



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2014
EMA/181960/2014

Summary on compassionate use for

Ledipasvir/Sofosbuvir

International non-proprietary name: ledipasvir, sofosbuvir

Procedure No. EMEA/H/K/003892/CU

Note

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



Product Information

Name of the medicinal product for Compassionate Use:	Ledipasvir/Sofosbuvir
Applicant:	Gilead Sciences
Active substance:	Ledipasvir, sofosbuvir
Target Population:	Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.
Pharmaceutical form(s):	Film-coated tablets
Strength(s):	90mg /400 mg
Route(s) of administration:	oral
Packaging:	High-density polyethylene (HDPE) bottles
Package size(s):	28 tablets/30 tablets

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1 Background information on the procedure

1.1. Submission of the dossier

Swedish National Competent Authority notified the Agency (EMA) on 5 September 2013 and requested a CHMP opinion on the compassionate use for the above mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004).

The legal basis for this application refers to:

Article 83(3) of Regulation (EC) No 726/2004 of the European Parliament and of the council (31 March 2004)

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

Rapporteur: Bengt Ljungberg

Co-Rapporteur: Joseph Emmerich

1.2. Steps taken for the assessment of the product

- Letters from the CHMP/EMA to the applicant with requests to provide data on 12 September 2013 and 13 December 2013.
- The timetable for the procedure was agreed-upon by CHMP on 23 January 2014.
- The dossier was received by the EMA on 7 February 2014
- The Rapporteur's preliminary Assessment Report was circulated to all CHMP members on 14 February 2014,
- The CHMP opinion was adopted on 20 February 2014

2 General conditions for the manufacturer

2.1 Manufacturers

Manufacturer(s) of the active substance – Sofosbuvir

The manufacturers for Sofosbuvir are the same as those listed in the marketing authorisation for Sovaldi 400 mg film-coated tablets (EU/1/13/894/001-002).

Manufacturer(s) of the active substance - Ledipasvir

The manufacturers for Ledipasvir are the same as those listed in the marketing authorisation application for Ledipasvir/Sofosbuvir 90 mg/400 mg film-coated tablets.

Manufacturer(s) of the finished product

The manufacturers of the finished product are the same as those listed in the marketing authorisation application for Ledipasvir/Sofosbuvir 90 mg/400 mg film-coated tablets.

Manufacturer responsible for import and batch release in the European Economic Area

Name: Gilead Sciences Limited

Address: IDA Business & Technology Park, Carraigtohill, Co. Cork

Country: Ireland

2.2 Conditions of distribution

Medicinal product subject to restricted medical prescription.

2.3 Conditions for update of Compassionate Use to be implemented by the manufacturer

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP on 20 February 2014, related to the conditions of use, distribution and targeted population of product, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4 Conditions for safety monitoring to be implemented by the manufacturer

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the applicant will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

2.5 Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3 Scientific Discussion

3.1 Introduction

As requested by the CHMP in September 2013, the applicant submitted a dossier to support the compassionate use of this product. The dossier was presented in CTA format.

There are currently no approved treatment options that are likely to be highly effective for patients that have failed to reach SVR when treated with a first generation NS4/4A protease inhibitor (telaprevir or boceprevir) in combination with peginterferon and ribavirin. In most cases, such patients will have selected for resistant variants that are likely to exhibit cross resistance among presently available agents of the NS3/4A inhibitor class. Many such patients have advanced liver disease and are in urgent need of therapy that induces a sustained virological response (SVR) in order to cease the progression of liver injury. Given their treatment history, such patients would be considered "difficult to cure"; i.e. the sum potency and barrier to resistance of a likely effective regimen needs to be high.

Furthermore, this unmet medical need extends generally to patients with hepatitis C virus infection and very advanced liver disease that have portal hypertension, as evidenced, e.g., by thrombocytopenia, and patients with hepatic impairment or a history of clinical decompensation. For such patients, regardless of viral genotype, interferon based treatment alternatives are either not tolerated with low effectiveness, or downright contraindicated due to the risk of precipitating further hepatic deterioration or serious bacterial infections. Also, the effectiveness of sofosbuvir+ribavirin bitherapy is likely to be

lower than what was seen when this treatment modality was studied in patients with less advanced liver disease.

The CHMP initially proposed that in the compassionate use setting ledipasvir/sofosbuvir fixed dose combination should be administered with or without ribavirin for the treatment of genotype 1 chronic HCV infection in patients who have previously failed on boceprevir or telaprevir based therapy and are in urgent medical need of effective treatment.

On 30 September 2013 Gilead responded to the CHMP request and agreed that the proposed compassionate use program should be discussed by CHMP. Gilead asked that CHMP defer the Article 83 request for data on the use of LDV/SOF (+/- ribavirin) in patients who have previously failed PI-based therapy and are in urgent medical need of effective treatment until the pertinent Phase 3 data became available. Subsequently, the proposed Article 83 request was discussed between Gilead and the CHMP on 23 January 2014. At this meeting it was agreed that a preliminary recommendation for compassionate use in some patients could be made based on the recently available Phase 3 clinical study data.

In this application the applicant has proposed an amended usage indication to that originally suggested by the CHMP. The applicant stated that for those subjects who are in urgent need of treatment (ie those with advanced disease who are at risk of decompensation or death in 12 months if left untreated) compassionate use should not be restricted based on prior PI treatment failure. Therefore Gilead proposed the removal of the PI failure statement in the usage indication:

Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.

Of note, the proposed expansion of indication is analogous to that previously adopted by the CHMP for compassionate use of NS5A inhibitor daclatasvir (same class as ledipasvir) in combination with sofosbuvir. However, in addition the indication for ledipasvir/sofosbuvir as proposed by the applicant would include patients regardless of viral genotype, whereas that of daclatasvir was formally limited to infections with viral genotype 1. The CHMP did not find that the submitted data were sufficiently in support of the proposed genotype unrestricted recommendation for sofosbuvir+ledipasvir (see below).

3.2 Quality aspects

Introduction

Ledipasvir/sofosbuvir fixed-dose combination tablets for compassionate use are formulated as film-coated tablets containing 90 mg of ledipasvir and 400 mg of sofosbuvir and packed in HDPE-bottles. The excipients used are copovidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silica, magnesium stearate and the film-coating agent containing polyvinyl alcohol, titanium dioxide, macrogol, talc, and and FD&C yellow #6/sunset yellow FCF aluminium lake (E110).

An application for the marketing authorisation of a fixed dose combination product containing ledipasvir and sofosbuvir as active substances has been submitted via the Centralised Procedure in the EU.

Sovaldi, a drug product presented as film-coated tablets containing 400 mg sofosbuvir as active substance, is currently approved for use in the European Union.

Drug Substance - sofosbuvir

Sofosbuvir is (S)- isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)-propanoate with the CAS number [1190307-88-0]. The molecular formula is C₂₂H₂₉FN₃O₉P and the molecular weight 529.45.

Sofosbuvir is a white to off-white powder, slightly soluble in water and freely soluble in ethanol. The drug substance has been appropriately characterised. The synthesis is described in satisfactory detail.

Control of Drug Substance

The drug substance specification covers appearance, identification, assay, related substances by HPLC, related substances by GC, residual solvents, residue on ignition and heavy metals. Impurities have been evaluated and found to be acceptable. Acceptable analytical results of nine batches of the active substance are included. The control of drug substance can be accepted.

Stability

In the marketing authorisation application for Sovaldi the active substance 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.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Drug Substance - ledipasvir

Ledipasvir is introduced in the drug product as ledipasvir acetone solvate. The acetone from ