% and M2 was present at 32%. In rat liver three metabolites, M1 (4.8%), M2 (0.9%, GS-566500) and M3 (GS-606965) were observed, the latter a minor component. The parent compound was not detected in plasma, urine or feces. The major pathway in rat was hydrolysis of GS-7977 to GS-331007 and minor pathways were hydrolysis of GS-7977 to GS-566500 and GS-606965.

In dogs following a single oral dose of 20 mg/kg of sofosbuvir three metabolites in plasma were identified, GS-331007, GS-566500 and M4 (proposed glucuronidation product of GS-606965), accounting for 93.4%, 1.6% and 0.5%, respectively, of total plasma AUC. Parent compound amounted to 4.5%. In dog (and mouse) the majority of a radioactive dose was recovered in urine within 8 to 12 hours.

GS-331007 and GS-566500 were detected in all species with GS-331007 being the major drug related material in all species and all matrices. In plasma, urine and feces of all species administered sofosbuvir the primary metabolite detected was GS-331007 accounting for >80% of total exposure. In rat liver and plasma GS-566500 was also detected. The metabolite profile was overall comparable between non-pregnant, pregnant and postpartum rats and in milk of postpartum rats with GS-331007 and 2 sulfate conjugates of GS-331007 being the major metabolites.

The major species used in toxicology studies, rat and dog appear to have been adequately characterised pharmacokinetically. Less data is available for the rabbit, the second species used in studies on reproduction toxicity, but it has been ascertained that GS-331007 is formed in this specie. Some data indicate species differences in the disposition of sofosbuvir that could partly relate both to rate of hydrolysis in primary matrices as well as to the extent of formation of the active triphosphate metabolite. Thus, sofosbuvir can be detected in human plasma, but not in species (rat) used in general toxicology studies, micronucleus study (mouse) and reproduction toxicity studies (rat) also indicating that, in contrast to the major metabolite (M1) that is formed in all species, the potential toxicity of sofosbuvir may

not have been fully characterised. In addition, the extent of exposure to the active triphosphate seemed variable and while this could be detected in rat liver, levels could not be determined in mouse liver. Formation of the triphosphate was shown in hepatocytes from human, dog, monkey and rat. In monkey, liver levels were below detection. Monkey was though not used in studies on general toxicology.

Ledipasvir

Ledipasvir has low aqueous solubility (<1 µg/ml at pH 7.0) and solubility in simulated intestinal fluid was shown to be low. Oral bioavailability of ledipasvir was 32% in rat, 53% in dog and 41% in monkey. In the mouse, rat and dog, the systemic exposure increased less than proportional with dose. In mouse exposure increased less than proportional with dose from 30 to 300 mg/kg, increasing dose from 300 to 600 mg/kg did not generally result in an increased exposure. In female New Zealand White rabbits systemic exposure to ledipasvir in a formulation containing 75% propylene glycol and 25% Solutol HS 15, increased greater than proportionally with oral doses from 10 to 100 mg/kg, and increased less than proportionally with dose from 100 to 300 mg/kg and no further increase in exposure from 300 to 600 mg/kg was evident.

Ledipasvir was highly protein bound, > 99.8 in all species. In male mouse given a single oral 20 mg/kg dose of ^{14}C-ledipasvir radioactivity was widely distributed to almost all tissues by 3 hours post-dose. Highest levels (not including the GI tract) were detected in gall bladder, liver, harderian gland, and kidney. Low and trace levels of radioactivity were measured in testes and brain, respectively, suggesting low transfer across the blood-testes and blood-brain barriers, but levels in brain choroid plexus were comparable with blood levels. The elimination half-lives (t½) for total radioactivity were 12.3 and 10.9 hours in blood and plasma, respectively.

In male intact and bile-duct cannulated Sprague-Dawley and intact Long-Evans (LE) rats given a single oral 10 mg/kg dose of ^{14}C-ledipasvir a wide distribution to most tissues was evident. Tissues with highest maximum concentrations of radioactivity (excluding the GI tract) included liver, adrenal gland, urinary bladder, kidney, and pancreas in both Sprague-Dawley and LE rats. Low levels of ^{14}C-ledipasvir -derived radioactivity persisted longer in the eye uveal tract of pigmented rats, but there was no marked difference in distribution to pigmented and non-pigmented skin. No radioactivity was detected in the brain cerebellum and cerebrum or the testes consistent with low levels of ^{14}C-ledipasvir-derived radioactivity crossing the blood-testes and blood-brain barriers.

In a peri/postnatal study in rat an approximate proportional with dose increase in systemic exposure in F0 female rats on gestation day 6 and lactation day 10 was recorded. Exposure in the F1 neonate rats increased greater than proportionally with the increase in the maternal dose level from 10 to 100 mg/kg/day, with no notable difference between sexes (< 2-fold).

Overall the *in vitro* metabolic stability of ledipasvir indicated slow rates of hepatic biotransformation.

The metabolite profiles of radioactivity derived from carbon 14 labelled ledipasvir showed that the major circulating component was the unchanged parent drug representing 96.9%, 97.2%, 87.1%, 87.5%, and 98.3% of total plasma AUC following oral administration of ^{14}C-ledipasvir to CD-1 mice, rasH2 transgenic mice, rats, dogs, and human subjects, respectively. Unchanged parent drug was also the major component in feces in mice, rats, dogs, and humans accounting for greater than 80% of the total in feces. Unchanged parent drug accounted for 43.5% and 79.8% of the radioactivity recovered in bile from bile duct cannulated rats and dogs, respectively.

Less than 1% of the total dose was recovered in urine from all nonclinical species, and 1.14% of total dose was recovered in urine from human subjects. No single metabolite in urine accounted for more than 1% of the total in any species.

Metabolites identified were primarily formed via oxidation and *N*-demethylcarboxylation.
Oxy-ledipasvir-A (M19) was present in feces of mouse and human and in the urine of mouse.

Oxy-ledipasvir-B (M15) was the only quantifiable circulating metabolite detected in dog plasma, contributing to approximately 5% of the total circulating radioactivity, and was also present in rat and dog bile and dog feces. Another oxidative metabolite, Oxy-ledipasvir-C (M16) was present in rat bile. *N*-descarboxymethyl-ledipasvir (M9) was identified in mouse plasma and feces, rat bile and feces, and in dog bile.

The excretion of ledipasvir was determined after administration of a single oral dose of ^{14}C ledipasvir to male CD-1 mouse at 20 mg/kg, to male intact and bile duct cannulated (BDC) Sprague-Dawley rats at 10 mg/kg, and to male intact and bile duct cannulated dogs at 10 mg/kg. Excretion of radioactivity was measured in urine, feces, and bile through 168 hours after dosing. A mean of 93.9%, 92.9%, and 95.8% of the administered radioactivity was excreted in feces from mouse, rat, and dog, respectively. Less than 0.9% of the administered radioactivity was excreted in urine from all three species.

By comparing the amount of radioactivity recovered in bile with the total amount of radioactivity in bile and urine, it was estimated that approximately 86% and 98% of the absorbed dose was eliminated via biliary excretion in BDC rats and dogs, respectively. Since unchanged parent drug accounted for 43.5% and 79.8% of the radioactivity recovered in bile from bile duct cannulated rats and dogs, respectively, biliary excretion of unchanged parent compound was a major route of elimination for ledipasvir. In rat, based on the radioactivity excreted in urine and bile after an oral dose, approximately 3.5% of the orally administered dose was absorbed. In another study on the excretion of ledipasvir in bile duct cannulated dogs, approximately 71% of the total dose was recovered as unchanged parent compound in bile after intravenous administration of 0.25 mg/kg. In dog, based on the radioactivity excreted in urine and bile after an oral dose, approximately 19% of the orally administered dose was absorbed. The apparent discrepancy between the estimated dose absorbed (in rat 3.5%) and oral bioavailability (in rat 32%) may relate partly to level of dose and partly to physiological constraints of the model used.

Based on the extent of metabolism and pattern of metabolites the species used in toxicology studies are considered relevant. There were no significant metabolites formed that were unique for humans.

Ledipasvir / sofosbuvir

Data generated from *in vitro* studies Caco-2 cell monolayers suggested that sofosbuvir intestinal absorption will be increased in the context of the fixed dose combination due to inhibition of intestinal transporters by ledipasvir.

The effect of ledipasvir on the formation of the active sofosbuvir triphosphate (GS-461203) in primary human hepatocytes after incubation with sofosbuvir was assessed *in vitro*. In the presence of 10 µM ledipasvir, GS-461203 increased from 49.7 to 69.8 pmol/million cells. In primary human hepatocytes, additive antiviral activity was observed for the combination of sofosbuvir and ledipasvir in an HCV genotype 1a replicon system.

No nonclinical excretion studies have been done with the combination. Based on the different routes of elimination, the coadministration of sofosbuvir and ledipasvir is not anticipated to change the excretion of the individual compounds. Sofosbuvir is eliminated, following metabolism to the predominant metabolite GS-331007 renally, while ledipasvir elimination as unchanged parent in bile is a major route of ledipasvir elimination.

2.3.4. Toxicology

Sofosbuvir

In the non-clinical testing program, sofosbuvir was administered orally to CD-1 mice, Sprague-Dawley rats, and Beagle dogs for general toxicity evaluation. The diastereomeric mixture GS-9851 was used in early nonclinical and clinical studies, but the single diastereomer sofosbuvir (SOF) was chosen for

development and registration. However, it should be noted that exposure to sofosbuvir was not obtained in rodents due to high esterase activity and that the level of exposure to the active moiety, the triphosphate, which is mainly present intracellular, is generally not known in the toxicology studies. Exposure margins are therefore primarily calculated using the major metabolite GS-331007. The only dose-related substance with a systemic exposure of >10% of total radioactivity was GS-331007 also indicating that only this metabolite would require qualification in non-clinical studies.

Single dose toxicity study was performed with GS 9851/PSI-7851 (the diastereomeric mixture). No adverse effects were noted in rat up to a highest dose of 1800 mg/kg.

Sofosbuvir was generally well tolerated for up to 3 months in the mouse, 6 months in the rat, and 9 months in the Beagle dog. Target organs for toxicity were the heart, liver, gastrointestinal tract, and hematopoietic cells. Pre-terminal mortalities occurred in rats at high dose levels (27- fold clinical exposure as based on AUC), and in a single dog dosed at 500 mg/kg/day for 6 months (24-fold clinical exposure as based on AUC).

In the 14-day dose range finding study in mice, one male dosed at 1500 mg/kg/day was found dead on day 10. The cause of death was not determined. In the 3-month mouse study, pre-terminal mortality occurred at all dose levels ($\geq$100 mg/kg/day), and also in controls and together the data do not substantiate a clear causative link between sofosbuvir treatment and pre-terminal mortality in mice. In the 7-day rat study, 2000 mg/kg/day resulted in early mortalities probably due to myocardial degeneration. This finding was also present in 2/3 surviving females dosed at 2000 mg/kg/day, as evaluated after a 14-day recovery period. The margin to the NOAEL for myocardial degeneration and associated mortality in the 7-day rat study is small (3-fold based on AUC) but cardiac toxicity/mortality occurred only at the highest dose level (2000 mg/kg/day) and no doses between 250 and 2000 mg/kg/day were tested. In longer duration studies (at 9-fold exposure levels to clinical AUC in 6 month study and in carcinogenicity study), no cardiac toxicity or associated mortalities occurred. In the 9-month dog study, one male dosed at 500 mg/kg/day was pre-terminally sacrificed on Day 172 with findings of vacuolar degeneration observed in the myocardial muscle fibers. This may have been a response to hypotension, tachycardia and hypovolaemia secondary to haemorrhagic enteritis. Overall due to the fact that hemorrhage in the stomach or intestine was observed in two high dose dogs in the 7-day and 1-month studies, respectively, it seemed likely that the hemorrhagic enteritis in the preterminally killed dog in the 9-month study was due to treatment with sofosbuvir. A direct effect on the myocardium cannot be completely excluded but no histopathological myocardial changes were observed in other dogs, in any of the conducted studies. In a 14-day bridging toxicity study comparing GS-9851 and SOF at 500 mg/kg/day, one male rat dosed with GS-9851 showed minimal myofiber degeneration located at the apex of the heart, a change which may potentially be treatment-related. No complement was requested to the applicant.

A short duration rat toxicology study with sofosbuvir at dose levels up to 2000 mg/kg to determine its contribution to the heart degeneration and inflammation observed with GS-9851 is ongoing. This study could not only more clearly define drug-related exposure multiples (based on heart findings) but, if indeed contributing to heart toxicity, further characterize this toxicity by including treatment-free groups (to evaluate reversibility) and additional study endpoints (e.g., circulating biomarkers of cardiac toxicity, heart specific sofosbuvir and related metabolite concentrations).The applicant will submit the final study report in Q1 2015.

QT prologation in the 7-day study, but not in longer dog studies, was present in males dosed at 1500 mg/kg/day, corresponding to levels 90-fold higher based on C_{max} of GS-331007 (likely exposure to sofosbuvir was also significant although not directly determined) than expected clinical. Taken together, the animal data do not indicate that sofosbuvir is likely to produce QT prolongation in patients treated at the recommended dose of 400 mg.

Diarrhea and other clinical signs related to effects on the gastrointestinal (GI) tract occurred in all repeated-dose toxicity studies in rats. Some of these effects also occurred in control animals, suggesting that the vehicle may have contributed. No related histopathological changes were noted and effects were reversible upon cessation of dosing, indicating no major concern for human safety despite the small exposure margins. Diarrhea and emesis were also present in all dog repeated-dose toxicity studies. The lowest NOAEL for GI effects in the dog was 20 mg/kg/day in the 3-month study, corresponding to a 2-fold exposure margin based on AUC. Hemorrhage was present in the lamina propria of the colon in one high dose recovery dog in the 7-day study, in the lamina propria of the stomach pylorus region in a dog treated at 500 mg/kg/day in the 3-month study and in the lamina propria of the jejunum in the preterminally killed high dose dog in the 9-month study. The lowest NOAEL for hemorrhage in the GI tract was 100 mg/kg/day in the 6-month phase of the 9-month study, corresponding to a 10-fold exposure margin based on AUC. Thus, there is an acceptable margin to these more severe GI effects in dogs.

Increased liver weights were observed at $\geq$ 100 mg/kg/day in the 1-month rat study, at $\geq$ 30 mg/kg/day in the 7-day dog study, and at 500 and $\geq$ 100 mg/kg/day in the 1-month and 3-month dog studies, respectively. At the high dose level (1500 mg/kg/day) in the 7-day dog study, this organ weight increase correlated with hepatocellular hypertrophy. The increased liver weights in both rats and dogs, as well as the hepatocellular hypertrophy in dogs, are most likely related to the induction of drug-metabolizing enzymes, which is an adaptive and non-adverse effect. Histopathological liver findings at 1500 mg/kg/day in the 7-day dog study included hepatocyte apoptosis, microvesiculation, decreased intracellular glycogen, and Kupffer cell pigmentation. These findings were associated with increased ALT, AST, ALP and bilirubin. Except for the decreased glycogen, the margin to the NOAEL for these effects was 13-fold based on AUC. No histopathological liver findings were present in the longer term dog studies at doses up to 500 mg/kg/day, corresponding to a 24-fold exposure margin (GS-331007) as based on AUC in the 9-month study.

Effects on erythropoiesis were present in the 7-day rat study and in all dog studies, from 7 days up to 9 months. The lowest exposure margin to NOAEL in dogs for these effects was 5-fold, as based on AUC. Hematology analysis showed decreased red blood cell count and lower haemoglobin and/or hematocrit concentrations. The decreased erythron mass was reflected in bone marrow changes such as lower percentage of erythroid precursors and depression of erythropoiesis. Both the peripheral and bone marrow changes were reversible. In the 6-month phase of the 9-month dog study, there were bone marrow alterations at the high dose (500 mg/kg/day), which were not present at the end of the 9-month study. Exposure margins were low. Such effects were also observed in Phase 2 and 3 clinical trials, when sofosbuvir has been co-administered with ribavirin with or without pegylated interferon. Both these substances are known to cause hematologic toxicity.

Lymphocyte depletion/necrosis and thymus atrophy occurred in rats and dogs treated at high dose levels and are considered to reflect generalized stress. Adrenal cortical hypertrophy at 1500 mg/kg/day in the 7-day dog study is also considered to be related to stress. These findings were reversible upon cessation of dosing.

Activated partial thromboplastin time was increased at 1500 mg/kg/day in the 7-day dog study (not reversible after 14 days), and at ≥ 100 mg/kg/day in the 6-month phase of the 9-month dog study (reversible after 1 month). The increase was slight, and there did not seem to be any correlation with the intestinal hemorrhage present in the pre-terminally killed high dose dog.

Transient lameness was noted in dogs at ≥ 100 mg/kg in the 9-month study possibly due to incidental injury. No incidents of lameness were observed in vehicle-treated control dogs. It should be noted that limping/lameness was present in single male dogs at 100 mg/kg/day in the 1- and 3-months studies. Even so, it is agreed that no causal relationship has been established.

A few other findings (e.g. organ weight changes, alterations in urine parameters, etc.) with potential or uncertain relationship to treatment with sofosbuvir were either of small magnitude or inconsistent between studies, and thus their relevance to the human clinical situation is questionable.

The diastereomeric mixture of SOF (GS 9851/PSI-7851) was shown to be negative *in vitro* in the *S typhimurium* reverse mutation assay and in a mammalian chromosome aberration test performed in primary human lymphocytes. An *in vivo* chromosome aberration assay in mouse was also negative. A sufficiently high exposure of the two metabolites GS-566500 (AUC_{last} 194(M)/134(F) µgxh/mL) and GS-331007 (AUC_{last} 133(M)/115(F) µgxh/mL) was achieved, while exposure to SOF (GS-9851) was low. The results suggest that SOF does not have any genotoxic potential.

There was no evidence of carcinogenic potential of sofosbuvir in rat and mouse carcinogenicity studies up to the highest dose tested where exposure to GS-331007 were 7/18 (male/female) and 9/11 (male/female) times higher in mice and rats, respectively, than the clinical exposure at 400 mg sofosbuvir once daily. Exposure to sofosbuvir was not obtained in rodents due to high esterase activity, and the exposure margins are therefore calculated using the major metabolite GS-331007. Treatment with PSI-7977 did not affect survival of animals, except for an increased early mortality in low dose male mice. No treatment-related tumours were observed. No PSI-7977-related cardiac or skeletal muscle toxicity was observed in the rodent carcinogenicity studies. The only treatment-related histopathological effect was inflammation in the nasal turbinates, probably due to local irritation in connection with reflux and gavage dosing.

Daily oral doses of SOF at up to 500 mg/kg for 28 days (males) or 14 days (females) prior to cohabitation, during cohabitation, and through scheduled termination (males) or Day 7 of gestation (females) did not adversely affect mating, fertility, or embryo survival at any dose level. In addition sofosbuvir did not affect reproductive organ weight or produce macroscopic findings or histopathologic findings in reproductive organs in either sex in the performed repeat dose toxicity studies. No effects on fertility are therefore expected.

Embryo-foetal studies were performed in rats and rabbits. In rats sofosbuvir did not affect intrauterine growth and survival. No effects were either seen on external, visceral, and skeletal foetal morphology at dose levels up to 500 mg/kg/day, considered the maternal and foetal NOAEL. At this dose, the margin of exposure for GS-331007 compared with expected clinical was 10. Pregnant rabbits tolerated daily oral doses of PSI-7977 up to 300 mg/kg during the period of major organogenesis without any adverse effects on either the dams or developing foetuses. The NOAEL for developmental toxicity is considered to be 300 mg/kg/day, which produced a systemic exposure of 8.66 and 200 µgxh/mL for SOF and its metabolite GS-331007, respectively, corresponding to exposure margins for SOF and GS-331007 of 10 and 28, respectively, when compared to the mean AUC at the recommended clinical dose (400 mg).

In the prenatal and postnatal development study performed in rats no adverse sofosbuvir-related effects were noted in F0 females at any dosage level during gestation and lactation and F1 postnatal survival, body weights, developmental landmarks, startle response, motor activity, learning and memory and reproductive performance were unaffected. Intrauterine growth and survival of F2 foetuses were also unaffected. No treatment-related external malformations or developmental variations were noted in F2 foetuses. Animals were not exposed to significant levels of SOF while exposure to the metabolite GS-331007 were 12 times the expected maximum clinical exposure in F0 dams after exposure to 500 mg/kg/day at lactation day 10 (AUC_{0-24} 83 µgxh/mL) and ~6 times at gestation day 6(AUC_{0-24} 40 µgxh/mL). F1 Pups were found to be exposed to significant but ~50 times lower levels of the metabolite GS-331007 (AUC_{0-24} 1.5 µgxh/mL in the 500 mg/kg/day group) on post-natal day 10, but not to be exposed to GS-566500.

According to the relevant Guideline the dose range tested by the applicant should have covered a dose resulting in minimal maternal toxicity such as e.g. decreased body weight or food consumption. No

effects were seen on body weight or food consumption in the studies performed and it is concluded that the dose range used in the studies was not high enough to fully explore the potential of sofosbuvir to induce reproductive and developmental toxicity. In addition, due to the high plasma esterase activity in rats and absence of sofosbuvir in plasma it is concluded that the studies on embryo foetal toxicity in rabbits, where plasma levels higher than that expected in the clinical situation was detected, is the only study where possible effects of sofosbuvir *per se* have been investigated. This is also reflected in the SmPC.

No toxicity studies in juvenile animals were conducted with SOF which is considered to be acceptable since sofosbuvir will initially be registered for adults only and since the repeat dose and developmental and reproductive toxicity studies did not reveal any adverse effects on tissues that may be developing in the paediatric population.

Sofosbuvir is predicted to be a non-corrosive/ non-severe eye irritant based on results from an *in vitro* Bovine Corneal Opacity and Permeability Assay and is classified as a "non-irritant" in a dermal irritation study in rabbits. In addition results from a Local lymph node assay indicate that SOF is not a skin sensitizer.

Phenol, GS-566500, GS-606965 and GS-331007 are metabolites of SOF and are considered to be toxicologically qualified at the proposed levels in drug product (0.5 % at shelf life). The proposed specification levels of 0.5 % (at shelf life), equal to ~0.04 mg/kg/day (2 mg/day/50kg), for GS-607699 and GS-607670 in drug product and the process impurities GS-491241, GS-615014 and GS-617190 present in the drug substance, are also considered to be acceptable from a toxicological point of view.

Fourteen day bridging toxicity studies comparing the isomeric mixture (PSI-7851) with the single isomer SOF (PSI-7977) have also been performed in rat and dog. No differences were detected and the toxicity and systemic exposure profiles were concluded to be similar for PSI-7851 and PSI-7977 in both studies.

No phototoxicity study has been performed with sofosbuvir. Sofosbuvir does not absorb light within the range of 290 to 700 nm and no accumulation in dermal or ocular tissues has been detected.

Ledipasvir

Overall the non-clinical toxicological documentation, although minimal, is considered to comply with current ICH and other relevant guidelines. In the non-clinical testing program, ledipasvir was administered orally to rasH2 transgenic mouse, Spraque-Dawley rat and Beagle dog for general toxicity evaluation. The oral route was chosen as this is the route of administration in patients. Non-clinical studies were performed using the free base of ledipasvir, the D-tartrate and the acetone solvate. The ledipasvir free base was used for the pivotal repeat dose toxicology studies and early non-clinical studies. The acetone solvate is considered the active pharmaceutical ingredient, which is converted to ledipasvir spray-dried dispersion, an amorphous free base, through downstream product manufacture.

General toxicity

No specific single dose toxicity studies were conducted which is acceptable. Acute effects were derived from repeat dose toxicity studies and pharmacokinetic studies and the micronucleus study indicated that single oral doses of ledipasvir are well tolerated up to 450/600 mg/kg in the rat.

Ledipasvir was generally well tolerated for up to 4 weeks in the mouse, 26 weeks in the rat and 39 weeks in the Beagle dog. Transient decreases in mean body weight gain and mean food consumption were noted both in rat and dog, although not in the 39-week dog study. Except for in the 2-week study in dog, effects on body weight and food consumption were not considered adverse. The maximum tolerated dose was not reached and no target organ of toxicity was identified by the applicant in any of the studies. In the mouse and rat studies, there were some equivocal signs indicative of adverse liver effects that overall

were concluded not related to the test article. Other, potentially test article-related microscopic findings noted in the 26 week rat study included:

- Minimal paracortical lymphocyte hyperplasia in the mesenteric lymph nodes (4/10 M at 100 mg/kg/d, and in F: 1, 3, 3, 2 at 0, 10, 30, 100 mg/kg) and an increase of the prostatic inflammation (4/10 M) at 100 mg/kg/d was observed with ledipasvir at the interim sacrifice (week 13) in the 26 week study. However, these effects were not observed at week 26.

- at week 26 in rats, a malignant C-cell carcinoma in the thyroid gland of a single male at 100 mg/kg/day was observed. This was not considered test article-related by the Applicant since neoplasia is occasionally seen as an incidental finding in rats. This carcinoma is more commonly observed in 104 week studies. The applicant will submit the final carcinogenicity for ledipasvir in December 2015.

In the dog effects on the brain in terms of large cerebral ventricles were indicated but concluded not related to the test article. Otherwise no potentially adverse test article-related clinical pathological or anatomic pathological findings were identified. Based on mean AUC_{0-24h} values at the proposed NOAELs of 100 mg/kg and 30 mg/kg in the chronic rat (56 µgxh/ml) and dog (62.6 µgxh/ml) studies, respectively, there is an approximately 7-fold (6.6- and 7.3-fold, respectively) margin to the mean AUC_{tau} at the clinical dose of 90 mg (8.53 µgxh/ml).

It should be noted that a rather high individual variability in toxicokinetics resulted in an overlapping exposure, especially between mid and high dose levels, and thus a lack of a dose-dependent response does not necessarily preclude a relation to the test article.

As the maximum tolerated dose was not reached and no clear target organ toxicity of ledipasvir could be identified, the repeat dose toxicity studies do not allow for a complete characterisation of the toxicological profile of ledipasvir. However, maximum feasible oral doses in optimised vehicles, though restricted by the limited solubility of Ledipasvir, have been used and the exposures achieved were estimated to be close to saturation.

Liver

In the 4-week mouse study, minor increases in mean absolute and relative liver weights and alkaline phosphatase were noted in males at the high dose level of 300 mg/kg. These effects were small and did not correlate with histopathological findings and could be considered as not adverse. In the 2-week rat study minor clinical pathological changes in the 100 mg/kg dose group or from the 30 mg/kg dose included increased cholesterol in females and males, increased alanine transferase and alkaline phosphatase in males and increased triglycerides in females. As the effects in males correlated with findings, although few and not clearly dose-dependent, of minor to moderate necrosis in hepatocytes, minor adverse test article-related effects in the liver cannot be excluded. In the 26-week rat study there were slight reversible increases in alanine transferase and minimal reversible decrease in glucose in males in the 100 mg/kg dose group at week 26. These findings were correlated with non-reversible bile duct hyperplasia (although present in 2-3 animals in all ledipasvir groups, in males). Based on the low incidence, the absence of a clear dose response, the lack of correlative effects on e.g. bilirubin, the presence in one of the female recovery control rats and being regarded as a common age-related finding in rats, bile duct hyperplasia was not considered test article-related.

Brain

Large cerebral ventricles with and without microscopic correlates of minimal dilatation of ventricles were observed in one female dog given 30 mg/kg and one female dog given 10 mg/kg, respectively, in the 2–week study. Due to the dose response in terms of presence of a microscopic correlate in the high dose animal it is not clear why this finding was judged as unrelated to the test article. Large cerebral ventricles were present also in the 39-week study at terminal sacrifice. One female dog in the mid dose group had large cerebral ventricles without microscopic findings and 1 male dog in the low dose group had large and

dilated cerebral ventricles. As the incidence was comparable to general historical control data, the large and dilated cerebral ventricles were considered as spontaneous and incidental findings.

Genotoxicity and carcinogenicity

Ledipasvir was tested *in vitro* for genotoxicity up to cytotoxic concentrations. Negative results were reported in gene mutation tests and tests for chromosomal aberrations in human lymphocytes. The *in vivo* rat micronucleus test was negative. Plasma exposure at the high dose in the rat micronucleus study was approximately 8-fold the expected human exposure. Taken together the data did not indicate any significant genotoxic potential of ledipasvir.

A 6-month rasH2 transgenic mouse study and a 2-year rat oral gavage carcinogenicity study with ledipasvir are being conducted. This is acceptable in view of the proposed short term treatment duration. The applicant will submit these studies in December 2015.

Reproduction toxicity

Reproductive function was evaluated in rat and rabbit. Daily oral doses of ledipasvir up to 100 mg/kg to rats for 28 days (males) or 15 days (females) prior to cohabitation, during cohabitation, and through scheduled termination (males) or Day 7 of gestation (females) did not affect mating and fertility parameters and no test article-related necropsy finding or effects on the reproduction organ weights were reported. All sperm parameters were considered unaffected. Slight decreases in mean numbers of corpora lutea, implantation and viable embryos in the 100 mg/kg dose group were considered adverse and potentially test article-related. Based on mean AUC values, the female reproductive NOEL of 30 mg/kg corresponds to a 2.8-fold margin to the expected clinical systemic exposure. For the male reproductive NOEL of 100 mg/kg the exposure margin is 7-fold.

In the pivotal embryofoetal developmental rat study of oral daily doses up to 100 mg/kg from the period of implantation to closure of the hard palate no relevant effects were observed on maternal macroscopy, uterine weight, embryo-foetal viability, mean foetal weights or foetal external or visceral variations or visceral and skeletal malformations. Increased total foetal and litter incidences of skeletal variations affecting the vertebrae, sternea and ribs were, however, evident at the high dose level of 100 mg/kg. In the absence of other evidence of foetal toxicity or associated malformations, these effects are likely secondary to the decrease in maternal body weight gain (-67%; control body weights 238.2±11.5 g to 247.0±13.5 g and high dose body weights of 239.8±12.2 g to 242.7±13.3 g on gestation days 6-8) and food reduction (-12% on gestation days 6-18) observed at 100 mg/kg. Based on mean AUC values on gestation day 17, the 100 and 30 mg/kg doses give a 4.6- and 2.1-fold margin, respectively, to the expected clinical systemic exposure.

Possible embryofetal developmental effects in terms of skeletal variations were observed also in the pivotal study in rabbits given oral daily doses up to 180 mg/kg during the organogenesis. While body weight loss and decreased food consumption were noted for does at the high dose of 300 mg/kg in the dose range finding study, there were no significant effects on body weight or food consumption at the high dose of 180 mg/kg in the pivotal study. Maternal macroscopy, uterine weight, embryo-foetal viability, mean foetal weights, foetal external or visceral variations and visceral or skeletal malformations also appeared unaffected by ledipasvir. Skeletal variations affecting the hyoid, vertebrae, sternea and ribs with a positive trend or a significant increase in foetal and/or litter incidence were not considered to be related to ledipasvir as they were either regarded as common variations or noted to be within laboratory historical control ranges and not associated with any increase in malformations.

Based on mean AUC values on gestation day 20, the 180, 60 and 30 mg/kg doses give a 2.4-, 2.3- and 0.80-fold margin, respectively, to the expected clinical systemic exposure. No metabolism data is available and so the rabbit data are subject to some uncertainties.

Overall, the skeletal variations in embryo-foetal development studies in rat and rabbit and the possible delayed foetal development could be considered non-adverse.

In the pre and postnatal study in rats oral administration of ledipasvir up to doses of 100 mg/kg from the period of implantation to weaning of offspring did not significantly affect maternal function such as maintenance of pregnancy, delivery and nursing. General toxic effects in F0 dams were evident at the high dose as decreases in mean body weight gain and mean food consumption resulting in a lower mean body weight. At the high dose decreased body weight gains were also noted in F1 offspring which resulted in a lower mean body weights throughout the postnatal period, but otherwise no explicit toxic effects were reported.

Based on the general toxic effects on body weight, and for F0 animals also on food consumption, F0 maternal NOAEL and F1 neonatal/developmental NOAEL were set to 30 mg/kg. Based on mean AUC, this dose level corresponds to exposure levels on gestation day 6 and lactation day 10 that are similar to and 1.3-fold, respectively, the expected clinical systemic exposure. For the F1 neurobehaviour/F1 reproductive and F2 neonatal NOAEL of 100 mg/kg the exposure margin is 2.6-fold at gestation day 6 and 4.4-fold at lactation day 10.

On lactation day 10 the mean AUC values in F1 pups were approximately 25% of that in maternal animals, which demonstrates that ledipasvir is transferred to the pups via the milk.

Local tolerance and antigenity

Based on results from an *in vitro* bovine corneal opacity and permeability and a dermal irritation study in rabbits, ledipasvir is not predicted to have any relevant potential for either eye irritation or dermal irritation. Furthermore, results from a local lymph node assay indicate that ledipasvir is not a skin sensitizer.

Impurities

Impurities, which may be present in the drug substance and/or the drug product, have been toxicologically qualified. Development and stability studies have identified ledipasvir related degradation product expected in ledipasvir/sofosbuvir tablets.

Bridging toxicity studies

The NOAEL for ledipasvir and ledipasvir tartrate following 2 weeks of oral once daily administration were set to 100 mg/kg/day. Based on mean AUC on Day 14, the exposure to ledipasvir for the ledipasvir tartrate salt was approximately 3-fold lower than for ledipasvir free base.

Phototoxicity

Ledipasvir did not exhibit any potential for phototoxicity in a mouse study at single oral doses up to 300 mg/kg. The female albino hairless mouse was selected for the study and cited as a documented test system for evaluating phototoxic potential of materials.

2.3.5. Ecotoxicity / environmental risk assessment

Sofosbuvir

Sofosbuvir is a pro-drug and the active substance is the triphosphate GS-461203. Neither the pro-drug/SOF nor the active moiety/GS-461203 enter the environment at >10% of the administered dose. The focus of the environmental risk assessment of SOF is instead GS-331007, the only drug residue detected in total excreta at >10% of the applied radioactive dose (GS-331007 accounted for 79.6%).

The mean partition coefficient was 0.398, 0.286 and 0.0593, at pH 4, 7 and 9, respectively, (log Kow -0.417, -0.576 and -1.28, respectively) and GS-331007 is therefore not a PBT-substance. A refined market penetration of 3.5% (the highest relevant nationwide estimated prevalence) was used to calculate a refined PECsurface water value. The refined PECsurface water of 7.0 µg/L is significantly higher than the action limit of 0.01 µg/L. A Phase IIA assessment has therefore been performed and since a partition to sediment was indicated (>10% AR shifted after 14 days) a further assessment with a sediment dweller in Phase IIB has also been initiated. Since results indicate that GS-331007 does not adsorb to soils or activated sludges, aquatic toxicity has been the focus of Phase IIA analysis.

None of the ratios between the predicted environmental concentrations and predicted no effect levels for the Sewage treatment plant-, Surface water- or Groundwater-compartment were above 1 and no further studies are therefore required. In the Phase IIB analysis on sediment dweller the risk quotient was also found to be below 1. Based on the data presented it is concluded that the environmentally relevant residue of sofosbuvir, GS-331007, is not expected to pose a risk to the environment.

Ledipasvir

The available data do not allow concluding definitively on the potential risk of ledipasvir to the environment.

Since the slow-stir 1-octanol/aqueous buffer pH 7.4 partition coefficient of LDV was determined to be log 6.9, the compound is considered to be potentially bioaccumulative (B) and a PBT assessment is required. However, the Applicant argues that ledipasvir is inherently unstable in aqueous solutions (due to

photolysis) and will not significantly exist in the aqueous phase (photolysis and sorption) and can therefore not be considered to be a PBT substance. This is not agreed based on available data indicating persistence (e.g. DT50 in sediment exceeds the PBT-criteria of 120 days, a significant shifting (> 10 %) to the sediment compartment where photolysis is not relevant), the lack of a fully investigation of the bioaccumulation criterion and that low water solubility and high degree of sorption is not considered as adequate data to conclude on the potential for bioaccumulation. The applicant will provide a bioaccumulation study in sediment dwellers (OECD 315) in 3Q 2015.

The worst case $PEC_{surfacewater}$ based on the daily dose of 90 mg is 0.45 µg/L and exceeds the action limit of 0.01 µg/L. A Phase II assessment has been performed.

The Risk Quotients (RQ;PEC/PNEC) for the different compartments are shown in the table below:

Compartment		**RQ**
Sewage Treatment Plant		$\leq 5.0 \times 10^{-7}$
Surface water	Fish	3.3×10^{-3}
	Aquatic invertebrates	6.8×10^{-2}
	Algae	$\leq 5.3 \times 10^{-4}$
Groundwater		9.3×10^{-4}

The PNEC for ledipasvir for sediment dwellers was derived by dividing the NOEC of 2133 mg/kg dwt by an assessment factor of 100. The $PEC_{sediment}$ was estimated using the equilibrium partitioning model for suspended matter (based on the refined $PEC_{surface\ water}$).

$PEC_{sediment}/PNEC_{sediment} = 0.13 / 21.33 = 6.1 \times 10^{-3}$

All risk quotients are well below 1. However, it is not possible to conclude definitively on the potential risk of ledipasvir to the environment until the results of the OECD 315 study is available.

2.3.6. Discussion on non-clinical aspects

Sofosbuvir

Sofosbuvir is a prodrug that is hydrolysed to an intermediate subsequently phosphorylated intracellularly to an active triphosphate form with activity against the HCV NS5B RNA polymerase. No significant inhibition of host polymerases by the active metabolite was evident. Sofosbuvir also had no remarkable effects on parameters monitored to investigate mitochondrial toxicity in cell based assays. Screening for secondary activity was conducted using the isomeric mixture and GS-331007 at concentrations of 10 µM.

Pharmacokinetic and toxicokinetic data with sofosbuvir seem overall sufficient. The parent drug sofosbuvir is, in contrast to in humans, not detectable in rodent plasma.

Sofosbuvir seemed overall well tolerated in general toxicity studies of up to 9 months in rat and dog. Effects at high doses noted in toxicity studies were coupled to the gastrointestinal tract, liver and the haematological system. Reproductive toxicity was studied in rat and rabbit and while no relevant potential for adverse reproductive effects was evident, the high dose likely was suboptimal in these studies. Studies *in vitro* and *in vivo* for genotoxic potential were negative and consistent with a low mutagenic potential of sofosbuvir. Long-term carcinogencity studies in mouse and rat did not indicate any treatment related tumourigenic potential of sofosbuvir.

Ledipasvir

Ledipasvir targets the NS5A protein of the viral genome. Antiviral activity against the 1a and 1b genotype *in vitro* was reflected in EC_{50} values from 0.031 to 0.004 nM. Secondary pharmacology screening and safety pharmacology studies encompassing respiratory, central nervous system and cardiovascular systems did not show any effects expected to be of relevance for the clinical use.

Pharmacokinetic studies with ledipasvir showed very high protein binding, wide distribution, slow metabolism and excretion primarily in bile and faeces mainly as the parent compound.

General toxicology studies in rat and dog up to 9 months did not identify any specific target organs of ledipasvir toxicity but there were some indications of a potential for test-article related unwanted effects on the liver. The high doses employed corresponded to systemic exposure levels approximately 7-fold expected clinical levels. Ledipasvir had no significant genotoxic potential in standard test *in vitro* and *in vivo*. Carcinogenicity studies in rat and transgenic mouse are ongoing. Reproduction toxicity studies with ledipasvir showed some slight effects on fertility parameters in females and increases in skeletal variations in rat embryo-foetal studies, likely related to maternal toxicity and considered non-adverse.

Ledipasvir / sofosbuvir

No specific studies with the fixed combination with respect to potential toxic interactions have been conducted.

2.3.7. Conclusion on the non-clinical aspects

Sofosbuvir

The review of non-clinical data available for sofosbuvir overall indicates that the compound has been adequately characterised. Gastrointestinal tract, liver and the haematological system were identified as target organs for toxicity. In some studies, the margin to clinical exposure was low at the NOAEL, however, overall available data do not indicate any major issues of clinical concern.

Ledipasvir

The non-clinical study programme for ledipasvir is rather limited and did not provide identification of any specific target organ toxicity was identified. Margins to clinical exposure were not very high, however, as maximum feasible oral doses have been used the non-clinical data submitted are considered adequate and no further studies are required.

Ledipasvir / sofosbuvir

No studies on general toxicology with the fixed dose combination were conducted. This is acceptable based on the non-clinical data for the individual compounds alone, indicating that the potential for overlapping toxicities would not be clinically significant.

2.4. Clinical aspects

2.4.1. Introduction

The SOF component of the FDC with SOF/LDV has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults in the EU (16 January 2014). However, the LDV component is a novel compound designed to inhibit HCV RNA replication and virion production by targeting the HCV NS5A protein.

According to the approval of SOF, a wealth of PK information on SOF is available. Hence, PK properties can be considered as well characterised. Consequently, this section will predominantly focus on specific and relevant PK aspects on LDV and on the combination SOF/LDV.

Clinical pharmacology studies

To support this application, a program of phase 1 clinical studies characterized the PK of SOF, LDV, and SOF/LDV. Additionally, intensive and/or sparse plasma concentration data from 391 healthy subjects and 2147 HCV-infected subjects who received SOF/LDV, SOF+LDV, or LDV single agent from 14 clinical studies (9 Phase 1, 2 Phase 2, and 3 Phase 3 studies) were used for population PK evaluations of SOF, its predominant circulating metabolite GS-331007, and LDV.

SOF single agent: There were 18 clinical pharmacology studies conducted with SOF and/or GS-9851 (as monotherapy or in combination with Peg-IFN and/or RBV). Those have already been presented in the Sofosbuvir single agent MAA dossier.

LDV single agent: There were 19 clinical pharmacology studies conducted with LDV single agent submitted pertaining to the clinical pharmacology package (Table 1).

SOF/LDV FDC: There were 10 clinical pharmacology studies conducted with SOF/LDV informing on the clinical pharmacology in Table 2 (phase II studies is given in Table 20 and phase III studies in Table 6).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1 Overview of LDV Clinical Studies (as a Single-Agent Tablet or in Combination with Other Compounds) Contributing Information on Clinical Pharmacology

Type of Study / Study Number / Phase / Location	Dosage form	Dose (mg)	N	Dosage Form of Coadministered or Control Drugs
Comparative Bioavailability / Bioequivalence Studies in Healthy Subjects				
GS-US-256-0110 Phase 1	LDV 30-mg tablet (test formulation) LDV 30-mg tablet (reference formulation)	30 120	33	Omeprazole (1 × 20-mg tablet)
PK and Initial Tolerability Studies in Healthy Subjects				
Mass Balance Study				
GS-US-256-0108 Phase 1	LDV capsule containing 1.65 mg [14C]LDV and 88.35 mg LDV	90	8	Not applicable
Single dose study				
GS-US-256-0101 Phase 1	LDV 1-mg tablet LDV 10-mg tablet	3 10 30 60 100	54	Placebo tablet
PK and initial tolerability in HCV infected subjects				
Multiple dose study in subjects with genotype 1 HCV infection				
GS-US-256-0102 Phase 1	LDV 1-mg tablet LDV 10-mg tablet	3 10 30 60	72	Placebo tablet

Type of Study / Study Number / Phase / Location	Dosage form	Dose (mg)	N	Dosage Form of Coadministered or Control Drugs
		100		
Intrinsic factor PK studies				
Renal impairment study				
GS-US-344-0108 Phase 1	LDV 90-mg tablet	90	20	Not applicable
Hepatic impairment study				
GS-US-248-0117 Phase 1	LDV 10-mg tablet	30	49	VDV (2 × 100-mg tablets) TGV (1 × 30-mg capsule)
GS-US-344-0101 Phase 1	LDV 90-mg tablet	90	20	Not applicable
Extrinsic factor PK studies				
Drug-Interaction Study Between LDV and SMV in Healthy Subjects				
GS-US-256-0129 Phase 1	LDV 10-mg tablet	30	50	SMV (1X 150 mg capsule)
Drug-Interaction Study Between LDV and MK-5172 in Healthy Subjects				
MK-5172 PN023 (GS-US-256-0153) Phase 1	LDV 10-mg tablet	90	17	MK-5172 (4 × 100-mg tablets) MK-5172 placebo tablet LDV placebo tablet
Drug-Interaction Study Between LDV and HIV ARVs in healthy subjects				
GS-US-248-0127 Phase 1	LDV 30-mg tablet	90	27	VDV (2 × 100-mg tablets) TGV (1 × 30-mg capsule) ATR (1 × 600-mg EFV/ 200 mg FTC/300 mg TDF tablet)
Drug-Interaction Study Between LDV and Probe Drugs in Healthy Subjects				
GS-US-248-0125 Phase 1	LDV 10-mg tablet	90	129	VDV (2 × 100-mg tablets) TGV (1 × 30-mg capsule) Pravastatin (1 × 40-mg tablet) Rosuvastatin (1 × 10-mg tablet) Digoxin (1 × 0.25-mg tablet) Rifampin (2 × 300-mg capsules) Verapamil SR (1 × 240-mg capsule) CsA (3 × 100-mg capsules)
Drug-Interaction Study Between LDV, VDV, and GS-9669 in Healthy Subjects				
GS-US-248-0107 Phase 1	LDV 30-mg tablet	90	36	GS-9669 (1 × 250-mg tablet) VDV (2 × 100-mg tablets)
Drug-Interaction Study Between LDV, GS-9256, VDV, TGV, and RBV in Healthy Subjects				
GS-US-248-0102 Phase 1	LDV 10-mg tablet	30	75	GS-9256 (1 × 100-mg capsule plus 1 or 2 × 25-mg capsules) VDV (2 × 100-mg tablets) TGV (2 × 10-mg capsules) RBV (3 × 200-mg tablets)
Drug-Interaction Study Between LDV or VDV and a Representative H2RA or PPI in Healthy Subjects				
GS-US-248-0104 Phase 1	LDV 10-mg tablet	30	75	VDV (2 × 100 mg-tablets) Famotidine (1 × 20-mg tablet) Omeprazole (1 × 20-mg capsule)
Drug-Interaction Study Between LDV, GS-9669, and SOF in Healthy Subjects				
GS-US-334-0101 Phase 1	LDV 30-mg tablet	90	49	SOF (1 × 400-mg tablet) GS-9669 (2 × 250-mg tablets)
Supratherapeutic Dose of LDV in Healthy Subjects				
GS-US-169-0105 Cohort 4	LDV 30-mg tablet	360	15	Not applicable

Type of Study / Study Number / Phase / Location	Dosage form	Dose (mg)	N	Dosage Form of Coadministered or Control Drugs
Phase 1				
Drug-Interaction Study Between LDV, VDV, and GS-6620 in Healthy Subjects				
GS-US-119-0113 Phase 1	LDV 30-mg tablet	90	12	
Drug-Interaction Study Between LDV or SOF and a Representative Hormonal Contraceptive in Healthy Women				
GS-US-334-0146 Phase 1	LDV 90-mg tablet	90	15	SOF (1 × 400-mg tablet) Ortho Tri-Cyclen® Lo (norgestimate 0.180 mg/ 0.215 mg/0.25 mg/ethinyl estradiol 0.025 mg)
PK / PD and PD Studies in Healthy Subjects (QT / QTc Interval Study)				
GS-US-344-0109 Phase 1	LDV 30-mg tablet	120	59	LDV placebo tablet Moxifloxacin (1 × 400-mg tablet)

[14C]- = radiolabeled carbon 14; ARV = antiretroviral; ATR = Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated); CsA = cyclosporine (cyclosporin A); EFV = efavirenz; FTC = emtricitabine; H2RA = H2-receptor antagonist; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV = ledipasvir; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PPI = proton-pump inhibitor; 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; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SR = sustained release; TDF = tenofovir disoproxil fumarate; TGV tegobuvir; VDV = vedroprevir

Table 2 Overview of SOF/ LDV Clinical Studies Contributing Information on Clinical Pharmacology

Type of Study / Study Number / Phase / Location	Dosage form	Dose (mg)	n	Dosage Form of Coadministered or Control Drugs
Comparative Bioavailability / Bioequivalence Study in Healthy Subjects				
GS-US-337-0101 Phase 1	SOF/LDV 400-mg/ 90-mg tablet	400 mg/ 90 mg	58	SOF (1 × 400-mg tablet) LDV (1 × 90-mg tablet)
PK and Initial Tolerability Studies in Healthy Subjects				
Single dose				
GS-US-334-0111 Phase 1	SOF/LDV 400-mg/ 90-mg tablet	400 mg/ 90 mg	64	SOF (1 × 200-mg tablet, 1 or 2 × 400-mg tablets)
Extrinsic factor PK studies				
Drug-Interaction Study Between LDV or SOF/LDV and HIV ARVs in Healthy Subjects				
GS-US-344-0102 Phase 1	SOF/LDV 400-mg/ 90-mg tablet	400 mg/ 90 mg	168	LDV (1 × 90-mg tablet) ATR (1 × 600-mg EFV/ 200 mg FTC/300 mg TDF tablet) DRV/r: DRV (2 × 400-mg tablets) + RTV (1 × 100-mg tablet) RAL (1 × 400-mg tablet) RPV (1 × 25-mg tablet) EVG (1 × 150-mg tablet) COBI (1 × 150-mg tablet) ATV (1 × 300-mg capsule)
GS-US-337-0128 Phase 1	SOF/LDV 400-mg/ 90-mg tablet	400 mg/ 90 mg	35	ABC/3TC (1 × 600-mg/300-mg tablet)
Drug-Interaction Study Between SOF/LDV and HIV ARVs, H2RA, or PPI in Healthy Subjects				
GS-US-337-0127 Phase 1	SOF/LDV 400-mg/ 90-mg tablet	400 mg/ 90 mg	92	ATR (1 × 600-mg EFV/ 200 mg FTC/300 mg TDF tablet) Complera (1 × 200-mg FTC/25 mg RPV/300 mg TDF tablet) Famotidine (1 × 40-mg tablet) Omeprazole (1 × 20-mg tablet)

3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATR = Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated); ATV = atazanavir; COBI = cobicistat; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; H2RA = H2-receptor antagonist; HIV = human immunodeficiency virus; LDV = ledipasvir; PK = pharmacokinetic(s); PPI = proton-pump inhibitor; /r = boosted with ritonavir; RAL = raltegravir; RBV = ribavirin;RPV = rilpivirine; RTV = ritonavir; SOF = sofosbuvir; TDF = tenofovir disoproxil fumarate

2.4.2. Pharmacokinetics

Analytical methods

The bioanalytical methods for the measurement of total LDV, SOF, GS-566500, and GS-331007 concentrations in human plasma and urine were based on deuterium labelled internal standards and LC/MS/MS with positive ionization. The sample preparation for LDV was liquid-liquid extraction and for SOF and metabolites sample preparation involved protein precipitation extraction. All methods were validated.

SOF and the new chemical entity LDV have respectively six stereo-centers, but the product is pure enantiomers. Interconversion between sofosbuvir and its diastereomer GS-491241 has not been observed, neither in vitro nor in vivo in preclinical species. The active metabolite GS-461203 has not been measured in vivo. Efficacy, in terms of rapid viral response, has been shown to correlate with exposure to sofosbuvir as well as GS-331007.

Formulations

Administration of SOF/LDV FDC or SOF and LDV as individual components results in similar systemic exposures of SOF, GS-566500, GS-331007, and LDV. All phase III studies and a majority of the DDI studies were performed with the commercial formulation SOF/LDV (400 mg/90 mg) FDC tablet, i.e. no bioequivalence study is needed.

Absorption

Ledipasvir

Ledipasvir was relatively rapidly absorbed with a t_{max} of 4 h after administration of the SOF/LDV FDC tablet in healthy volunteers. The solubility is low and pH dependent (<1 µM at pH >3). LDV is a BRCP and P-gp substrate. The absolute bioavailability of LDV has not been determined in humans. However, the oral bioavailability of LDV is expected to be ≤ 30%.

Sofosbuvir

For sofosbuvir, following a single dose of the SOF/LDV FDC tablet in fasted state, the PK profile of SOF show rapid turnover with a t_{max} of 0.8 h and a short half-life of approximately 0.5 h. T_{max} of GS-331007 was observed at 3.5 h post-dose. The bioavailability of drug related material is moderate to high, at least 50%, although the absolute value is unknown.

In vitro studies show that SOF is subject to marked efflux, probably mediated by P-gp and/or BCRP. Co-administration of a single dose of 600 mg Cyclosporin A (CsA) increased the exposure to sofosbuvir 4.5 fold providing further evidence of sofosbuvir being a sensitive substrate to efflux transporters.

Food effect SOF/LDV

The effect of food on PK after a single-dose of SOF/LDV FDC tablet was investigated in healthy volunteers. Administration with food increased AUC of SOF by 95% and 79% and C_{max} 26% and 15%, after a moderate and high fat meal respectively. Corresponding figures for GS-331017 was an increase of 17% and 12% (AUC), and 18% increase and 30% decrease (C_{max}). Similar plasma exposure was achieved for LDV upon administration of SOF/LDV under fasted or fed conditions (within ±15%). In clinical phase III, SOF/LDV has been administered without regard to food. It is supported that SOF/LDV can be administered without regard to food.

Distribution

Ledipasvir is highly protein bound in plasma. In vivo, the mean unbound LDV was approximately 0.2%, in healthy volunteers and subjects with severe hepatic or renal impairment. The mean whole blood-to-plasma concentration ratio ranged from 0.51 to 0.66.

Plasma protein binding of SOF (the fraction unbound is 18%) seems to be independent of concentration and no effect of renal impairment was seen on degree of binding. GS-331007 is minimally bound to plasma proteins.

Metabolism

Ledipasvir

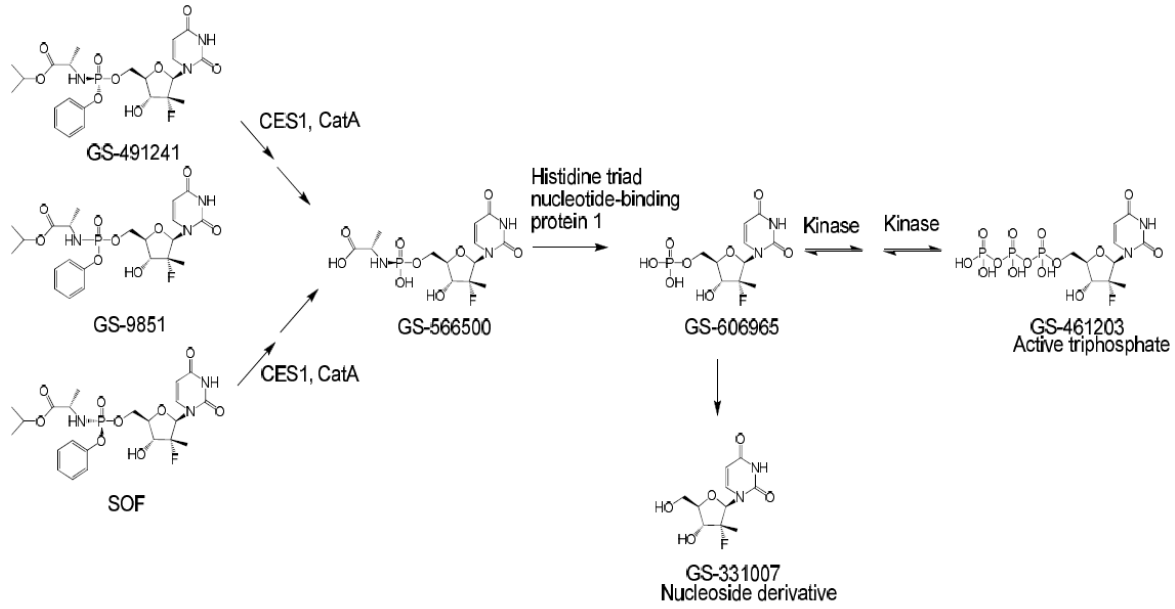
LDV is metabolically stable in incubations in human microsomes and hepatocytes. Ledipasvir was also the major compound found in faeces accounting for on average 70% of the administered dose (84% of total in feaces), followed by the proposed oxidative metabolite M19 (Oxy-LDV-3, 2.2% of dose). This indicates that metabolism is not important in the elimination of LDV.

Sofosbuvir

Sofosbuvir is subject to extensive first-pass metabolism in the intestine and in the liver. The active metabolite GS-461203 is formed through several metabolic steps (Figure 1). In vitro, SOF is rapidly hydrolysed by CatA and CES1 to form GS-566500 which is further metabolised to eventually form the active triphosphate nucleoside analogue GS-461203. Involvement of CYP enzymes in the metabolism of sofosbuvir cannot currently be ruled out.

In plasma, GS-331007 constituted the majority (90%) of measured radioactivity. In the mass balance study the intermediate metabolite GS-566500 had a t_{max} of 1 h and a half-life of 2 h. The major metabolite GS-331007 peaked at 2 h and had a half-life of 26 h.

Figure 1 Intracellular metabolism pathway of GS-9851, GS-491241 and SOF (GS-7977)



Elimination

Excretion

Ledipasvir

In the human mass balance study the mean (SD) cumulative urinary and fecal recovery of [^{14}C]-radioactivity was 87% (7.8%) with relative recovery of 1.2% (0.08%) in urine and 86% (7.8%) in faeces. Ledipasvir was the major compound found in faeces accounting for on average 70% of the administered dose. No unchanged parent drug was detected in the urine. LDV is not a substrate for hepatic uptake transporters OATP1B1, OATP1B3 or OCT1.

Sofosbuvir

Following a single 400 mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, faeces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. This data indicate that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. The transporters involved are unknown.

Dose proportionality and time dependency

LDV appears to be dose proportional within the range investigated (3-100 mg) and thus also at therapeutic exposure. Based on PopPK analysis of pooled single agent LDV no time dependency was

observed. For SOF no indication of non-linearity was observed in the range 200-1200 mg. There was no evidence of time-dependent PK for SOF over a 7 day period.

Intra- and inter-individual variability

Inter-individual variability for the PK of ledipasvir was 47.6% for CL, 56% for Vc, 78% for Vp and 45.9% for Ka, respectively. For the QD regimen of SOF/LDV FDC, model predicted steady state AUC was 6888 ng·hr/mL for a typical HCV-infected subject (treatment naïve, male, 80 kg in weight and without RBV usage). The model predicted 5 to 95%tile AUC values of the population were 3181 ng·hr/mL to 18722 ng·hr/mL, which is -54% to 172% difference from the typical value, respectively. A majority of the PK variability of LDV was unexplained by the model.

Pharmacokinetics in target population

Ledipasvir

The exposure of LDV after dosing once daily of SOF/LDV (400 mg/90 mg) in the patient population was predicted by PopPK analysis and the resulting AUC_{tau} was (mean (CV%)) 8530 (61) and C_{max} 364 (51), respectively. Based on the population PK analysis, CL/F and half-life for LDV in patients (for a typical HCV-infected subject treatment naïve, male, 80 kg body weight and without RBV usage) was determined to be approximately 13 L/h and 23 h, respectively. The CL/F and median half-life with rich PK sampling in healthy volunteers receiving SOF/LDV FDC was 14 L/h and 40 h, respectively.

Sofosbuvir

Population PK analyses of GS-331007 and SOF were performed using all available intensive and sparse PK samples collected in Phase 1, 2, and 3 studies in healthy and HCV-infected subjects. In the sofosbuvir Population PK model, apparent oral clearance after administration of the dose (CL/F) was approximately 30% lower in patients compared to healthy volunteers. In the GS-331007 Population PK model, the different HCV genotypes were associated with 50% to 60% higher CL/F as compared to healthy volunteers. The differing effect of patient status has not been explained. The population PK models can currently only be used for description of the observed data and not for predictions.

Special Populations

Hepatic impairment

Ledipasvir

Single dose PK of LDV was investigated in subjects with severe hepatic impairment (HI, Child-Pugh-Turcotte (CPT) score ≥10 at screening). A single oral dose of 90 mg LDV was administered with a moderate fat meal. Mean (CV%) $AUC_{(0\text{-}inf)}$ was 9567 (68) ng*h/mL and 7616(31) ng*h/mL in severe HI subjects and healthy controls, respectively. Ledipasvir Cmax was approximately 35% lower and terminal t1/2 was prolonged (median 84 h vs. 46 h) in subjects with severe HI. The geometric mean ratio (90% CI) of $AUC_{(0\text{-}inf)}$ (severe HI/normal controls) was 108 (70 to 165). The unbound plasma exposure was similar in subjects with severe hepatic impairment and control subjects with normal hepatic function.

Sofosbuvir

Exposure to SOF and GS-566500 increased approximately 2-fold in patients with moderate (median Child-Pugh score of 8) and severe (median Child-Pugh score of 10) hepatic impairment. The exposure to GS-331007 was essentially unchanged. Of note, the viral response was numerically lower in patients with hepatic impairment compared to historical controls.

Renal impairment

Ledipasvir

The pharmacokinetics of ledipasvir was studied with a single dose of 90 mg ledipasvir in HCV negative subjects with severe renal impairment median [range] calculated CLCr 22 [17 to 29] mL/min). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment. The unbound plasma exposure was similar in subjects with severe renal impairment and control subjects with normal renal function.

Sofosbuvir

Severe renal impairment led to a more than 7-fold increase in exposure to GS-331007 while mild and moderate renal impairment increased GS-331007 exposure less than 2-fold. Exposure to SOF and GS-566500 was increased approximately 3-fold in subjects with severe renal impairment. Safety margins calculated from results of toxicology studies are 5.4 to 11.6 for SOF and 1.6 to 3.5 for GS-331007 in subjects with mild and moderate renal impairment. The haemodialysis extraction ratio for GS-331007 was approximately 50%. Treatment of patients with severe renal impairment/end-stage renal disease (ESRD) is not recommended.

Age, sex, race, body weight

Female subjects had a significant lower CL of LDV than male subjects, resulting in higher exposure. No apparent relation has been observed between adverse events and exposure. The increased exposure in women is therefore not considered clinically relevant. The Population PK analyses of SOF and GS-331007 did not suggest a significant effect of gender on the kinetics of either compound.

The Population PK analyses of SOF, GS-331007 and LDV did not suggest a significant effect of race (described as White, Black, Asian and Other) on the kinetics of either compound. No dose adjustment of SOF/LDV combination is needed respective to race.

Baseline body weight was identified as a statistically significant covariate on the PK of LDV. CL and Vc values increase in heavier subjects. Simulated steady state AUC of the subjects at the heaviest quartile (90 kg to 163 kg) was 5990 (2860 13500, 5-95%tile) ng.hr/mL, which is 45% lower than those at the lowest quartile (42 kg to 67 kg). Although the exposure to LDV decreases with increasing body weight, the effect is not considered clinically relevant. Body weight did not have a clinically significant effect on SOF exposure according to a population pharmacokinetic analysis.

No formal PK study in elderly patients has been conducted. The impact of age on the PK of SOF, GS-331007, and LDV has been evaluated as a covariate in the population PK analyses. The reporting of the PK population data doses not allow a clear evaluation of PK in elderly (>75 years).

The safety and efficacy of SOF/LDV in children and adolescents aged <18 years have not yet been established. The SOF/LDV FDC is not indicated in patients under 18 years.

Pharmacokinetic interaction studies

Co-administration of ledipasvir has an effect on exposure of sofosbuvir (approx. 2-fold increase). This is likely due to the inhibitory effects of LDV on P-gp and/or BCRP, for which SOF is a substrate. Exposure of metabolite GS-566500 was also increased nearly 2-fold, while GS-331007 was in general unaffected. There was no relevant change of LDV steady state PK parameters when co-administrated with single dose SOF at fasting state.

Effects of other drugs on the pharmacokinetics of ledipasvir and SOF/LDV

Metabolism is not important in the elimination of LDV. LDV is a P-gp and BCRP substrate and in vitro data shows that LDV is not a substrate for OATP1B1, OATP1B3 or OCT1. The elimination of LDV is not fully understood, e.g. whether other hepatic uptake transporters than those investigated are involved.

In vivo the inducer rifampicin caused a decrease in LDV exposure (AUC -60% and C_{max} -35%). Co-administration with EFV/FTC/TDF also resulted in a decrease of LDV exposure (-33% both AUC and Cmax). In both cases the decrease is most likely mediated by the inductive effects of efavirenz and rifampicin on drug transporters e.g. P-gp.

The "boosters" ritonavir and COBI seem to have an effect on the exposure of LDV. In the combination with DRV/r (+40%), ATZ/r (2-fold) and EVG/COBI (+60-80%) increases were observed. Darunavir and atazanavir are also BCRP and/or P-gp inhibitors, contributing to the observed effect on LDV exposure.

The solubility of LDV is low and decreases with increasing pH. Therefore, medical products that increase gastric pH are expected to decrease plasma concentration of LDV. The Applicant has submitted three studies with omeprazole 20 mg (SOF/LDV FDC was used in one study). In the two studies with LDV as single agent, LDV was dosed staggered 2 h after OMZ and a reduction of LDV exposure of 40-50% was observed. Dosing the SOF/LDV FDC simultaneously with OMZ (≥5 days dosing) did not have an effect on LDV exposure.

Effects of ledipasvir and SOF/LDV on the pharmacokinetics of other drugs

The inhibition data for ledipasvir showed no effect on CYP1A2, 2B6 2C8, 2C9, 2C19, 2D6. However, for CYP3A4, UGT1A1, P-gp and BCRP there were signals of in vitro inhibition at the estimated intestinal concentration and a risk of clinically relevant intestinal DDI cannot be excluded. Also, based on in vitro data a clinically relevant DDI via induction of PXR at intestinal level cannot be excluded. Ledipasvir was not in vitro an inhibitor of BSEP, OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MRP2 or MRP4 at clinically relevant concentrations.

Ledipasvir has no effect on oral contraceptives as determined by both PK and PD measures.

Pravastatin AUC and C_{max} increased approximately 3-fold when co-administrated with LDV/VDV/TGV. Rosuvastatin AUC increased 8-9-fold and C_{max} approximately 18-fold. The increase in rosuvastatin exposure is likely mediated by the inhibition of several uptake or efflux transporters of rosuvastatin (i.e. OATPs and BCRP). However, it is not possible to distinguish the contribution of the individual compounds (LDV, VDV or TGV) to the observed increase since it was administered as a mixture.

SOF/LDV FDC has been studied in several combinations of antiretroviral agents (EFV/FTC/TDF, FTC/RPV/TDF, DRV/r, RAL, RPV, ABC/3TC, ATV/r, EVG/COBI). SOF/LDV seems to have an effect on exposure of COBI. The increase of exposure of COBI was prominent at C_{min} (+325%) and less for AUC (+59%). In the same combination LDV exposure is increased 60-80%. The mechanism for this is unknown.

Tenofovir data from DDI studies with SOF/LDV, showed that tenofovir exposure was increased 2-fold when simultaneously co-administered with EFV/FTC/TDF, and 1.5-fold with FTC/RPV/TDF, ATV/r+FTC/TDF or DRV/r+FTC/TDF, respectively.

Sofosbuvir

Effects of other drugs on the pharmacokinetics of sofosbuvir

Renal secretion is involved in the elimination of GS-566500 and GS-331007. The transporter(s) involved are unknown. It is also unknown whether hepatic transporters are involved in the uptake of the polar SOF and its metabolites into the hepatocytes.

A 600 mg single dose of CsA had a large effect on SOF exposure with a 4.5-fold increase. However, the exposure to GS-331007 was not statistically different. Tacrolimus did not affect exposure to SOF or its metabolites. Darunavir/ritonavir (800/100 mg daily [QD]) increased exposure to SOF (34% increase) and to GS-566500 (80% increase), but not exposure to GS-331007.

In vitro data indicate P-gp involvement in the absorption. Inducible enzymes may be involved in the elimination. The effect of strong P-gp inducers on SOF exposure has not been studied in vivo. Due to the risk of under-exposure, a warning has been included in the SmPC and concomitant use of strong P-gp inducers is not recommended.

Effects of sofosbuvir on the pharmacokinetics of other drugs

Sofosbuvir and its metabolite, GS-331007 did not show detectable inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6, or of CYP3A except for sofosbuvir which inhibited CYP3A4 by 22% concentration of 50 µM with midazolam as substrate. Sofosbuvir and GS-331007 show low or no significant inhibition of UGT1A1.

Induction of CYP3A4 and CYP2B6 was observed in vitro. An in vivo DDI study with oral contraceptives co-administered with sofosbuvir for 7 days did not show any sign of reduced exposure. The study is considered to be too short to fully exclude a minor induction. However, a clinically relevant effect is not expected based on the observed data.

Sofosbuvir showed no inhibition of P-gp up to the highest concentration tested (300 µM) covering the calculated intestine concentration of sofosbuvir. GS-331007 is not a substrate or inhibitor for OAT1.

DDI studies have been performed in healthy volunteers and patients to evaluate effect of SOF on the PK of antiretroviral agents (ARVs), methadone, CsA and tacrolimus. Further, the effect of these medications on the PK of SOF and its metabolites has been evaluated. Generally, SOF had no or limited effect on the PK of co-administrated ARVs; only for raltegravir AUC was decreased by 27%. Methadone exposure was unaffected by SOF as were exposures to CsA and tacrolimus, although C_{max} for tacrolimus was decreased by almost 30%.

Potential interactions with telaprevir or boceprevir have not been studied.

2.4.3. Discussion on clinical pharmacokinetics

The clinical pharmacokinetic properties of ledispasvir and sofosbuvir have been sufficiently characterized.

Bioavailability and Elimination of LDV

The absorbed fraction of LDV is ≥ 30% (mass balance study) while the oral bioavailability of LDV in the FDC formulation is expected to be ≤ 30%. The 86% of radioactive dose recovered in the faeces represents unabsorbed drug as well as drug eliminated by biliary excretion as either unchanged parent or metabolites.

The hepatic uptake transporters OATP1B1/3 and OCT1 have been investigated and LDV was found not to be a substrate of these. The Applicant states that the uptake into hepatocytes could be mediated by passive diffusion. No data was presented to support this, i.e. full understanding of the elimination process remains unclear.

Drug- drug interactions

There were in vitro signals for both inhibition and induction of CYP3A4 and a clinical relevant drug-drug interaction at intestinal level cannot be excluded based on these data. The applicant has performed a study investigating the mechanism based inhibition (MBI) of Ledipasvir on all relevant CYPs. No MBI was revealed, however the concentration investigated did not cover intestinal levels which is relevant for

CYP3A4. A study will be conducted to measure the unbound fraction in microsomes (Fu,mic) and the nominal test concentration (ie, nonspecific binding). The study will be completed by the end of 4Q 2014 and the final study report will be submitted in 1Q 2015.

The effect of LDV/VDV/TGV on the exposure of rosuvastatin was large. Rosuvastatin AUC increased 8-9-fold and C_{max} ca. 18-fold in, likely due to the inhibition of several uptake or efflux transporters (i.e. OATPs and BCRP). However, it is not possible to distinguish the contribution of the individual compounds (LDV, VDV or TGV) to the observed increase since it was administered as a mixture. Based on this information rosuvastatin is contraindicated and this is adequately reflected in the SmPC. The applicant is recommended to perform a new DDI study with the LDV/SOF FDC formulation.

The combination of SOF/LDV with several HIV regimens containing tenofovir was questioned for reasons of renal safety. The concentration of tenofovir which carries an exposure dependent risk for renal tubular toxicity is substantially increased when SOF/LDV is given in combination with various tenofovir-containing regimens (tenofovir exposure was increased 2-fold when SOF/LDV was simultaneously co-administered with TDF/FTC/EFV, and 1.5-fold with TDF/FTC/RPV). The applicant provided new data in this regard.The cautionary use for combination of LDV/SOF with tenofovir containing regimens is reflected in the SmPC.

2.4.4. Conclusions on clinical pharmacokinetics

The clinical pharmacology data for ledipasvir/sofosbuvir FDC is considered acceptable by the CHMP. All the concerns emerged during the evaluation were adequeately addressed.

2.4.5. Pharmacodynamics

In this section data on LDV as single agent is presented. In vitro data, including resistance selection experiments, are discussed. Results obtained during 3 days of monotherapy (LDV given in various doses) in genotype-1 infection are also presented in here, including short term activity in vivo and NS5A resistance selected during those 3 days. LDV monotherapy is not further discussed in the efficacy section.

A short summary of NS5A resistance selected in the phase 3 study is presented in this section (for more details refer to the efficacy section).

The pharmacodynamics of SOF as a single agent is well established. This agent (a nucleotide HCV-polymerase inhibitor) has potent activity against all HCV-genotypes. Only one mutation of relevance for SOF resistance (S282T) has been found during in vitro studies. This mutation has been detected at a very low frequency in patients who failed a SOF-containing regimen through relapse, and in these cases the virus reverted back to wild type virus within short (i.e. viral fitness much hampered by this substitution). S282T has not been seen as a naturally occurring polymorphism. There is no cross resistance between NS5A inhibitors and SOF. SOF has been shown to retain its efficacy on retreatment.

Mechanism of Action and in vitro activity (LDV)

While enzymatic assays are not available as NS5A lack a known enzymatic function, LDV has been shown to select for mutations within the NS5A gene in the replicon system conferring a reduction in viral susceptibility. Furthermore, replicons with resistance mutations associated with other NS5A inhibitors are cross resistant to LDV.

It was shown that LDV lacks activity against NS3/4A protease, NS3 helicase, NS5B polymerase, the HCV internal ribosome entry site (IRES), and a broad panel of kinases.

The mean EC_{50} values for genotype 1a and 1b was 0.03 and 0.004, respectively. Since LDV is highly protein bound, EC_{50}-values were around 10 times higher when adding 40% human serum to cell based assays. The in vitro activity to non-1 subtypes are lower, and variable (Table 3).

Table 3 LDV in vitro susceptibility for various genotypes

Genotype	HCV Isolate	EC50 nM
1a		0.031
1b		0.004
2a	JFH-1 (L31 in NS5A)	21
2a	J6 (M31 in NS5A)	249
2b	MD2b8-2 (L31 in NS5A)	16
2b	MD2b-1 (M31 in NS5A)	530
3a	S52	168
4a	ED43	0.39
5a	SA13	0.15
6a	Consensus	1.1
6e	D88	264

It is noted that the EC_{50} value for GT3 is much higher than that for GT1. Still, clinical data do indicate that LDV adds relevant activity also for this genotype (see efficacy section). The issues concerning traditional in vitro/in vivo correlation as regards the relation between replicon EC_{50} and anticipated unbound plasma exposure has previously been noted by the CHMP. NS5A is a polyfunctional protein involved both in the replication complex as well as in viral assembly. In general, it is not clear whether replicon assays fully represent the impact of NS5A inhibitors on the HCV life cycle, as there is no viral assembly and release (see e.g., McGivern et al, Gastroenterology 2014).

In GT-2 infection the frequency of NS5A RAVs occurring as natural polymorphisms is very high (with consequent substantial effects on LDV susceptibility). The role of SOF/LDV for this subtype would need to be justified on the basis of clinical studies, such studies have not been performed.

In vitro resistance selections in replicon cells yielded the primary NS5A substitution Y93H in both genotype 1a and 1b. Additionally, a Q30E substitution emerged in genotype 1a replicons.

In studies with site-directed mutagenesis (SDM, evaluating activity after the introduction of known NS5A mutations, vs the activity seen with WT virus) LDV showed reduced activity (FC>10) against HCV

replicons encoding a number of mutations: K24G/N, M28T/A/G, Q30E/G/H/K/R, L31M/V/I, P32L, S38F, H58D, A92T, and Y93C/H/N/S in genotype 1a; and L31V/I, P58D, A92K and Y93H in genotype 1b.

Both selection experiments and SDM studies show that the intrinsic resistance barrier of LDV is slightly lower for GT1a than for GT1b.

GS-US-256-0102 - LDV monotherapy

Viral decay

This was a 3-day monotherapy study in previously untreated non-cirrhotic patients with GT 1a/1b-infection.

Multiple doses of LDV (1, 3, 10, 30 or 90 mg qd) or placebo for 3 consecutive days were given to patients with GT1a-infection (12 per cohort). Patients with genotype 1b were given 10 mg qd or placebo. Treatment was given fasted.

The greatest median reductions from baseline in HVC RNA were generally observed on Day 2 (36 hours). For genotype 1a (several doses) the response was modestly dose dependent up to 30 mg (for max reduction values, 36 hrs).

Table 4 Median (Q1,Q2) HCV-RNA decay (log_{10}) during LDV monotherapy

Timepoint	**1 mg GT 1a (N=10)**	**3 mg GT1a (N=10)**	**10 mg GT1a (N=10)**	**10 mg GT1b (N=10)**	**30 mg GT1a (N=10)**	**90 mg GT1a (N=10)**	**Placebo (N=12)**
Baseline	7.01	6.47	6.63	6.48	6.18	6.61	6.80
at 24 hrs	-1.4 (-1.8, -0.8)	-2.4 (-2.75, -2.33)	-2.9 (-3.22, -2.24)	-3.1 (-3.3, -2.4)	-3.1 (-3.3, -2.3)	-3.0 (-3.3, -2.6)	0.1 (0.0, 0.3)
At 36 hrs	-2.3 (-2.9,-1.9)	-3.1 (-3.3, -3.0)	-3.2 (-3-3,-2-3)	-3.3 (-3.8, -3.2)	-3.2 (-3.6,-2.6)	-3.1 (-3.7,-2.7)	-0.3 (-0.3, -0.2)
at 48 hrs	-2.1 (-2.3, -1.4)	-3.0 (-3.1, -2.9)	-3.0 (-3.1, -2.3)	-3.1 (-3.7, -2.9)	-3.1 (-3.4, -2.4)	-2.9 (-3.5, -2.5)	0.03 (-0.1, 0.2)
at 72 hrs	-2.0 (-2.3, -1.9)	-2.9 (-3.0, -2.7)	-2.8 (-3.0, -2.2)	-3.3 (-3.4, -2.8)	-2.7 (-3.3, -2.0)	-2.9 (-3.5, -2.6)	0.04 (-0.2, 0.2)
LDV exposure, mean (%CV)							
AUCtau (ng·h/mL)	34.0 (29.8)b	89.7 (54.6)	323.6 (27.9)	409.5 (42.5)	1592.4 (59.5)	3815.5 (42.1)	NA

In monotherapy maximal short term activity is seen at a dose of 30 mg and above (GT-1 infection). In combination with SOF only the highest dose (90 mg) has been studied. To be noted, the LDV exposure in this monotherapy study was considerable lower than the LDV exposure seen in the phase 3 program (SOF 400 mg/LDV 90 mg; AUC t_{au} around 8500 ng·h/mL).

Resistance selection during monotherapy

All patients dosed LDV ≥ 3 mg/day had RAMs detected at follow-up (day 4 and day 14). Mutations selected (detected *by population sequencing*) are shown below. The same primary NS5A resistance mutations were selected here, as discussed above (28, 30, 31, and 93), and the same patterns were seen in isolates from patients who relapsed in the phase 3 studies.

The fold shift in EC_{50} to LDV by type of mutation varied extensively, but was generally lower for M28T and the highest for Y93H, Q30H being in between. The fact that M28T and Q30H were only detected in the groups treated with doses up to 10 mg but not detected in patients treated with 30-90 mg, is consistent with suppression of lower-level resistance variants at higher doses. Conversely, the highest-level resistant variants among subjects with genotype 1a virus (Y93C and Y93H) were selected more frequently in subjects who received 90 mg. All 10 subjects with genotype 1b HCV, who received 10 mg, harbored

Y93H following treatment, consistent with Y93H being the primary LDV RAM selected in the genotype 1b replicon.

Table 5 De novo NS5A Mutations at Day 4 and/or Day 14 after 3 days of monotherapy

Mutation	1 mg Genotype 1a (N=10)	3 mg Genotype 1a (N=10)	10 mg Genotype 1a (N=10)	30 mg Genotype 1a (N=10)	90 mg Genotype 1a (N=10)	10 mg Genotype 1b (N=10)
M28T	-	6	1	-	-	-
Q30H	1	3	1	-	-	-
L31M	1	6	4	5	4	-
Q30R	3	9	7	7	7	-
Y93C	-	1	3	2	5	-
Y93H	-	-	-	1	2	10

Virus from all patients in the phase 3 studies were analyzed for baseline NS5A RAVs. With the use of deep sequencing with a sensitivity cut-off at 1% of the circulating viral population, such RAVs were seen in around in 15% of the patients (i.e. naturally occurring) in varying proportions from very low (some few percent of the viral populations) to very high (dominating the viral population). In the efficacy section the impact of such naturally occurring NS5A RAVs on treatment outcomes is further discussed.

The totality of available evidence indicates that there is little reversion to wildtype after the selection of NS5A-inhibitor resistant variants.

Preliminary data provided on re-treatment with SOF/LDV (+ RBV) is discussed in the efficacy section.

Resistance selected in the phase 3 program (SOF/LDV +/- RBV)

NS5A resistance-associated variants (RAVs) were observed in post-baseline isolates from 29/37 patients not achieving sustained virological response (SVR). Of the 29 genotype 1a patients who qualified for resistance testing, 22/29 (76%) patients harboured one or more NS5A RAVs at positions K24, M28, Q30, L31, S38 and Y93 at failure, while the remaining 7/29 patients had no NS5A RAVs detected at failure. The most common variants were Q30R, Y93H and L31M. Of the 8 genotype 1b patients who qualified for resistance testing, 7/8 (88%) harboured one or more NS5A RAVs at positions L31 and Y93 at failure, while 1/8 patients had no NS5A RAVs at failure. The most common variant was Y93H. Ledipasvir is thus anticipated to be cross-resistant to other NS5A inhibitors approved or in late development.

There was no apparent selection of resistance in patients with genotype 3 infection relapsing after SOF/DV therapy.

Relationship between plasma concentration and effect

The main dose response study of LDV was described above (study GS-US-256-0102, monotherapy over 3 days). As mentioned, for HCV GT1a, a modest dose response was seen up to a dose of 30 mg and above (90 mg). The exposure (AUC_{tau}) of LDV in this study was around 1600 and 3800 h·ng/mL for the 30 and 90 mg dose, respectively.

LDV in different doses (30 or 90 mg qd) was also studied in a phase 2 study (GS-US-0120). This study was initiated prior to the acquisition SOF by the applicant. Here LDV was combined with other non-approved agents, tegobuvir (TGV, a non-nucleoside NS5B inhibitor) + vedroprevir (VDV, an NS3-inhibitor) plus ribavirin. In this combination the LDV exposure (AUC_{tau}) was around 1700 and 5900 h·ng/mL, respectively. In that regimen (not further studied) the 90 mg dose yielded a clearly higher SVR rate than did the 30 mg dose (where both viral breakthrough and relapses were frequent).

As mentioned LDV AUC_{tau} was around 8500 h·ng/mL in the phase 3 studies (pop-PK).

2.4.6. Discussion and conclusions on clinical pharmacodynamics

The pharmacodynamics of SOF has been well characterized and has been presented during the approval procedure for sofosbuvir (SOF as single agent). In summary, SOF has a pangenotypic activity, and has a very high barrier to resistance. There seems to be only one key mutation (S282T) that has relevant effects on susceptibility, and confers partial resistance to SOF. However, that mutation has a profound effect on viral fitness, and mutant virus was shown to rapidly revert back to WT virus when drug pressure ceases. SOF can therefore be used in re-treatment of patients who failed sofosbuvir-containing treatment.

LDV is highly potent in vitro, with pico- to low nanomolar EC50s against genotype 1a and-b. Resistance selection for GT-1 has been characterised in vitro, with mutations at Y93 as a key mutation (FC>1000) for both GT 1a and 1b, and for GT1a also mutations at Q30. The in vitro activity is high also for GT 4a and -d. EC_{50} values for GT 2a are highly dependent on the presence or absence of a prevalent polymorphism at L31. In vitro data per se does not justify the use of SOF/LDV for the treatment of genotype-2 infection and clinical data is lacking.

The in vitro susceptibility of genotype 3 is markedly lower (EC_{50} 168 nM). However, clinical data (refer to efficacy section) indicate that LDV still adds relevant activity also for this genotype.

LDV given as monotherapy for 3 days to patients with GT 1a and 1b yielded a 3 log_{10} reduction in HCV-RNA. In monotherapy in genotype 1a infection, maximal short term activity is seen at a dose of 30 mg and above. In combination with SOF only 90mg, the highest dose of LDV tested, has been studied. To be noted, the LDV exposure in this monotherapy study was considerable lower than the LDV exposure seen in the phase 3 program. The selected dose is anticipated to yield maximal activity against genotype 1; however, the exposure reduction at which activity declines against partially resistant variants is unknown. There has been no dose ranging against any other genotype; a similar dose as for GT1 has been used for GT3 and GT4.

Resistance mutations were selected in all patients in the monotherapy study; LDV has a low barrier to resistance which is typical for the class. The pattern, which is similar to that of other agents in this class, was dose dependent in patients with genotype 1a.

Published data on long term follow-up after failure with other NS5A inhibitors indicate that NS5A resistant variants persist.

2.5. Clinical efficacy

The main studies that provide the evidence for efficacy of SOF/LDV against genotype 1 chroninc HCV infection are the ION-1, 2 and 3 studies.

ION-1 and -3 concerns previously untreated patients, while ION-2 included those who had failed therapy with peg+IFN or peg+IFN+ boceprevir/telaprevir (HCV protease inhibitors). Up to 20% of cirrhotic patients were allowed in ION-1 and ION-2, while ION-3 only included non-cirrhotic patients.

Table 6 Overview of SOF/LDV Phase 3 Studies

Study Number	Design	Population
GS-US-337-0102 (ION-1) N=865	Randomized, parallel group-study 1:1:1:1 open label (1) SOF/LDV 24 Weeks (2) SOF/LDV+RBV 24 Weeks (3) SOF/LDV 12 Weeks (4) SOF/LDV+RBV 12 Weeks	**treatment-naïve** HCV GT 1a/1b or mixed Cirrhotics (compensated) allowed (≤ 20%) 100 centers, 62 in the US, 48 in Europe First Subject Screened: 26 September 2012 Last Observation for interim report: 25 November 2013
GS-US-337-0108 (ION-3) N=647	Randomized, parallel group-study 1:1:1 open label • SOF/LDV 8 Weeks: • SOF/LDV+RBV 8 Weeks: • SOF/LDV 12 Weeks:	**treatment-naïve** HCV GT 1a/1b or mixed Only non-cirrhotic 59 centers in the US First Subject Screened: 06 May 2013 Last Subject Observation: 13 December 2013
GS-US-337-0109 (ION-2) N=440	Randomized, parallel group-study 1:1:1:1 open label • SOF/LDV 12 Weeks: • SOF/LDV+RBV 12 Weeks • SOF/LDV 24 Weeks: • SOF/LDV+RBV 24 Weeks:	**treatment-experienced** (peg-IFN/RBV +/- NS3A inhibitor) HCV GT 1a/1b or mixed Cirrhotics (compensated) allowed (≤ 20%) 64 centers in the US First Subject Screened: 03 January 2013 Last Subject Observation: 04 December 2013

For the ION-1 study the initial application only concerned the final results of the 12 week treatment arms. The final results for 24 weeks trtetament arms were provided during the evaluation.

Data from ELECTRON 2 study (proof-of-concept study with decompensated liver disease [Child-Pugh-Turcotte-B]) and from the SOLAR-1 study which investigate the efficacy of LDV/SOF+RBV in patients with decompensated cirrhosis and/or post transplantation were provided. Furthermore data of patients infected with genotype 3 from ELECTRON and ELECTRON -2 studies was provided as supporting evidence. Data on the treatment of HIV coinfected patients and patients with genotype 4 were also provided. These data considered of clinical relevance are discussed below.

2.5.1. Main studies

Design aspects of the ION studies (genotype 1)

In the phase 3 studies patients were stratified by genotype (1a, 1b, or mixed 1a/1b) and the presence of cirrhosis at screening (ION-1 and-2). All treatment was given open-label (including ribavirin).

The primary objective was to determine the antiviral activity of combination treatment with SOF/LDV with and without RBV as measured by the proportion of subjects with sustained virologic response 12 weeks after discontinuation of therapy (SVR12), which in practice is equivalent to cure.

On-treatment HCV-RNA results were not blinded to the investigator, while post-treatment HCV-RNA levels were blinded to the investigator and the sponsor.

Previously untreated patients (ION-1 and ION-3)

ION-1 Study Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naïve Subjects with Chronic Genotype 1 HCV Infection.

ION-3 Study Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naïve Subjects with Chronic Genotype 1 HCV Infection.

These studies included monoinfected patients (no HBV or HIV coinfection) with genotype 1 infection. Similar inclusion criteria applied, except with regards to compensated cirrhosis (allowed in ≤20% of patients in ION-1, not allowed in ION-3).

Absence of cirrhosis was defined as any one of the following:

- Liver biopsy within 2 years of screening showing absence of cirrhosis, or
- Fibroscan within 6 months with a result of ≤ 12.5 kPa, or
- FibroTest score of ≤ 0.48 and an APRI of ≤ 1 during screening

The following biochemistry had to be met at screening:

- ALT and AST ≤ 10 ULN
- Direct bilirubin ≤ 1.5 ULN
- Platelets ≥ 50,000
- Creatinine clearance (CLcr) ≥ 60 mL /min
- Hemoglobin ≥ 11/12 g/dL for females/males.
- Albumin ≥ 3g/dL
- INR ≤ 1.5 ULN

Randomisation

Randomization was stratified by genotype (1a or 1b; subjects with mixed genotype 1a/1b were stratified as 1a). In ION-1, subjects were stratified by the the presence or absence of cirrhosis at screening. Approximately 20% of the subjects enrolled may have had evidence of cirrhosis at screening in ION-1.

Results

The screening failure rate was 14% (N=145) in ION-1, primarily for laboratory values not being within specified ranges, clinically relevant drug abuse and HCV RNA being too low. That rate was higher, 22% for ION-3, for the same reasons and added to that, absence of cirrhosis not documented.

Demographics were similar in ION-1 and ION3, except that 20% of patients had cirrhosis in ION-1. Races other than white (77-85%) or black (12-21%) were not well represented. Around 40% were females. Median age was 53 years (Q1, Q3 = 47 and 59). Genotype 1a was predominant, as expected in studies conducted in the US. Of note, the total number of TN cirrhotic treated with SOF/LDV for 12 weeks is very limited (n=34). Patients with baseline platelets count as low as 50.000/µL were eligible for the study. However, most of the cirrhotics in ION-1 had baseline platelets counts indicative of cirrhosis without significant portal hypertension.

Table 7 Main disease characteristics in previously untreated, phase 3 (FAS/Safety analysis set)

	ION-3			ION-1				
Characteristics	SOF/LDV 8 Wks	SOF/LDV +RBV 8 Wks	SOF/LDV 12 Wks	SOF/LDV 12 Wks	SOF/LDV +RBV 12 Wks	SOF/LDV 24 Wks	SOF/LDV +RBV 24 Wks	Total
N	215	216	216	214	217	217	217	1512
Genotype 1a	171 (79.5%)	172 (79.6%)	172 (79.6%)	144 (67.3%)	148 (68.2%)	146 (67.3)	143 (65.9)	
HCV-RNA, Mean Log_{10} mL	6.5	6.4	6.4	6.4	6.4	6.3	6.3	
IL28B CC	56 (26.0)	60 (27.8)	56 (25.9)	55 (25.7)	76 (35.0)	52 (24.0)	73 (33.6)	
Cirrhotic	0	0	0	34 (15.9%)	33 (15.2%)	33 (15.2)	36 (16.6)	136 (9.0)
Platelets/ml								
Median				123	150	117	159	
Q1, Q3				103, 169	101, 216	90, 144	122, 182	
Min. max				50, 411	53, 402	61, 302	66, 489	

The proportion of patients who discontinued therapy was very low (1.3% in the studies combined) and only occasional patients stopped therapy for reasons of AEs (3 out of total 1082). Loss to follow-up was infrequent.

High response rates were seen across all treatment arms (Table 8).

In ION-1 (12 weeks therapy) there was a very low relapse rate in both arms (without or with RBV). However, the number of cirrhotics treated for 12 weeks (34 with SOF/LDV, 33 with SOF/LDV + RBV) is too low to make definitive conclusions on the relative efficacy of 12 and 24 weeks of therapy for this group.

In ION-3 the excellent results with SOF/LDV for 12 weeks treatment in TN naïve patients without cirrhosis are confirmed (in large numbers). However, the relapse rate is clearly higher when the treatment duration is lowered to 8 weeks, regardless if adding RBV to the regimen.

Table 8 SVR12 by regimen in the phase 3 studies, treatment naïve patients

	ION-3			ION-1			
	SOF/LDV 8 Week (N = 215)	SOF/LDV +RBV 8 Week (N = 216)	SOF/LDV 12 Week (N = 216)	SOF/LDV 12 Week (N = 217)	SOF/LDV +RBV 12 Week (N = 217)	SOF/LDV 24 Week (N = 217)	SOF/LDV +RBV 24 Week (N = 217)
SVR12							
All patients	202/215 (94.0%)	201/216 (93.1%)	206/216 (95.4%)	209/214 (97.7%)	211/217 (97.2%)	213/217 (98.2%)	215/217 (99.1%)
Non-cirrhotic	202/215 (94.0%)	201/216 (93.1%)	206/216(95.4%)	177/180 (98.3)	178/184 (96.7%)	181/184 (98.4%)	179/181 (98.9%)
Cirrhotic	-	-	-	32/34 (94.1%)	33/33 (100.0%)	32/33 (97.0%)	36/36 (100.0%)
Non-response	13/215	15/216	10/216	5/217	6/217	4/217	2/217
On treatment failure	0	0	0	0	0	1	0
Relapse	11/215 (5.1%)	9/216 (4.2%)	2/216 (0.9%)	1	0	1	0
Other#	2	6	8	4	6	2	2

#Reasons (Lost to follow-up, Withdrew consent)

The higher relapse rate in patients treated for 8 weeks was driven by male patients, those with IL28 non-CC genotype and/or high baseline viral load, as shown in Table 9. All patients with a non-response for other reasons that relapse had undetectable HCV-RNA at time for leaving the study (if passed week 2). For the most it concerns patients who did not return for follow-up, but had finished the full treatment course with an end-of treatment response. Consequently, in order to compare the antiviral efficacy of treatment arms, relapse rates are the most sensitive measure.

Table 9 Relapse rate by baseline VL and treatment duration, arms 1 +3, ION-3

	SOF/LDV 8 Weeks (N=215)	**SOF/LDV 12 Weeks (N= 216)**
Number of responders at end of treatment	215/215 (100%)	216/216 (100%)
Genotype		
Genotype 1a	10/171 (5.85%)	2/172 (1.16%)
Genotype 1b	1/43 (2.33%)	1/44 (2.27%)
Baseline HCV RNA		
HCV RNA <1.5 Million IU/ml	0/52	0/60
HCV RNA ≥1.5 Million IU/ml	11/163 (6.75%)	3/156 (1.92%)
HCV RNA <6 Million IU/ml	2/123 (1.63%)	2/131 (1.53%)
HCV RNA ≥ 6 Million IU/ml	9/92 (9.78%)	1/85 (1.18%)
Presence of baseline NS5A Resistance associated substitutions		
Yes	3/48 (6.25%)	0/56
No	8/167 (4.79%)	3/158 (1.90%)
Il28B status		
CC	2/56 (3.57%)	0/56
Non- CC	9/159 (5.66%)	3/160 (1.88%)

Of interest, an even shorter duration of SOF/LDV (6 weeks) was tested in phase 2 (ELECTRON study, part 6, group 18). This concerned treatment naïve patients with GT-1 infection, and without cirrhosis (i.e. same as in ION-3). The relapse rate was high, 8/25.

Previously treated patients (ION-2)

ION-2 Study Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection.

ION-2 included patients with prior failure to treatment with a Peg-IFN+RBV regimen, +/- boceprevir or telaprevir (NS3/4A inhibitors). Around half had failed therapy that included an NS3/4A protease inhibitor.

The prior failure had to be due to insufficient virological efficacy (i.e. not AEs or other causes for discontinuation). Medical records sufficiently detailed to categorize prior non-response (non-response vs relapse/viral breakthrough) was requested.

Cirrhosis was defined as described for ION-1 and 3, and the same baseline blood chemistry had to be fulfilled as in those studies.

Randomisation

Randomization was stratified by HCV genotype (1a or 1b; subjects with mixed genotype 1a/1b were stratified as 1a), the presence or absence of cirrhosis at screening, and response to prior HCV therapy (relapse/breakthrough or nonresponse) at screening.

Results

Of 550 screening, 110 subjects (20.0%) failed to be included, for reasons similar to those in the other studies.

Dropout rates were low and violations were uncommon, 99.3% of patients completed study treatment.

The main demographics were fairly identical to those shown for ION-1. As expected, the IL28B CC genotype (favourable predictor for outcomes with peg-IFN-based therapy) was seen in lower proportions. Of note, among cirrhotics, IL-28CC genotype was seen in 30% in ION-1 as compared to 9% in ION. The proportion of patients with cirrhosis was maximized in accordance with the protocol (20%) and was balanced between arms (stratification factor). Just like in ION-1, the baseline platelet count was indicative of uncomplicated compensated cirrhosis (i.e. no significant portal hypertension) in the majority of cirrhotic patients. Indeed, in two out of four arms, the median count was well within normal range (Table 10).

Table 10 Main baseline characteristics, ION-2

Characteristics	SOF/LDV 12 Weeks (N=109)	SOF/LDV+RBV 12 Weeks	SOF/LDV 24 Weeks (N=109)	SOF/LDV+RBV 24 Weeks (N=111)
Age, Median	57	59	58	56
Male gender	74 (67.9%)	71 (64.0%)	74 (67.9%)	68 (61.3%)
Race, white	84 (77.1%)	94 (84.7%)	91 (83.5%)	89 (80.2%)
Black/African American	24 (22.0%)	16 (14.4%)	17 (15.6%)	20 (18.0%)
IL-28-CC	10 (9.2%)	11 (9.9%)	16 (14.7%)	18 (16.2%)
HCV-RNA, Mean log_{10} IU/mL	6.5	6.4	6.4	6.5
BL platelets (/ml) in patients with cirrhosis				
median	130	175	129	190
Q1,Q3	101, 177	119, 221	110, 184	121, 242
Min. Max	52, 263	67, 342	59, 245	75, 331

Types of prior treatment and response for those randomized are shown below.

Table 11 Prior HCV Treatments and prior response categories, ION-2

	SOF/LDV 12 Weeks	SOF/LDV +RBV 12 Weeks	SOF/LDV 24 Weeks	SOF/LDV +RBV 24 Weeks	Total
N	109	111	110	111	441
Peg-IFN+RBV	43 (39.4%)	47 (42.3%)	58 (53.2%)	59 (53.2%)	207 (47.0%)
Relapse/Breakthrough	21 (48.8%)	23 (48.9%)	25 (43.1%)	32 (54.2%)	101 (48.8%)
Non-Responder	22 (51.2%)	24 (51.1%)	33 (56.9%)	27 (45.8%)	106 (51.2%)
Null	17 (77.3%)	12 (50.0%)	19 (57.6%)	16 (59.3%)	64 (60.4%)
Partial	5 (22.7%)	12 (50.0%)	14 (42.4%)	11 (40.7%)	42 (39.6%)
PI+Peg-IFN+RBV	66 (60.6%)	64 (57.7%)	50 (45.9%)	51 (45.9%)	231 (52.5%)
Relapse/Breakthrough	39 (59.1%)	42 (65.6%)	35 (70.0%)	28 (54.9%)	144 (62.3%)
Non-Responder	27 (40.9%)	22 (34.4%)	15 (30.0%)	23 (45.1%)	87 (37.7%)
Other treatment	0	0	1 (0.9%)	1 (0.9%)	2 (0.5%)
Relapse/Breakthrough	0	0	0	0	0
Non-Responder	0	0	1 (100.0%)	1 (100.0%)	2 (100.0%)

High SVR rates were observed across treatments groups (12 or 24 weeks, with and without added weight based ribavirin), as shown in Table 12. Relapse consisted of virological non-response in all patients but one (arm 4, virological breakthrough).

Relapses, more frequent in the 12-week arms, occurred within week 4 after stopping therapy in 9/11 cases.

Table 12 SVR12 in ION-2 (treatment experienced patients)

	SOF/LDV 12 Weeks (N = 109)	SOF/LDV+RBV 12 Weeks (N = 111)	SOF/LDV 24 Weeks (N = 109)	SOF/LDV+RBV 24 Weeks (N = 111)
RESPONSE				
All	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
Non-cirrhotic	83/87 (95.4%)	89/89 (100.0%)	86/87 (98.9%)	88/89 (98.9%)
Cirrhotic	19/22 (86.4%)	18/22 (81.8%)	22/22 (100.0%)	22/22 (100.0%)
Genotype 1a	82/86 (95.3%)	84/88 (95.5%)	84/85 (98.8%)	87/88 (98.9%)
1b	20/23 (87.0%)	23/23 (100.0%)	24/24 (100.0%)	23/23 (100.0%)
Prior Relapse/breaktrough	57/60 (95.0%)	63/65 (96.9%)	60/60 (100.0%)	59/60 (98.3%)
Prior Non-response	45/49 (91.8%)	44/46 (95.7%)	48/49 (98.0%)	51/51 (100.0%)
NON-RESPONSE				
All	7/109	4/111	1/109	1/111
Viral breakthrough	0	0	0	1
Relapse	7 (6.4%)	4 (3.6%)	1 (0.9%)	0

An analysis of virological failure in ION-2

As evident, the strongest predictor of virological failure (i.e. relapse) was a shorter treatment duration (in practice all patients achieved SVR with the 24 week regimen, including the compensated cirrhotics).

For the 12-week treatment groups 14 factors were analyzed by univariate logistic regression (RBV +/-, age, sex, race, ethnicity, GT 1a vs b, cirrhosis status, response to prior HCV therapy, prior HCV therapy, BL viral load, BMI, IL28B alleles, GGT-levels and platelets). Two were found significant as predictors of relapse: the presence of cirrhosis and having a baseline platelet count ≤125,000/mL (all patients with low platelets are anticipated to be cirrhotic).

Relapse by baseline NS5A resistance

Likewise as in ION-3 the outcomes by the presence or absence of baseline NS5a RAVs were studied.

In ION-2 it is noted that, despite that these patients are selected for negative predictive factor for cure, the relapse rate with 12 weeks of therapy was zero for non-cirrhotic patients, in the absence of BL NS5A RAVs (with or without RBV). Although numbers are low, it is also noted that in non-cirrhotic *with* such BL RAV, there was no relapses with triple therapy including RBV.

Table 13 Relapse Rates by Baseline NS5A and Cirrhosis Status for the 12-Week Treatment Groups (Full Analysis Set)

	LDV/SOF 12 Weeks	LDV/SOF+RBV 12 Weeks
Baseline RAVs	17/109 (15.6%)	17/111 (15.3%)
Relapse rate	7/108[a] (6.5%)	4/111 (3.6%)
Baseline RAVs present	4/17 (23.5%)	2/17 (11.8%)
Subjects with cirrhosis	0/3 (0%)	2/5 (40.0%)
Subjects without cirrhosis	4/14 (28.6%)	0/12 (0%)
Baseline RAVS absent	3/91 (3.3%)	2/94 (2.1%)
Subjects with cirrhosis	3/19 (15.8%)	2/17 (11.8%)
Subjects without cirrhosis	0/72 (0%)	0/76 (0%)
Subjects with missing cirrhosis status	0	0/1 (0%)

[a] One subject in LDV/SOF treatment group did not achieve HCV RNA< LLOQ at the end of treatment (42 IU/mL) and is not included in relapse rate calculation. This subject did not have a baseline RAV but achieved SVR4, SVR12, and SVR24.

In patients with cirrhosis the relapse rate was not nominally lowered by adding RBV (3/22 vs 4/22), and relapses occurred also in the absence of BL NS5A RAVs. However, data from the ELECTRON 2 and SOLAR-1 study in patients with decompensated liver disease support the incremental effect of RBV when treating patients with very advanced liver disease for 12 weeks.

Tretament of patients with decompensated liver disease and/or post-transplantation

Data from the expanding ELECTRON-2 study was recently presented (EASL conference 2014). SOF/LDV (without RBV) had been given for 12 weeks to patients with decompensated cirrhosis (Child Pugh B). The relapse rate was high (7/20). It is notable that RBV was not given in this study.

For the larger SOLAR-1 study the conservative decision to give triple therapy including RBV to all patients was chosen. This study is conducted in patients with genotype 1 or -4 infection, decompensated liver disease and/or post transplantation. Subjects are treatment naive or treatment-experienced and have documentation of the presence or absence of cirrhosis.

Interim data has been provided by the applicant. Among patients with decompensated liver disease and no previous transplantation, the mean age was 57. 66% were male, 90% white. Approximately 70% had genotype 1a infection and only 3 patients had GT4. 20% of patients had the IL28B C/C genotype and 65% had received prior treatment. 26% of patients had a MELD score >15.

Among cirrhotic patients post transplantation, the mean age was 60. The cohort was 85% male and predominantly white. 70% had GT1a infection and one patient had GT4. 19% had the IL28B C/C genotype and 78% had received prior treatment. 11% had a MELD score >15.

Table 14 Outcomes and reasons for non-response in SOLAR-1 (Full Analysis Set, 18 July 2014)

	LDV/SOF+RBV													
	Cohort A (Decompensated Cirrhosis)				Cohort B (Posttransplant)									
	Group 1 CPT B n/N (%)		Group 2 CPT C) n/N (%)		Group 3 Fibrosis Stage F0-F3 n/N (%)		Group 4 CPT A n/N (%)		Group 5 CPT B n/N (%)		Group 6 CPT C n/N (%)		Group 7 Aggressive Recurrent Disease n/N (%)	
	12 wk	24 wk	12 wk	24 wk	12 wk	24 wk	12 wk	24 wk	12 wk	24 wk	12 wk	24 wk	12 wk	24 wk
SVR4	24/27 (88.9)	24/26 (92.3)	21/23 (91.3)	19/21 (90.5)	53/55 (96.4)	53/54 (98.1)	25/26 (96.2)	24/24 (100)	20/23 (87.0)	13/16 (81.3)	5/5 (100)	1/2 (50.0)	4/4 (100)	0/0
Relapse	2	1	1	0	2	1	0	0	1	0	0	1	0	0
AE->D/C	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Death	1	1	1	2	0	0	1	0	1	2	0	0	0	0
Withdrew Consent	0	0	0	0	0	0	0	0	1	0	0	0	0	0
SVR12	23/27 (85.2)	NA	18/20 (90.0)	NA	53/55 (96.4)	NA	25/26 (96.2)	NA	14/17 (82.4)	NA	3/5 (60.0)	NA	2/2 (100)	NA
Relapse	3	NA	1	NA	2	NA	0	NA	1	NA	2	NA	0	NA

ChildPugh scores: A: 5-6, B: 7-9, C 10-12

Thus, SVR12 data are immature. SVR4 data however, indicate that SOF/LDV + RBV (the latter initiated at a starting dose of 600 mg/day in patients with decompensated liver disease) for 12 or 24 weeks is effective also in patients with decompensated liver disease. SVR4 generally has approximately 90% predictive value of SVR12. In this small dataset, a somewhat higher proportion of relapses seem to occur between week 4-12 than is usual in patients with compensated liver disease. Further observation will clarify if this is a real phenomenon.

Treatment of genotype 3

The efficacy and safety of SOF/LDV with or without RBV for 12 weeks was studied under the ELECTRON 2 protocol. Among 51 treatment naïve patients, 8 had cirrhosis. Results are shown in Table 15. Notably, as there was no control group receiving only SOF+RBV, the contribution of LDV to regimen efficacy needs to be assessed through cross study comparison with the phase III trials of SOF+RBV in genotype 3 (Table

15). Further, while the efficacy of SOF monotherapy against GT3 is not well characterised, efficacy would be anticipated to be low.

Table 15 SVR rates with various non-interferon regimens, GT3

	FISSION	**FUSION**		**VALENCE**	**ELECTRON-2**	
	SOF+RBV 12 weeks (n = 183)	**SOF+RBV 12 weeks (n = 64)**	**SOF+RBV 16 weeks (n = 63)**	**SOF+RBV 24 weeks (n = 250)**	**SOF+RBV+LDV 12 weeks (N=26)**	**SOF + LDV 12 weeks (N=25)**
SVR12						
TN	56%			93% (98/105)	100% (26/26)	64% (16/25)
Cirrhosis						
No	61%			94% (86/92)	21/21	15/22
Yes	34% (13/38)			92% (12/13)	5/5	1/3
TE		30% (19/64)	62% (39/63)	77% (112/145)		
Cirrhosis						
No		37% (14/38)	63% (25/40)	85% (85/100)		
Yes		19% (5/26)	61% (14/23)	60% (27/45)		

During the evaluation, preliminary data from ELECTRON-2 were provided for another 50 patients with GT-3 infection, who were treatment experienced with (n=22) or without (n=28) cirrhosis. Also these patients were treated with SOF/LDV + RBV for 12 weeks, with SVR4 results as shown in Table 16. Of note, not all patients had reached week 8 at the time of analysis.

Table 16 Preliminary outcomes with SOF/LDV+RBV in TE patients with GT3-infection (ELECTRON-2, cohort 2, group 6)

	Non-cirrhotic (N=28)	Cirrhotic (N=22)	Total (N=50)
SVR4	25/28 (89%)	17/22 (77%)	42/50 (84%)
relapse	2/28 (7%)	5/22 (23%)	7/50 (14%)
viral breaktrough [a]	1		1/50
SVR8	22/25	14/20	36/45 (80%)

The patient with viral breaktrough was non-cirrhotic, had IL28B CC- genotype 3a –infection. HCV-RNA was <LLOQ at week 4, and the week 10 visit was missing; lack of compliance is the suspected cause of failure.

Of the subjects for whom posttreatment Week 8 and 12 data is available, one additional subject, with cirrhosis, relapsed at the posttreatment Week 8 time point; this is the only subject that has relapsed after having achieved SVR4.

Despite the fact that the GT3 in vitro susceptibility for LDV is considerably lower than that seen in GT1 virus (see pharmacodynamics section), results in Electron-2 supports that LDV adds activity also in GT-3. A cure rate of 100%, including in 5/5 cirrhotic patients treated SOF/LDV + RBV for 12 weeks is considered informative, despite the low numbers. As regards a 64% SVR rate with only SOF/LDV, it also seems unlikely that this would be achieved with SOF alone for 12 weeks. However, the relapse rate in the TE cohort (Table 16), in particular those with cirrhosis (6/22 up to week 8 post treatment) also indicate that the triple regimen given for 12 weeks is not an optimized treatment duration, as difficult to cure patients will likely have a relatively high relapse rate. Of note, there are no data to compare the present interferon-free standard of SOF+RBV for 24 weeks with SOF/LDV+RBV for 12 weeks, nor any data on the efficacy of SOF/LDV+RBV with 24 weeks of therapy.

The applicant has presented data indicating that there was no selection of resistant variants to LDV in the patients that relapsed. This is in stark contrast to what is seen in GT1, and is indicative that the absolute antiviral potency and therefore selection pressure of LDV is lower in GT3, which would also be anticipated based on EC_{50} values. The applicant does not have any early viral kinetic data to support the additive effect of LDV in the regimen, as relevant samples are not available from the first week of therapy, where an effect could have been detected. Still, clinically relevant efficacy is considered likely (refer also to section on pharmacodynamics).

Treatment of genotype 4

The in vitro EC50 for LDV against GT4 (GT4a 0.39 nM, GT4d 0.6 nM) is intermediate between that recorded for GT1 (0.004-0.031 nM), where the bulk of clinical efficacy data are available, and GT3 (168 nM) where data indicate that LDV does retain clinically relevant, albeit reduced, activity. Furthermore, SOF is equally effective against GT1 and GT4.

Preliminary data are available from Group E of the NIAID/NIH collaborative Study CO-US-337-0117. In this group, 21 subjects with genotype 4 HCV infection (13 TN, 8 TE, total 6 with cirrhosis) are receiving 12 weeks of LDV/SOF treatment. 15/15 with available data achieved SVR4 including 6 TE, of whom 3 have cirrhosis. SVR 12 was achieved for 5/5 with available data.. The study described is ongoing as well as other studies.

Treatment of patients with HIV co-infection

Patients with HIV co-infection respond similarly to therapy with direct acting antivirals as do those without HIV infection. Preliminary data from the NIAID-13-1-0159 study support this assertion. Here non-cirrhotic, co-infected patients with genotype 1 virus are treated with SOF/LDV for 12 weeks. Among patients for whom SVR12 are available 39/40 have reached this. Another 10/10 patients have achieved SVR4.

Resistance in patients failing therapy in phase 3

Resistance Analysis Population (RAP)

Population and/or deep sequencing of NS5A was performed at baseline for all subjects enrolled in the phase 2b/3 studies. The RAP includes any patient who received at least one dose of a SOF/LDV-containing regimen, but did not achieve SVR12 due to virologic failure (on-treatment or relapse) or early discontinuation, had HCV RNA ≥ 1000 IU/ml and had a plasma sample available for analysis. For the phase 3 studies, it concerns in practice the patients with relapse (n=36) as a cause of failure. Those with

non-response for other causes had in practice always HCV-RNA below detection limit as their last sample in study, as clarified previously.

Resistance analyses included NS5A and NS5B deep sequencing. Phenotypic analysis was attempted for the majority of cases and was successful for a subset of patients.

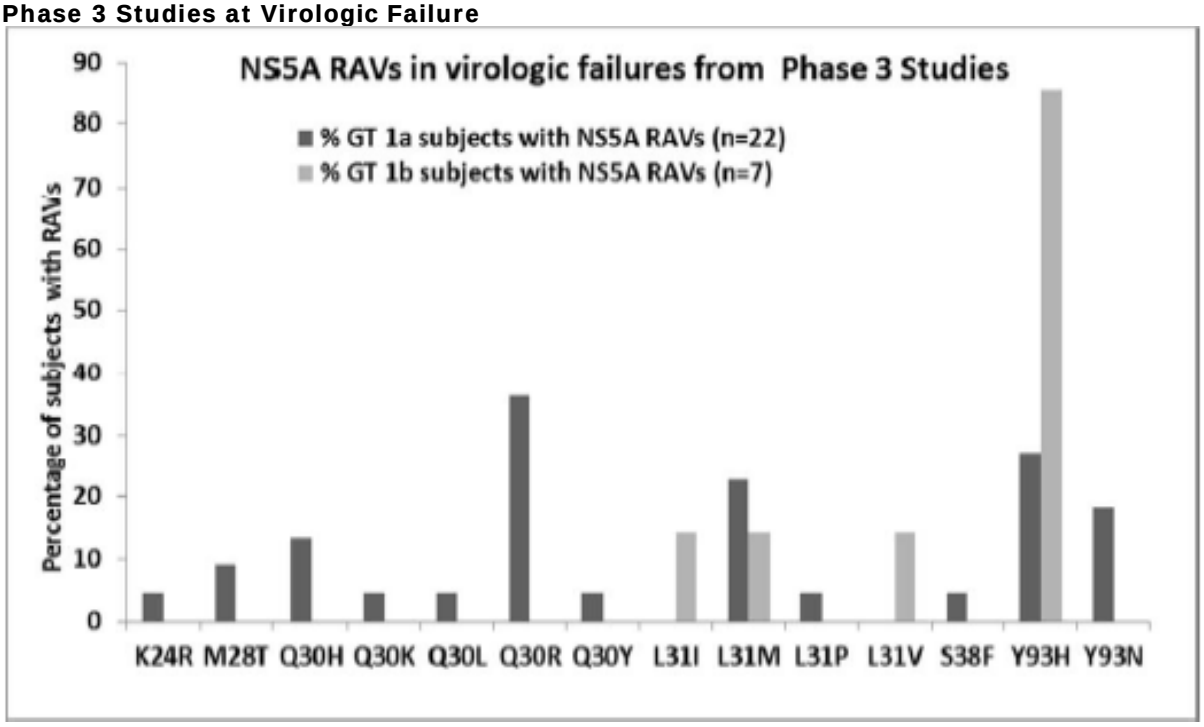
Table 18 summarizes NS5A resistance (BL and failure) for the 36 patients with a relapse. The percentage given (%) shows the proportion of the viral population that carries the mutation (lower cut off value=1%). In summary NS5A resistance was generally seen in patients failing therapy (28/36, 78%). In the majority of such cases (19/28, 68%) there was a selection of resistance from none or low level (low proportion) at baseline, to a high resistance (high proportion, high FC) at time of failure. In the other 9 cases FC was high already at baseline (with high proportions of mutations present in the baseline viral population.

Table 18 NS5A resistance in failures analyzed for resistance, in ION-1,-2 and -3

ID	GT	Treatment	NS5A mutations		LDV FC	
			BL	Failure	BL	Failure
ION-3 (previously untreated, non-cirrhotic)						
73114	1a	SOF/LDV 8 Weeks	None	None	1.3	1.6
73227	1a		Y93N(15.37%)	Y93N(>99%)	0.83	>42
73274	1a		M28T(93.52%) M28A(6.09%)	M28T(>99%)	17.6	20
73300	1b		None	Y93H(>99%)	0.61	>243
73313	1a		Q30Y(2.04%) Q30H(1.16%) Y93H(3.60%)	Q30Y(>99%) Y93H(>99%)	0.83	>52
73453	1a		None	Y93H(>99%)	1.1	>42
73490	1a		None	Q30R(>99%)	0.83	>52
73514	1a		None	None	1.3	1.0
73538	1a		None	Q30R(>99%)	0.80	>58
73408	1a		None	None	0.63	NA
73049	1b	SOF/LDV + RBV 8 Weeks	None	None	1.3	1.5
73185	1a		Q30R(71.06%) Q30H(28.84%) Y93H(24.58%)	Q30R(>99%) L31P(1.13%)	>42	>42
73277	1a		L31M(1.12%)	L31M(>99%)	0.94	>58
73335	1b		Y93H(63.83%)	Y93H(>99%)	2.1	>192
73385	1a		Y93N(>99%)	Y93N(>99%)	>58	NA
73416	1a		Y93C(8.65%)	None	0.71	0.63
73445	1a		None	None	2.3	2.2
73564	1a		None	S38F(>99%) Y93H(>99%)	0.49	>42
73610	1a		None	None	0.68	0.60
73078	1a	SOF/LDV 12 Weeks	Y93F(10.81%) Y93N(1.71%)	Y93N(>99%)	0.83	>42
73124	1b		None	L31I(>99%) Y93H(>99%)	1.4	>212
73230	1a		None	None	0.53	0.54
ION-1 (previously untreated, cirrhotics included))						
1603-7 1276	1a	SOF/LDV 12 WKS	L31M (>99%)	L31M(>99%)	>42	>42
5663-7 1589	1b	SOF/LDV 24 WKS	None	Y93H (>99%)	0.67	>208
ION-2 (previous non-responders, cirrhotics included)						
79003	1b	SOF/LDV 12 Weeks	None	L31M(96.81%); Y93H(>99%)	0.65	143
79051	1b		None	L31V(>99%)	0.76	109
79062	1a		None	Q30H(9.80%); Y93H(93.93%)	0.72	20
79214	1a		Q30R(1.43%); Y93N(97.60%)	Y93N(>99%)	>42	>42
79303	1a		M28T(1.03%); Q30R(>99%); L31M(>99%)	Q30R(>99%); L31M(>99%)	>42	>42
79378	1a		Q30H (98.76%); Y93H (98.07%)	Q30H(98.92%); Y93H(>99%)	>42	>42
79179	1b		Y93H (59.82%)	Y93H(>99%)	21	>243
79034	1a	SOF/LDV + RBV 12 Weeks	L31M(>99%)	Q30H(>99%); L31M(>99%)	>42	>42
79041	1a		None	M28T(>99%); Q30R(>99%)	0.68	30
79063	1a		None	Q30K(>99%)	0.61	24
79070	1a		Y93H(1.2%)	Q30L(76.43%); Q30R(22.94%); Y93H(>99%)	1.3	>42
79383	1a	SOF/LDV + RBV 24 Weeks	K24R (1.06%); Q30R (2.61%)	K24R(79.95%); Q30R(98.37%)	0.38	>42

The frequency of different mutations seen at time of failure is presented in the graph below. The pattern relates to subtype (1a vs 1b), where Y93 as a single mutation dominates for GT1b, while 1 or more LDVs were detected in the 1a isolates (mainly Y93, Q30, L31, and M28).

Prevalence of Specific NS5A RAVs Detected in Virologic Failure Subjects in the SOF/LDV Phase 3 Studies at Virologic Failure



Data on reversion of selected NS5a resistance (i.e. during follow-up of patients who failed therapy in phase 3) was not presented, however the totality of data indicates that persistence is likely.

The applicant has provided data on emergent resistance in 11 relapsed patients with genotype 3 infection. There wea no clear evidence of selection of resistance variants. This cannot be due toa higher barrier to resistance, but rather to lower activity and subsequently lower selection pressure.

In contrast to the high frequency of NS5a resistance in patients failing therapy, there was a total lack of NS5B-resistance (i.e. resistance to SOF). This is in accordance with findings available at the time of approval of SOF (refer to section on pharmacodynamics).

Preliminary retreatment data

The applicant provided data for 20 patients with GT-1 infection who failed an initial SOF-containing regimen in the LONESTAR or ELECTRON studies. These patients were re-treated with SOF/LDV + RBV for 12 weeks (n=19) or 24 weeks (n=1, a patient who had the S282T mutation detected at time of prior failure). All patients achieved SVR4-12.

Of note, LDV had been part of prior therapy in only 9/20. Among these 9 patients, NS5A resistance at time of prior relapse was infrequent; in 5 no NS5A RAVs were seen, and among the other four patients only single mutations with limited impact on LDV susceptibility was seen in 3 out 4 patients and in varying proportions of viral loads as measured by deep sequencing. Only one patient had substantial NS5A resistance. This patient was re-treated for 24 weeks. This was a non-cirrhotic patient that may well have been cured by SOF+RBV alone.

In summary, this data provides further evidence that SOF can be re-used without any evident loss of efficacy. This is re-assuring but also expected, taking the pharmacodynamics of SOF into account. However, available data does not provide compelling evidence for LDV being useful in the re-treatment of patients who failed an NS5A-containing regimen with class resistance.

2.5.2. Discussion on clinical efficacy

The main clinical data underlying this application are three phase III trials (ION-1, -2 and -3). In these, non-cirrhotic patients with genotype 1a or -1b infection were treated with SOF/LDV +/- RBV for 8, 12 or 24 weeks. Furthermore, patients with compensated cirrhosis were treated with SOF/LDV +/- RBV for 12 or 24 weeks. Supplementary studies of importance for the recommended use of SOF/LDV according to the SmPC cover the use of SOF/LDV +/- RBV in patients with genotype 1 infection and decompensated liver disease (SOLAR-1, ELECTRON 2), the use of SOF/LDV +/- RBV in patients with genotype 3 infection (ELECTRON 2) and the use of SOF/LDV in genotype 4 infection (GS-US-337-1119).

All in all, the rationale for the study designs is understood and the trials appear to have been well-conducted. Data from some of the supporting studies are immature and mainly comprise SVR4 data. This, however, is not considered to preclude general conclusions.

The main results in the phase 3 studies are summarized in the phase 3 outcome summary table.

Outcome summary, Phase 3

Study	Pop, Genotype	+/-RBV	Duration, weeks	SVR12 all	SVR12 cirrhotics	Relapse rate (all)
Phase 3 studies						
GS-US-337-0 108 (ION-3)	TN GT 1		8	94.0%	NA	11/215
		+RBV		93.1%		9/216
			12	95.4%		2/216
GS-US-337-0 102 (ION-1)	TN GT 1		12	97.7%	32/34 (94.1%)	1/217
		+RBV		97.2%	33/33 (100.0%)	0/217
GS-US-337-0 109 (ION-2)	TE GT 1		12	93.6%	19/22 (86.4%)	7/109
		+RBV		96.4%	18/22 (81.8%)	4/111
			24	99.1%	22/22 (100.0%)	1/109
		+RBV		99.1%	22/22 (100.0%)	0/111

The overall efficacy of SOF/LDV in the absence of ribavirin is excellent. No compelling evidence for additive effects of RBV in patients with compensated liver disease has emerged. The relapse rate in treatment naïve non-cirrhotic patients treated for 8 weeks was somewhat higher than in those treated for 12 weeks. It is notable that treatment naïve non-cirrhotic patients that relapse will have likely effective retreatment options. Given a summary relapse rate of 0.5% (3/650) with 12 weeks of therapy in ION-1 and -3, there was no indication that longer treatment duration than this would be of value in an unselected treatment naïve population with compensated liver disease.

The ION-2 study included a substantial number of patients with prior failure on NS3/4A protease inhibitors in combination with pegIFN/RBV. As there is no cross resistance between any of these drugs and SOF/LDV, the ION-2 study population may be considered an enriched subset of patients with negative prognostic factors. Therefore, results are considered of relevance also for treatment naïve patients that are difficult to cure. Also in treatment experienced patients, the efficacy of SOF/LDV was excellent. However, relapse rates overall were higher with 12 weeks of therapy (5%, 11/220) compared to 24 weeks (0.5%, 1/220). This difference was driven by patients that either had detectable baseline variants with reduced susceptibility to LDV, or had cirrhosis. In the former category 12 weeks of therapy was associated with a 18% (6/34) risk of relapse, compared to 3% (5/184) among those without such baseline variants. For cirrhotics, 12 weeks of therapy was associated with a relapse rate of 16% (7/44), versus 0% (0/44) among those with the same condition treated for 24 weeks. It is recognized that the dataset is small and absolute differences uncertain. However, these data must be placed in a clinical

context. As opposed to the case for non-cirrhotic patients without prior exposure to direct acting antivirals who can readily be retreated, clinical harm may be incurred in those with cirrhosis and/or with prior exposure to NS3/4A protease inhibitors, in case of not reaching SVR. For cirrhotics, failure to achieve viral clearance may equal failure to prevent clinical disease progression. For patients with prior NS3/4A exposure, the efficacy of retreatment options is unclear, as it has not been shown that NS3/4A inhibitors retain efficacy in case of prior failure with selection of resistance to a drug of this class, and as failure of SOF/LDV is generally accompanied by selection of variants resistant to available NS5A inhibitors. Therefore, albeit the high efficacy shown with both 12 and 24 weeks of therapy, the difference in SVR rates with 12 weeks of therapy cannot be disregarded. The issue of recommended treatment durations is further discussed under the benefit-risk section.

SOF has pangenotypic activity. However, for both genotype 2 and -3, the in vitro efficacy of LDV is considerably lower than for genotype 1. While no role is foreseen for LDV in the treatment of genotype 2 infection, clinical data in genotype 3 are available from the ELECTRON 2 study. In a small sample of treatment naïve patients, some of whom had cirrhosis, 12 weeks of SOF/LDV therapy was associated with a 64% SVR rate (16/25) with the remaining patients relapsing. While not well characterized, it seems unlikely that SOF monotherapy for 12 weeks would have achieved a 64% response rate in 12 weeks of therapy for genotype 3. Furthermore, SOF/LDV+RBV for 12 weeks yielded a 100% SVR rate (26/26) including five cirrhotics all reaching SVR. As the efficacy of SOF+RBV alone when used for 12 weeks in a treatment naïve genotype 3 population was around 60% in phase III trials, these data are also indicative that LDV has clinically relevant activity within a combination regimen for the treatment of genotype 3. However, as noted above, EC50 is substantially higher in GT3 compared to GT1 (168 nM versus 0.004-0.031 nM). Further, there are no viral kinetic data to show a direct effect of LDV on genotype 3 virus and there is no clear evidence of a selection pressure of LDV in genotype 3. Therefore, it is recognized that any conclusions that LDV has activity against genotype 3 rests on cross-study comparisons of the anticipated activity of the background regimens (SOF and SOF+RBV). On this basis, activity is anticipated that would be clinically relevant in patients for whom the present standard interferon-free regimen (SOF+RBV for 24 weeks) would be expected to yield inoptimal SVR rates based on available evidence (cirrhotics and/or treatment experienced patients). LDV might be added to such a regimen in order to increase antiviral drug pressure and presumably efficacy. It is recognized that there is no metric to quantify the presumed benefit of this.

The in vitro activity of LDV against genotype 4 is 0.39-0.6 nM and thus higher than for GT1 but substantially lower than for GT3. The applicant has submitted data from a cohort of patients with GT4, including treatment experienced patients and a few patients with cirrhosis that have been treated with SOF/LDV for 12 weeks. While it is recognized that these data are immature, such results would be very unlikely with SOF alone, and are indicative of a substantial contribution of LDV to efficacy, which is anticipated to be high. The combination of in vitro data and available clinical outcomes are indicative that SOF/LDV for 12 weeks is an effective regimen for the treatment of GT4 infection.

When SOF/LDV was used for 12 weeks without RBV in patients with genotype 1 infection and decompensated cirrhosis, the relapse rate was high (7/20). Interim data from the SOLAR-1 study, where patients are treated with SOF/LDV + RBV show SVR12 data of 87% (83/95) in patients treated for 12 weeks. Only SVR4 data are available for 24 weeks and the potential increment in response with this treatment duration in decompensated patients cannot be clearly assessed presently.

As anticipated based on previous data with direct acting antiviral treatment regimens, available data from the ERADICATE study are not indicative that HIV coinfection impacts response to SOF/LDV.

The efficacy of LDV as part of a retreatment regimen in patients with prior virological failure and selection of resistance to NS5A inhibitors has not been demonstrated.

2.5.3. Conclusions on the clinical efficacy

SOF/LDV is a highly effective treatment regimen for genotype 1 infection. 8 weeks of therapy suffices in many treatment-naïve patients. In general, treatment for more than 12 weeks or the addition of ribavirin is not needed to increase efficacy. In patients with compensated cirrhosis and/or patients with reduced viral susceptibility to LDV at baseline, the relapse rate is higher with 12 weeks than with 24 weeks of therapy. The increment with an extra 12 weeks is not well characterised, and likely depends on a number of host and viral factors. For patients with decompensated liver disease, available data are indicative that RBV should be added to the regimen.

SOF has genuine pangenotypic activity (similar against all genotypes). LDV likely has clinically relevant activity against GT3, albeit lower than against GT1. LDV has clinically relevant activity against GT4 virus.

Factors to take into account when evaluating the incremental benefit of a marginal increase in SVR with prolonged therapy includes the risk of clinical disease progression in case of failure to clear virus, as well as available effective retreatment options in case of failure with selection of resistant variants. Recommendations on regimens in different populations are discussed in the benefit-risk section.

2.6. Clinical safety

The safety of SOF has been evaluated as part of the sofosbuvir single agent marketing authorization application. Tolerability is not clearly different from placebo, and no specific side effects have been attributed to SOF. The clinical safety of LDV has predominantly been studied in combination with SOF. To date, no particular side effects have been reported for NS5A-inhibitors.

The safety of SOF/LDV generated from the phase 3 studies is summarized in Table 19. Exposure data from the phase 2 program is provided in Table 20. There are no studies from the phase 2 program where the exposure to SOF or LDV was higher than in phase III (as a consequence of higher dose or other regimens).

In the phase 3 studies (total 1952 patients) a limited number were >65 years old (152, 8%), the median age was 55. Around 40% of patients were females. Most patients were white (82%), and the remaining patients were predominantly black.

A creatinine clearance <60 ml/min was an exclusion criterion. Around 70% had GFR>90.

Patient exposure

Table 19 Exposure to study regimen, and study treatment status, phase 3

	ION-3	ION-1 ION-2 ION-3	ION-1 ION-2	ION-3	ION-1 ION-2	ION-1 ION-2	Total
Regimen	**SOF/LDV**			**SOF/LDV+ RBV**			
Exposure							
Duration	8 Week	12 Week	24 Week	8 Week	12 Week	24 Week	
N	215	539	326	216	328	328	1952
N with cirrhosis	0	56	55	0	55	58	224 (11.5%)
Study treatment status							
Completed	215 (100.0%)	532 (98.7%)	315 (96.6%)	213 (98.6%)	324 (98.8%)	315 (96.0%)	1914 (98.1%)
Discontinued	0	7 (1.3%)	11 (3.4%)	3 (1.4%)	4 (1.2%)	13 (4.0%)	38 (1.9%)
Reason for Premature Discontinuation of Study Treatment, n (%)							
Adverse Event	0	2 (0.4%)	4 (1.2%)	1 (0.5%)	0	6 (1.8%)	13 (0.7%)
Lost to Follow-Up	0	3 (0.6%)	0	2 (0.9%)	2 (0.6%)	1 (0.3%)	8 (0.4%)
Withdrew Consent	0	0	3 (0.9%)	0	1 (0.3%)	3 (0.9%)	7 (0.4%)
Protocol Violation	0	1 (0.2%)	2 (0.6%)	0	1 (0.3%)	2 (0.6%)	6 (0.3%)
Lack Of Efficacy	0	0	1 (0.3%)	0	0	1 (0.3%)	2 (0.1%)
Non-Compliance With Study Drug	0	1 (0.2%)	0	0	0	0	1 (< 0.1%)
Pregnancy	0	0	1 (0.3%)	0	0	0	1 (< 0.1%)

Table 20 Phase 2 studies, providing safety data

Study	Study Design	Treatment Regimen	Nb	Subject Population
P7977-0523 (ELECTRON; Part 4, Groups 12, 13; Part 6, Groups 16-18, 20, 21)	Open-label, multicenter	SOF 400 mg QD + LDV 90 mg QD +/- RBV for 6-12 weeks	102	Treatment-naive and experienced, genotype 1, 2, or 3
GS-US-337-0118 (LONESTAR)	Randomized, open-label	SOF 400 mg QD + LDV 90 mg QD +/- RBV for 8 or 12weeks	100	Treatment-naive and experienced, genotype 1
GS-US-337-0122 (ELECTRON-2; Cohort 2, Groups 3 and 4)	Open-label, multicenter	SOF/LDV +/- RBV for 12 weeks	51	Treatment-naïve, genotype 3

During the evaluation, the applicant provided placebo controlled safety data from the double blinded SIRIUS study (GS_US-337-0121) performed in treatment experienced cirrhotic patients (n=155), as well as safety data from the open label SOLAR-1 study (GS-US-337-0113) in which patients with decompensated liver disease and/or post transplantation are treated (n=337).

Discontinuation due to adverse events

The number of patients stopping therapy due to AEs was very low (<1%). This observation was also applicable for the patients receiving RBV in addition to SOF/LDV.

Table 21 Frequency of AEs and discontinuations for reasons of AEs, phase 3 studies

	SOF/LDV				SOF/LDV + RBV				Total
Duration (weeks)	8	12	24	total	8	12	24	total	
AE	145 (67.4%)	390 (72.4%)	265 (81.3%)	800 (74.1%)	165 (76.4%)	280 (85.4%)	300 (91.5%)	745 (85.4%)	1545 (79.1%)
Grade 3 or 4	2 (0.9%)	13 (2.4%)	31 (9.5%)	46 (4.3%)	8 (3.7%)	17 (5.2%)	20 (6.1%)	45 (5.2%)	91 (4.7%)
Treatment-Related	82 (38.1%)	237 (44.0%)	165 (50.6%)	484 (44.8%)	133 (61.6%)	229 (69.8%)	255 (77.7%)	617 (70.8%)	1101 (56.4%)
Grade 3 or 4	0	2 (0.4%)	9 (2.8%)	11 (1.0%)	6 (2.8%)	10 (3.0%)	11 (3.4%)	27 (3.1%)	38 (1.9%)
SAE	4 (1.9%)	6 (1.1%)	24 (7.4%)	34 (3.1%)	1 (0.5%)	7 (2.1%)	9 (2.7%)	17 (1.9%)	51 (2.6%)
Treatment-Related	0	0	4 (1.2%)	4 (0.4%)	0	1 (0.3%)	0	1 (0.1%)	5 (0.3%)
Leading to Permanent Discontinuation of study drug	0	2 (0.4%)	4 (1.2%)	6 (0.6%)	2 (0.9%)	1 (0.3%)	8 (2.4%)	11 (1.3%)	17 (0.9%)
of SOF/LDV	0	2 (0.4%)	4 (1.2%)	6 (0.6%)	1 (0.5%)	0	6 (1.8%)	7 (0.8%)	13 (0.7%)
to Modification or interruption of Any Study Drug	0	2 (0.4%)	4 (1.2%)	6 (0.6%)	17 (7.9%)	46 (14.0%)	55 (16.8%)	118 (13.5%)	124 (6.4%)
to Interruption of SOF/LDV	0	2 (0.4%)	4 (1.2%)	6 (0.6%)	1 (0.5%)	1 (0.3%)	5 (1.5%)	7 (0.8%)	13 (0.7%)
Treatment-Emergent Death	0	0	0	0	0	0	0	0	0

A causative relationship to SOF/LDV in those patients who discontinued treatment was difficult to established. One case of Factor VIII inhibition was reported as related to study-drug. And the case of hemorrhage occurred during a biopsy procedure.

Table 22 Adverse Events Leading to Discontinuation of SOF/LDV, phase 3 studies

Preferred Term	SOF/LDV (N = 1080)	SOF/LDV+RBV (N = 872)	Overall (N = 1952)
Number of Subjects (%) Experiencing Any AE Leading to Permanent Discontinuation of SOF/LDV	6 (0.6%)	7 (0.8%)	13 (0.7%)
Anxiety	0	2 (0.2%)	2 (0.1%)
Palpitations	1 (< 0.1%)	1 (0.1%)	2 (0.1%)
Fatigue	0	1 (0.1%)	1 (< 0.1%)
Arthralgia	1 (< 0.1%)	0	1 (< 0.1%)
Chest Pain	1 (< 0.1%)	0	1 (< 0.1%)
Dizziness	1 (< 0.1%)	0	1 (< 0.1%)
Dyspnoea	0	1 (0.1%)	1 (< 0.1%)
Ear Pain	0	1 (0.1%)	1 (< 0.1%)
Eyelid Oedema	0	1 (0.1%)	1 (< 0.1%)
Factor VIII Inhibition	1 (< 0.1%)	0	1 (< 0.1%)
Gastrointestinal Viral Infection	0	1 (0.1%)	1 (< 0.1%)
Haemorrhage	1 (< 0.1%)	0	1 (< 0.1%)
Headache	0	1 (0.1%)	1 (< 0.1%)
Road Traffic Accident	0	1 (0.1%)	1 (< 0.1%)
Sensory Disturbance	0	1 (0.1%)	1 (< 0.1%)
Squamous Cell Carcinoma of Lung	1 (< 0.1%)	0	1 (< 0.1%)
Throat Tightness	1 (< 0.1%)	0	1 (< 0.1%)
Vertigo	0	1 (0.1%)	1 (< 0.1%)

Adverse events

Common AEs

The frequency of AEs of grade >2 was low. The frequency of a number of common AEs were more frequent in those treated with the triple regimen including ribavirin, as expected. AEs seen in higher frequency with the triple regimen are those previously well described as RBV-associated. To elucidate any contribution of LDV to the side effect profile of SOF/LDV, Table 23 shows cross study comparison to studies performed as part of the SOF program.

Table 23 shows the adverse events in the SOF/LDV treatment arms without RBV by duration of therapy with frequencies of common AEs by duration of therapy.

Table 23 Common AEs in the SOF/LDV-arms (without RBV) in phase 3

	8 Week (N = 215)	**12 Week (N = 539**	**24 Week (N = 326)**	**Overall (N = 1080)**	Placebo (for SOF and RBV)* 12 weeks (N=71)
Number of Subjects (%) Experiencing Any AE	145 (67.4%)	390 (72.4%)	265 (81.3%)	745 (85.4%)	55 (77.5%)
Fatigue	45 (20.9%)	116 (21.5%)	79 (24.2%)	331 (38.0%)	17 (23.9%)
Headache	30 (14.0%)	113 (21.0%)	79 (24.2%)	228 (26.1%)	14 (19.7%)
Nausea	15 (7.0%)	61 (11.3%)	36 (11.0%)	152 (17.4%)	13 (18.3%)
Insomnia	11 (5.1%)	41 (7.6%)	30 (9.2%)	155 (17.8%)	3 (4.2%)
Diarrhoea	15 (7.0%)	40 (7.4%)	33 (10.1%)	67 (7.7%)	4 (5.6%)
Irritability	3 (1.4%)	22 (4.1%)	21 (6.4%)	95 (10.9%)	1 (1.4%)
Rash	3 (1.4%)	23 (4.3%)	21 (6.4%)	94 (10.8%)	6 (8.5%)
Arthralgia	9 (4.2%)	32 (5.9%)	27 (8.3%)	66 (7.6%)	1 (1.4%)
Cough	3 (1.4%)	18 (3.3%)	21 (6.4%)	90 (10.3%)	2 (2.8%)
Pruritus	2 (0.9%)	21 (3.9%)	10 (3.1%)	78 (8.9%)	6 (8.5%)
Dizziness	6 (2.8%)	21 (3.9%)	20 (6.1%)	61 (7.0%)	5 (7.0%)
Constipation	9 (4.2%)	23 (4.3%)	21 (6.4%)	42 (4.8%)	-
Myalgia	7 (3.3%)	20 (3.7%)	20 (6.1%)	48 (5.5%)	-
Asthenia	1 (0.5%)	15 (2.8%)	22 (6.7%)	56 (6.4%)	-
Anaemia	2 (0.9%)	2 (0.4%)	1 (0.3%)	5 (0.5%)	0
Muscle Spasms	3 (1.4%)	14 (2.6%)	11 (3.4%)	28 (2.6%)	-
Back Pain	6 (2.8%)	21 (3.9%)	16 (4.9%)	43 (4.0%)	-
Dyspnoea	0	4 (0.7%)	8 (2.5%)	12 (1.1%)	-
Anxiety	5 (2.3%)	9 (1.7%)	16 (4.9%)	30 (2.8%)	-
Nasopharyngitis	3 (1.4%)	19 (3.5%)	16 (4.9%)	38 (3.5%)	-
Vomiting	6 (2.8%)	12 (2.2%)	6 (1.8%)	24 (2.2%)	5 (7.0%)
Dry Skin	1 (0.5%)	3 (0.6%)	6 (1.8%)	10 (0.9%)	-
Dyspnoea Exertional	0	4 (0.7%)	2 (0.6%)	6 (0.6%)	-
Decreased Appetite					7 (9.9%)
Influenza Like Illness					2 (2.8%)
Pain					2 (2.8%)
Chills					1 (1.4%)

When evaluating common adverse events seen in the phase 3 studies in various ways, the side effect profile of LDV/SOF seems rather similar to that that has been reported for placebo in similar HCV populations in other studies. To further describe the side effect profile of SOF/LDV versus placebo, the applicant submitted safety data from the double-blinded SIRIUS study, where patients were randomized to SOF/LDV (n=77) or to placebo (n=78) for 12 weeks and subsequently SOF/LDV. A comparison of side effects during the 12 weeks that are placebo controlled.

The overall safety profile of SOF/LDV and placebo was very similar, with 84.4 and 83.3% of patients reporting any treatment emergent adverse event. The following adverse event, however, stand out as more common in the SOF/LDV group: Fatigue was reported in 16.9% of SOF/LDV treated patients versus 3.8% of placebo patients (13 versus 3). Furthermore, headache was reported in 35.1% of patients treated with SOF/LDV versus 20.5% of those treated with placebo (27 versus 16).

AEs of special interest

Given toxicities associated with nucleoside inhibitors/ polymerase inhibitors in the past, renal failure, cardiac failure, rhabdomyolysis/myopathy, and pancreatitis events were followed closely. Of note, none of those AEs were observed with sofosbuvir. No particular AEs associated with the NS5A class are known so far.

Apart from one patient in the phase 3 studies, who had a history of chronic pancreatitis and who had an episode of acute pancreatitis during study, none of the events were observed in the Phse III studies ION-1, -2 and -3.

Grade 3 and 4 adverse events

Any Grade 4 AEs were seen in 4 patients treated with SOF/LDV (out of total 1078), none considered related to study drug:

1 patient with 6 AEs following a road traffic accident,

1 with unstable angina,

1 with anaphylactic reaction (to triamcinolone),

1 patient with hypoglycemia (patient with diabetes, on insulin treatment).

Grade 3 AEs were seen in <5% of patients, and with large a spectrum of different preferred terms reported. There is no particular AE that stands out as more likely related to therapy. AEs of grade 3 or higher were seen in fully similar frequencies with and without RBV. Interestingly, the increase in common AEs, observed when RBV was added to the regimen, wer eof low intensity.

Table 24 AEs of grade 3 by regimen, phase 3 studies

Preferred Term	SOF/LDV (N = 1080)	SOF/LDV+RBV (N = 872)	Overall (N = 1952)
Numbers (%) with any Grade 3 AE	42 (3.9%)	45 (5.2%)	87 (4.5%)
Fatigue	3 (0.3%)	11 (1.3%)	14 (0.7%)
Headache	6 (0.6%)	5 (0.6%)	11 (0.6%)
Anaemia	0	5 (0.6%)	5 (0.3%)
Migraine	3 (0.3%)	1 (0.1%)	4 (0.2%)
Abdominal Pain	3 (0.3%)	0	3 (0.2%)
Hypertension	2 (0.2%)	1 (0.1%)	3 (0.2%)
Back Pain	1 (< 0.1%)	1 (0.1%)	2 (0.1%)
Cellulitis	1 (< 0.1%)	1 (0.1%)	2 (0.1%)
Chest Pain	2 (0.2%)	0	2 (0.1%)
Hypokalaemia	0	2 (0.2%)	2 (0.1%)
Jaundice	1 (< 0.1%)	1 (0.1%)	2 (0.1%)
Nausea	0	2 (0.2%)	2 (0.1%)
Neck Pain	2 (0.2%)	0	2 (0.1%)
Non-Cardiac Chest Pain	1 (< 0.1%)	1 (0.1%)	2 (0.1%)

While headache and fatigue may be side effects associated with SOF/LDV, severe events were rare.

Serious adverse events

Serious AEs were more frequently reported in ION-1 than in the following studies. A summary of AE preferred terms reported and sorted in alphabetic order is shown in Table 25. The pattern does not seem indicative for any event likely associated with SOF/LDV. For example, the number of fractures was considerable - all related to accidents/trauma.

Table 25 Serious AEs reported in ION-1, sorted in alphabetic order

anemia	Gastrointestinal upset
atypical chest pain	Gastroparesis
carotid stenosis	Headache
Cellulitis, bursitis left olecranon	Hemoptysis, Pneumonia
cellulitis, Right jaw/facial	Herniated disc
Chest pain	Hospitalization for mammarian nodule
Chest pain	Hypertension
chest pain	Lumbar spinal stenosis
chest pain	Migraine headache
Colitis	multifocal leukoencephalopathy
Concussion	osteoarthritis of the knee
Detoxification (alcoholic withdrawal)	pancreatic adenocarcinoma
Development of factor VIII inhibitor in haemophilia patient	Pneumonia
Fall	Pneumonia
fracture, arm	Salpingitis
Fracture, foot	Small subcapsular hematoma post ct guided liver biopsy
Fracture, hand	Squamous cell carcinoma
fracture, leg	Superior mesenteric venous thrombosis
fracture, leg	ureteral stone
Gastroenteritis	Urinary tract infection

A total of 6 serious adverse events in five patients were reported as related to study drug:

- anemia, 2 occasions in 1 patient (SOF/LDV + RBV), related to RBV therapy, resolved after RBV dose reduction.
- acute mesenteric vein thrombosis (SOF/LDV) in a patient with a history of cirrhosis, hypersplenomegaly,intravenous drug use and alcoholism. Therapy was stopped for 2 days, and then continued. The thrombosis resolved after around 4 months of anti-coagulants (warfarin).
- factor VIII inhibition (SOF/LDV) in a patient with known mild hemophilia. Continuous bleeding after blood sampling noted after 5 months of treatment and 1 month later the patient was admitted to hospital for spontaneous bleeding in pelvic area. Inhibition of Factor VIII was documented, and reported as a serious adverse event related to therapy.
- salpingitis (SOF/LDV) of grade 3, event resolved without interrupting therapy.
- headache (SOF/LDV) of grade 3, starting after 6 days of treatment - not reported as resolved.

Of note, there was no pre-clinical signal for effects on blood coagulation, and factor VIII inhibition is a known complication of hemophilia.

Deaths

No treatment related deaths were reported in the SOF/LDV Phase 3 Safety Population.

Laboratory findings

Liver chemistry

Transaminases normalized during therapy, and liver chemistry was overall without specific signs of concern (Table 26).

Table 26 Liver chemistry events in the phase 3 studies

	SOF/LDV			SOF/LDV + RBV		
Duration (weeks)	8	12	24	8	12	24
AST or ALT > 3 x ULN and Total Bilirubin > 2 x ULN	0/215	0/538	0/325	0/214	1/328 (0.3%)	0/328
ALT > 5 x ULN	0/215	2/538 (0.4%)	2/325 (0.6%)	0/214	0/328	0/328
Total Bilirubin > 2 x ULN	0/215	0/538	2/325 (0.6%)	6/214 (2.8%)	19/328 (5.8%)	19/328 (5.8%)

One patient (with cirrhosis in ION-1, treated with SOF/LDV + RBV for 12 weeks) met Hy's law criteria. The bilirubin elevation, peaking during weak 2 and then declining, was considered related to RBV. Treatment was continued throughout the 12 weeks, and AST and ALT levels subsequently decreased.

ALT levels of >5 x ULN were seen in 4 patients. None of the events was considered related to study drug, or clinically significant. Study treatment was completed in 4/4.

Of the 46 patients with a total bilirubin >2 x ULN, 44 were receiving RBV-containing treatment, which is known to cause hemolysis. The other 2 had increased bilirubin already at baseline, suggesting pre-existing conditions. The frequency of BIL>2 xULN in patients treated with SOF/LDV + RBV (5.8% in ams 12-24 weeks), is fairly identical to the frequency observed with SOF + RBV in the sofosbuvir program, further supporting that neither SOF nor LDV (cleared via liver and bile) cause an increase in bilirubin.

Other blood chemistry

For patients treated with SOF/LDV no relevant change from baseline was seen for hemoglobin, white blood cells (including lymphocytes) or platelets. Creatinine levels were not impacted by treatment.

Reductions in hemoglobin and lymphocytes were seen when adding RBV, as expected. In ION-1 around 15% of patients in the RBV-containing arms had a dose reduction in RBV (35/217 in 12 weeks-arm and 38/217 in 24 weeks-arm) - all achieved SVR. In ION-2 those numbers were 10% and 15%, respectively.

Lipase increases of grade 3 or 4 were seen in a limited number of patients, with a higher frequency in those treated longer. All except 1 (acute pancreatitis, discussed previously) were asymptomatic, and the lab disturbance resolved/normalized with time, without interruptions of therapy in any patient and there was no trend for lipase elevations over time was seen in general. Hence, an association to SOF/LDV seems unlikely.

Electrocardiograms

Thorough QTc studies have been performed for the individual components, SOF and LDV, and neither agent showed any effects on cardiac repolarization or prolongation of the QTcF interval.

Safety in special populations

Hepatic Impairment

The SOF/LDV Phase 3 program excluded subjects with Child-Pugh B/C cirrhosis. The percentages of subjects with any AE, Grade 3 or 4 AE, and AEs leading to study drug modification or interruption were similar for noncirrhotic subjects (73.8%, 4.0%, and 0.5%, respectively) and cirrhotic subjects (76.6%, 6.3%, and 0.9%) treated with SOF/LDV in phase 3.

During the evaluation, the applicant submitted safety data from the SOLAR-1 study performed in patients with decompensated cirrhosis (Child-Pugh B and –C). The summary of the reported adverse events is provided in Table 28.

Table 28 Summary of Adverse Events (Safety Analysis Set), SOLAR-1

Number (%) of Subjects Experiencing	LDV/SOF+RBV													
	Cohort A (Decompensated Cirrhosis)				Cohort B (Posttransplant)									
	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		Group 7	
	CPT B)		CPT C		Fibrosis F0-F3		CPT A		CPT B		CPT C		Aggressive Recurrent Disease	
	12 wk (27)	24 wk (28)	12 wk (26)	24 wk (27)	12 wk (55)	24 wk (57)	12 wk (26)	24 wk (26)	12 wk (26)	24 wk (24)	12 wk (5)	24 wk (4)	12 wk (4)	24 wk (2)
Any AE	26 (96.3)	26 (92.9)	25 (96.2)	27 (100)	55 (100)	56 (98.2)	25 (96.2)	25 (96.2)	25 (96.2)	23 (95.8)	4 (80.0)	4 (100)	4 (100)	1 (50.0)
Treatment-related AE	22 (81.5)	21 (75.0)	19 (73.1)	24 (88.9)	46 (83.6)	46 (80.7)	20 (76.9)	19 (73.1)	17 (65.4)	17 (70.8)	3 (60.0)	2 (50.0)	2 (50.0)	1 (50.0)
Grade 3 or 4 AE	2 (7.4)	6 (21.4)	6 (23.1)	12 (44.4)	15 (27.3)	13 (22.8)	4 (15.4)	7 (26.9)	6 (23.1)	6 (25.0)	1 (20.0)	1 (25.0)	1 (25.0)	0
Treatment-related Grade 3 or 4 AE	0	0	1 (3.8)	6 (22.2)	10 (18.2)	8 (14.0)	2 (7.7)	3 (11.5)	1 (3.8)	3 (12.5)	0	0	1 (25.0)	0
SAE	3 (11.1)	8 (28.6)	6 (23.1)	11 (40.7)	6 (10.9)	10 (17.5)	3 (11.5)	4 (15.4)	5 (19.2)	7 (29.2)	1 (20.0)	4 (100)	1 (25.0)	0
Treatment-related SAE	2 (7.4)	0	0	2 (7.4)	2 (3.6)	1 (1.8)	2 (7.7)	2 (7.7)	0	1 (4.2)	0	0	0	0
AE Leading to Discontinuation from LDV/SOF	0	0	0	3 (11.1)	0	2 (3.5)	1 (3.8)	0	0	2 (8.3)	0	0	0	0

Within Cohort A, the incidence of treatment-related AEs, treatment-related Grade 3 or 4 AEs, treatment-related serious adverse events (SAEs), and treatment-emergent deaths observed was similar between subjects with CPT B and C decompensated cirrhosis. This result is supported by the data from Cohort B. Across these groups of post-transplantation subjects, ranging from subjects with no cirrhosis to those with compensated cirrhosis to decompensated cirrhosis, there was no apparent trend to suggest worsening hepatic function is associated with a safety signal attributable to LDV/SOF.

Across treatment groups (N = 337) the most commonly reported AEs were fatigue (49.3%), headache (30.6%) and anemia (30.3%). Ten treatment-emergent deaths were reported, none of which were considered related to study drug by the investigators. Causes included complications of cirrhosis such as septicemia.

The study design without a placebo control precludes a precise characterization of the safety of SOF/LDV is this severely ill population. All in all, however, the emerging safety profile seems compatible with what might be anticipated as the natural course of very advanced liver disease, and no toxicity signal specific for patients with decompensated liver disease is apparent.

Renal Impairment

In phase 3 patients with an eGFR of < 60 mL/min at screening were excluded. A summary of available data in patients with reduced renal function, including many of the patients treated in the SOLAR-1 study,

does not identify any specific emerging safety concern in this population. A dedicated study of SOF+RBV in severe renal failure is ongoing.

Elderly

Across the treatment groups in the SOF/LDV Phase 3 Safety Population, 7.8% of subjects were ≥ 65 years of age. None of the SOF/LDV Phase 3 studies imposed an upper age limit as part of the study entry criteria.

For the RBV-free (SOF/LDV) groups, the percentages of subjects with any AE, Grade 3 or 4 AE, and AEs leading to study drug modification or interruption was similar for subjects aged < 65 years (73.8%, 4.1%, and 0.5%, respectively) and ≥ 65 years (76.7%, 5.6%, and 1.1%, respectively).

For the RBV-containing (SOF/LDV+RBV) groups, higher percentages of subjects aged ≥65 years (90.3% and 11.3%, respectively) experienced any AE and Grade 3 or 4 AE compared with subjects aged < 65 years (85.1% and 4.7%, respectively). Additionally, in subjects receiving SOF/LDV+RBV, AEs leading to study drug modification or interruption were also reported at an approximately 3-fold higher incidence in subjects aged ≥65 years (33.9%) compared with subjects aged < 65 years (12.0%). Consistent with the increase in AEs leading to study drug modification or interruption in RBV-containing (SOF/LDV+RBV) groups, anaemia was reported at a higher incidence in subjects aged ≥ 65 years (22.6%) compared with subjects aged < 65 years (8.5%).

2.6.1. Discussion on clinical safety

Sofosbuvir as a single agent has a large safety data base with a favourable tolerability and safety profile that is not clearly distinct from placebo. That data was to a considerable extent generated in combination with RBV or peg-IFN + RBV (with associated side effects). Section 4.8 of the Sovaldi SmPC therefore includes AEs that are actually related to RBV and/or peg-IFN.

The safety of SOF/LDV is mainly based on the phase 3 studies (ION-1 to -3), where 1080 patients received SOF/LDV and 834 received SOF/LDV + RBV. The former group reported common AEs of a type and frequency that is quite in line with those reported for placebo in the sofosbuvir program. Safety in the RBV containing arms was typical of the AE profile previously described for this agent.

The addition of RBV increased the frequency of grade 1-2 AEs (of the pattern typical for this agent); the frequency of grade 3-4 AEs was similarly low as with SOF/LDV alone, and there was no increase in treatment discontinuations when RBV was added to the regimen. Hence, the addition of RBV to minimize the risk for relapse in certain patients is not associated with any major safety issues.

During the evaluation, the applicant submitted safety data from the double blind placebo controlled SIRIUS study, performed in patients with cirrhosis. This study is indicative that headache and fatigue may be specific side effects of SOF/LDV. These events observed were generally mild in intensity.

When scrutinizing all severe AEs, there was no cases that seemed likely related to treatment. No treatment-emergent deaths were reported.

Apart from RBV-related haemolysis with reductions in Hb and increased indirect bilirubin, there are no haematological or blood chemistry findings of particular concern or considered likely related to treatment. No case suggestive of DILI was observed.

There was no trend towards a significant deterioration of the safety profile of SOF/LDV in compensated cirrhotics (n=224). Furthermore, during the review process the applicant submitted safety data from the SOLAR-1 study, where SOF/LDV + RBV was given to patients with decompensated liver disease (n=167) and/or status post transplantation. RBV was given at a reduced starting dose in those with hepatic

impairment. A considerable proportion of the decompensated patients in SOLAR-1 had MELD scores >15. While treatment appears to have been well tolerated with low rates of discontinuations due to AEs, as anticipated the frequency of serious adverse events and deaths were higher in this population compared to those with compensated liver disease. Events were characteristic of the natural course of end stage liver disease. While in the absence of a placebo control, any contribution of SOF/LDV to the treatment emergent adverse effect profile cannot be ascertained with certainty, no signal of toxicity specific to this population has been identified.

All the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of SOF/LDV in patients with compensated liver disease due to HCV infection, and a calculated GFR >60 ml/min, is favorable. Mild headache and fatigue may be side effects typical of this drug combination. The addition of RBV increased the frequency of AEs typical of this agent but these were generally mild and do not result in increased discontinuation rates. The safety database in decompensated liver disease is non-comparative which to some extent limits interpretability; however, SOF/LDV appears well tolerated and no specific safety concern has been identified.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.0 is acceptable. The PRAC advice is attached.

The CHMP endorsed this advice without changes.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Important Identified Risks	**None**
Important Potential Risks	Drug-drug interaction with potent P-glycoprotein (Pgp) inducers (Sofosbuvir [SOF], Ledipasvir [LDV])
	Administration of proton pump inhibitors (PPIs) (LDV)
	Drug-drug interaction with TDF + PK enhancer (LDV)
	Drug-drug interaction with rosuvastatin (LDV)
	Drug-drug interaction with digoxin (LDV)
Missing Information	Safety in children

	Safety in pregnant or breastfeeding women
	Safety in patients with HCV/HIV coinfection
	Safety in patients with HCV/HBV coinfection
	Safety in patients with severe renal impairment or end-stage renal disease
	Development of resistance

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 3 (Interventional studies)				
GS-US-337-1115 (formerly BP-US-337-0103) Randomized, open-label, single-center, 2-period, crossover, single-dose study of adults versus age-appropriate pediatric formulations of LDV/SOF fixed-dose combination (FDC) in healthy adult subjects	To evaluate the relative bioavailability and safety of an age-appropriate pediatric SOF formulation in healthy adult volunteers	Safety of age-appropriate pediatric SOF formulation	Planned	Final study report April 2016
GS-US-337-1116 (formerly BP-US-337-0104) A 2-part, open-label, single-arm study to investigate pharmacokinetics (PK), biodistribution, efficacy and safety of LDV/SOF for 12 weeks in adolescents and children with genotype (GT) 1-6 chronic hepatitis C virus (HCV) infection	To evaluate the PK, efficacy, and safety of LDV/SOF for 12 weeks in adolescents and children	Safety in children	Planned	Final study report June 2019
GS-US-334-0154 A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency	To evaluate the safety, efficacy and PK of SOF+RBV for 24 weeks in subjects with chronic genotype 1 or 3 HCV infection and severe renal impairment	Safety in patients with severe renal impairment or end-stage renal disease	Started	Final study report July 2017
GS-US-337-0115 A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 or 24 Weeks in Subjects with Chronic Genotype Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Coinfection	To evaluate the safety and efficacy of treatment with LDV/SOF ± RBV in subjects with HCV/HIV coinfection	Safety in patients with HCV/HIV coinfection	Started	March 2017

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
GS-US-337-0122 Electron 2: A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection.	To evaluate the safety and efficacy of combination therapy with SOF-containing regimens for the treatment of chronic HCV infection	One cohort will provide safety information in patients with HCV/HBV coinfection	Started	June 2016
GS-US-337-1118 An Open-Label, Multicenter Study To Evaluate The Efficacy And Safety Of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin For 12 or 24 Weeks In Chronic Genotype 1 HCV Infected Subjects Who Participated In A Prior Gilead-Sponsored HCV Treatment Study	To determine the efficacy of SOF/LDV±RBV and to evaluate the emergence of viral resistance to LDV and SOF during and after treatment discontinuation	Safety, efficacy, and development of resistance	Started	January 2017
Category 3 (Noninterventional studies)				
BP-US-337-1117 A 5-year follow-up study of pediatric patients from study GS-US-337-1116 (formerly BP-US-337-0104)	To evaluate growth, development, and viral relapse in adolescents and children who received LDV/SOF in study GS-US-337-1116	Growth Long-term safety	Planned	March 2024
GS-US-248-0123 A Long Term Follow-up Registry Study of Subjects Who Did Not Achieve Sustained Virologic Response in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection	To evaluate HCV viral sequences and the persistence or evolution of treatment-emergent viral mutations in subjects who fail to achieve an SVR after treatment with a Gilead oral antiviral containing regimen in a previous Gilead-sponsored hepatitis C study	Development of resistance	Started	July 2020
GS-XX-XXX-XXXX A prospective observational drug utilization study of LDV/SOF in adults with HCV/HIV coinfection is planned	To characterize the frequency of postmarketing co-use of LDV/SOF+TDF+PK enhancer in adult HCV/HIV coinfected patients and the rates of renal ADRs	HCV/HIV coinfection	Planned	To be determined
GS-XX-XXX-XXXX A clinical study to assess the effect of LDV on CYP3A probe midazolam	To assess the effect of LDV on a CYP3A probe drug	Drug interaction	Plannned	To be determined

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks		
Drug-drug interaction with potent Pgp inducers (LDV, SOF)	The Summary of Product Characteristics (SmPC; Sections 4.4 and 4.5) includes information that potent Pgp inducers (eg, rifampicin, carbamazepine, and phenytoin) should not be used with LDV/SOF due to the potential for significant decreases in LDV/SOF plasma concentrations, which may lead to reduced therapeutic effect of LDV/SOF. St. John's wort is contraindicated in Section 4.3.	None
Administration with proton pump inhibitors (LDV)	The SmPC (Section 4.5) includes information about the maximum allowed dose and simultaneous coadministration of LDV/SOF and proton pump inhibitors, as staggered dosing has the potential for decreases in LDV plasma concentrations, which may lead to reduced therapeutic effect of LDV/SOF.	None
Drug-drug interaction with TDF + PK enhancer (LDV)	The SmPC (Sections 4.4 and 4.5) includes information of how LDV/SOF co-use with TDF+PK enhancer increases tenofovir concentrations, safety is not established, consider risks and benefits particularly in patients at increased risk for renal dysfunction, monitor for tenofovir-associated ADRs, and refer to SmPCs for Viread, Truvada, or Stribild for renal monitoring recommendations.	None
Drug-drug interaction with rosuvastatin (LDV)	The SmPC (Section 4.3, 4.5) includes information that use of rosuvastatin with LDV/SOF is contraindicated due to the potential for significant increases in rosuvastatin.	None
Drug-drug interaction with digoxin (LDV)	The SmPC (Section 4.5) includes information that coadministration of LDV/SOF and digoxin should be used with caution due to the potential for an increase in digoxin concentration and that therapeutic concentration monitoring of digoxin is recommended.	None
Missing Information		
Safety in children	The SmPC states that the safety and efficacy of LDV/SOF in pediatric subjects have not been established and that LDV/SOF is not recommended for use in children and adolescents < 18 years of age (Sections 4.2, 4.4, 4.8) and that the PK of LDV/SOF and GS-331007 have not been established in children (Section 5.2).	None
Safety in pregnant or breastfeeding women	The SmPC states that, as a precautionary measure, it is preferable to avoid use of LDV/SOF during pregnancy and that LDV/SOF should not be used during breastfeeding.	None
Safety in patients with HCV/HIV coinfection	The SmPC (Sections 4.4 and 4.5) provide warnings and information on administration of LDV/SOF with many HIV medicines. No additional risk minimization measures are considered necessary for this population at this time. The need for risk minimization measures will be reassessed following the availability of the results from ongoing studies.	None
Safety in patients with HCV/HBV coinfection	The SmPC (Section 4.4) states that no data are available in this population. No additional risk minimization measures are considered necessary for this population. The need for risk minimization measures will be reassessed following the availability of the results from 1 cohort of a clinical trial or from routine pharmacovigilance.	None
Safety in patients with severe renal impairment or end-stage renal disease	The SmPC (Sections 4.2, 4.4, and 5.2) states that no dose adjustment of LDV/SOF is required for patients with mild or moderate renal impairment and that the safety of LDV/SOF has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m2) or end stage renal disease (ESRD) requiring hemodialysis.	None
Development of resistance	The SmPC (Section 4.4) states that in patients who fail treatment with LDV/SOF, selection of NS5A resistance mutations that substantially reduce the susceptibility to LDV is seen in the majority of cases. Limited data indicate that such NS5A mutations do not revert on long term follow up. The efficacy of LDV as part of a retreatment regimen in patients with prior exposure and selection of resistance to a NS5A inhibitor has not been established. The need for risk minimization measures will be reassessed following the availability of the results from studies or from routine pharmacovigilance.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The use of SOF/LDV in HCV genotype 1 infection

In previously untreated patients, with or without compensated cirrhosis, 12 weeks of therapy +/- ribavirin gave an overall SVR rate of 97.3-97.7%. Sixty-five out of sixty-seven treatment naïve compensated cirrhotics reached SVR (ION-1).

In previously untreated patients without cirrhosis, 8 weeks of therapy +/- ribavirin yielded overall SVR rates of 93.1-94%, while 12 weeks of therapy without ribavirin gave an SVR rate of 95.4% (ION-3).

In treatment experienced patients (previous non-response to pegIFN+RBV or pegIFN+RBV+an NS3/4A inhibitor), with or without compensated cirrhosis, 12 weeks of therapy, +/- ribavirin, yielded SVR rates of 93.6 and 96.4%, respectively, while 24 weeks of therapy +/- ribavirin gave an SVR rate of 99.1% (ION-2).

The use of SOF/LDV in HCV genotype 3 infection

In a small sample of previously untreated patients with genotype 3 virus infection, 8 of whom had cirrhosis, SOD/LDV for 12 weeks; an SVR rate of 64% (16/25) was achieved. When ribavirin was added to the same regimen, the SVR rate was 100% (26/26), including 5/5 compensated cirrhotics (data from ELECTRON- 2 study). Interim data from the same study showed that in treatment experienced patients without cirrhosis, SVR4 was reached in 89% (25/28) patients. In cirrhotic treatment experienced patients SVR4 was reached in 17/22 (77%) of patients.

The use of SOF/LDV in HCV genotype 4 infection

Preliminary data from clinical studies are indicative of a substantial contribution of LDV to efficacy in the tretamenbt of GT4 infection. The combination of in vitro data and these available clinical outcomes are indicative that SOF/LDV for 12 weeks is an effective regimen for the treatment of GT4 infection.

The use of SOF/LDV in patients with decompensated liver disease and/or post transplantation

Interim data from the SOLAR-1 study performed in genotype 1 and -4 patients (genotype 1 infection in the vast majority) showed an SVR4 rate of 90% (70/78) in patients with CPT-B or –C and treated with SOF/LDV+RBV for 12 weeks. The SVR12 rate was 84% (58/69). When treatment was extended to 24 weeks, the SVR4 rate was 88% (57/65). SVR12 data are not available.

In the same study, among post-transplant patients without cirrhosis, the SVR12 rate was 96% (53/55) with 12 weeks of SOF/LDV+RBV. When treatment was extended to 24 weeks the SVR4 rate was 98% (53/54). In post-transplant patients with compensated or decompensated cirrhosis, SVR12 rates with 12 weeks of SOF/LDV+RBV was 87% (42/48). With 24 weeks of therapy, the SVR4 rate was 90% (38/42).

In patients with fibrosing cholestatic hepatitis 4/4 achieved SVR4 after 12 weeks of therapy.

Uncertainty in the knowledge about the beneficial effects

The relative efficacy observed when SOF/LDV is administered for 24 versus 12 weeks in compensated cirrhotics with genotype 1 infection is not fully clarified.

While a cross study comparison of the efficacy of SOF/LDV +/- RBV for 12 weeks in genotype 3 is indicative that LDV contributes to efficacy on top of the background therapy of SOF +/- RBV, it is notable that data do not show a strong selective pressure of LDV on the virus (i.e. NS5A RAVs were not detected at time of relapse in majority of patients who failed therapy). Furthermore, there are no monotherapy data or on-treatment viral kinetics data to support the contribution of LDV to this regimen. The magnitude of the contribution of LDV to a regimen of SOF/LDV+RBV in genotype 3 is unclear. The relative efficacy of SOF/LDV+RBV for 12 weeks versus SOF+RBV for 24 weeks also remains unclear; a relapse rate prior to week 4 of 23% in treatment experienced cirrhotics, however, indicate that 12 weeks of therapy does not yield maximal efficacy in the most difficult to treat subgroup of patients.The applicant is not planning a phase III study in GT3. In vitro data as well as clinical efficacy data indicate the SOF/LDV for 12 weeks is a highly effective regimen for the treatment of genotype 4, however clinical data are sparse and immature (SVR4).

The relative efficacy of 12 versus 24 weeks of SOF/LDV+RBV in patients with decompensated liver disease is unclear given that the SOLAR-1 study results are interim.

Risks

Unfavourable effects

The safety database for SOF/LDV contains around 2000 patients. The safety profile is favourable, with very few treatment discontinuations. Furthermore, while the typical side effects of ribavirin (e.g., anemia) are noted, this drug was generally well tolerated when used in combination with SOF/LDV. SOF/LDV is associated with an increased rate of headache and fatigue, which were mild in intensity. No other side effects were observed with this drug combination.

There were virtually no on-treatment virological breakthroughs; therefore virological failure may be considered equal to relapse after the end of treatment. The main determinant for risk of relapse was treatment duration.

Virological relapse is often associated with the selection of viral variants resistant to LDV as well as to other available NS5A inhibitors. Available data are indicative that such variants persist after discontinuation of drug related selection pressure. This is anticipated to impact the efficacy of NS5A inhibitors as part of a retreatment regimen. Therefore, an unfavourable effect observed in the study program was virologic relapse, presumably due to an insufficient duration of therapy, or the lack of a fully active regimen due to BL NS5A resistance in some patients.

Uncertainty in the knowledge about the unfavourable effects

The consequence of relapse in terms of potential retreatment strategies is unclear. Previously untreated patients that relapse with NS5A inhibitor resistance have likely effective re-treatment options. However, this is less clear for those patients that previously failed therapy containing an NS3/4A inhibitor.

The role and potential residual efficacy of LDV within a retreatment regimen in patients with pre-selected NS5A resistance remains unclear.

While available data indicate that SOF/LDV is well tolerated without any specific side effects in patients with decompensated liver disease, the lack of a placebo control in this population hampers the certainty of this observation.

The appropriate dosing of SOF and the safety of SOF/LDV has not been clarified in patients with severe renal impairment.

There are some unclarities related to drug-drug interactions; e.g, what is the minimal exposure to LDV that is associated with retaining maximal efficacy.

Benefit-risk balance

Discussion on the benefit-risk balance

SOF/LDV with or without ribavirin has shown high efficacy against genotypes 1, including patients post-transplant and/or with compensated or decompensated cirrhosis.

While SOF is fully active against GT-3, the activity of LDV is poorly characterized virologically against this genotype. However, available clinical data are indicative that LDV does contribute to the antiviral efficacy when used in combination with SOF+RBV.

In vitro data and limited clinical data indicate high efficacy of SOF/LDV, also in GT-4. This treatment regimen is well tolerated and the benefit-risk balance is clearly positive.

The type of treatment regimen (treatment duration, addition of ribavirin) to be recommended in different clinical situations is not self-evident based on available data. A regimen of insufficient duration or lacking ribavirin may be associated with a suboptimal virological response, which is translated in an increased relapse rate. In case of relapse, until proven otherwise, it is presumed that LDV as well as other NS5A inhibitors generally loose a considerable part of their antiviral efficacy due to the selection of resistant variants that persist despite the discontinuation of drug pressure. This fact would limit retreatment options.

In most cases, relapse would not be an immediate and urgent clinical concern, as non-cirrhotic patients would not be at short term risk of clinical disease progression, and as patients without prior exposure to a NS3/4A inhibitor would have other likely curative retreatment option. However, for patients with advanced liver disease, manifested, e.g., by low platelet counts or by biochemical abnormalities related to liver function, failure to achieve viral clearance may be associated with a tangible short term risk of disease progression. Furthermore, all presently available combination DAA treatment options might have reduced efficacy in patients that have preselected for viral resistance against both NS3/4A inhibitors as well as NS5A inhibitors. Therefore, it is considered particularly important to avoid unnecessary relapses in patients with advanced liver disease and in patients with prior NS3/4A experience. These considerations are reflected in the recommended treatment regimens in section 4.2 of the SmPC.

Recommended regimens for patients with genotype 1 infection

Eight and 12 weeks of SOF/LDV have been compared in *non-cirrhotic treatment naïve patients*. There is no difference in tolerability depending on treatment duration. The relapse rate is higher with 8 weeks of therapy as compared to 12 weeks of therapy (5.1 versus 1.4%). Moreover, 6 weeks treatment duration in ELECTRON study has shown to be sub-optimal. While 12 weeks of therapy will yield a higher SVR rate, the number needed to treat for an extra SVR above 8 weeks will be high. Furthermore, patients within this category that relapse are anticipated to have effective retreatment options available. In addition, the short term risk of clinical disease progression in non-cirrhotic patients is very low. In explorative analyses, male gender, IL28B C/C genotype and higher baseline viral load were associated with an increased risk of relapse in case of 8 rather than 12 weeks of therapy. While 12 weeks may be optimal in terms of

benefit-risk, the clinician may consider an 8 week treatment course on a case to case basis. Information on predictors of relapse with 8 weeks of therapy is included in section 5.1. of the SmPC

In the absence of cross resistance, *treatment experienced* patients are considered a functional subgroup of the treatment naïve population preselected by response to prior therapy, were negative predictive factors for cure (such as IL-28 non-CC genotype) are enriched. A such-defined patient population has not been studied with 8 weeks of therapy. However, data indicate that 12 weeks of treatment with SOF/LDV is highly effective in *non-cirrhotic treatment experienced patients*. Therefore, this is the general recommendation. However, it is notable that the term “treatment experienced” today encompasses also patients with experience of prior treatment failure on direct acting antivirals such as NS3/4A inhibitors. While numbers are small, the relapse rate in the ION-2 study was higher with 12 compared to 24 weeks, and most evident in those patients that had baseline viral variants with reduced LDV susceptibility that were detectable with deep sequencing (detected in ~15% of the general genotype 1 population). The utility of baseline resistance testing to guide regimen selection (duration, addition of ribavirin) has been considered. However, due to uncertainties on both utility and availability of such testing, the applicant suggests that this should not be generally recommended in order to define the appropriate regimen. The CHMP concurs with this argument. However, the relevant dat on impact of baseline NS5A variants of efficacy have been included in section 5.1. of the SmPC. Furthermore, while 12 weeks of SOF/LDV is the generally recommended treatment regimen for treatment experienced non-cirrhotic patients, section 4.2 of the SmPC states that a prolongation of therapy to 24 weeks should be considered in those patients where there is uncertainty about the effectiveness of retreatment options.

In *treatment naïve patients with compensated cirrhosis*, 12 weeks of SOF/LDV yielded high SVR ratesand the addition of RBV did not confer any apparent increase in efficacy. However, numbers are small and there are reasons to believe that in an unselected treatment naïve cirrhotic population, 24 weeks of therapy may be associated with a lower relapse rate.

The rationale for this consideration comes from ION-2. As previously stated, treatment experienced patients are considered a difficult to cure subgroup of a general population, preselected by their previous failure to clear virus on therapy. While the small sample size is recognized, the relapse rate in cirrhotics in ION-2 ranged from 14-18% with 12 weeks of therapy versus 0% with 24 weeks treatment. Therefore, available data indicate that 24 weeks of SOF/LDV would be the primary option in patients with compensated cirrhosis. However, it is proposed that in such patients that have likely effective retreatment options, and that are deemed by the prescriber to be at a negligible short-term risk of clinical disease progression, 12 weeks of therapy may be considered, as the absolute SVR rate would still be high.

A considerable umber of *decompensated cirrhotics* is studied in the SOLAR-studies, but data are preliminary. It is of some interest that, from a numerical point of view, treatment duration rather than the addition of RBV seemed to impact outcomes in compensated cirrhotics in the ION-2 study. With decompensated cirrhosis, however, a cross study comparison on ELECTRON 2 and SOLAR-1 would indicate that the addition of RBV increases regimen efficacy. If this is indeed correct, it could be due to issues of the activation of SOF into its active moiety in patients with hepatic impairment. As all regimens in SOLAR 1 contained RBV, the recommended regimen in patients with decompensated liver disease is SOF/LDV+RBV (this is also applicable for patients post-transplant in general, regardless of hepatic function). These preliminary data preclude the analysis of the relative efficacy of SOF/LDV+RBV for 12 versus 24 weeks. In the absence of a clear understanding of the relative efficacy of the shorter treatment duration compared to the longer in these patients with very advanced disease, a conservative recommendation of 24 weeks of therapy seems warranted and as the regimen of SOF/LDV + RBV, (the latter initiated at a lower dose) is adequately tolerated in decompensated cirrhotics.

Genotype 2

The use of LDV is not recommended in genotype 2 due to the absence of data.

Recommendations for genotype 3

While the totality of evidence indicates that LDV adds activity against genotype 3, no extrapolations from genotype 1 can be made, due to the considerably higher EC_{50} value in genotype 3. Furthermore, available clinical data are scarce, and the absolute efficacy of SOF/LDV+RBV for 12 weeks in a broad population is unknown. SOF+RBV for 24 weeks (the presently approved IFN-free regimen for GT-3 infection) has not been compared to SOF/LDV + RBV for 12 weeks within the same study (the latter may in fact be inferior). The only conclusion on appropriate use that can be drawn is that the addition of LDV to a regimen of SOF+RBV most likely increases the chance for SVR in those patients where SOF+RBV alone is not an optimal treatment regimen. On this basis, the use of SOF/LDV + RBV (rather than SOF + RBV) for 24 weeks may be recommended in treatment experienced and/or cirrhotic patients with genotype 3-infection.

Recommendations for genotype 4

In vitro data are indicative that SOF/LDV for 12 weeks should be an effective regimen against genotype 4. This is supported by SVR4 data. By extrapolation, the regimens studied in different clinical situations for genotype 1 are considered of relevance also for genotype 4. However, EC_{50} values are higher than in GT1. Furthermore, patients with genotype 4 infection tend on average to have lower plasma HCV-RNA than patients with genotype 1 infection. These circumstances create some uncertainty to relative efficacy of 8 versus 12 weeks of therapy in genotype 4. For this reason, a sufficient basis for an 8 week recommendation in genotype 4 is considered lacking.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Harvoni in the treatment of chronic hepatitis C (CHC) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed

RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

New Active Substance Status

Based on the CHMP review of data of the active substance, the CHMP considers that ledispasvir is qualified as a new active substance.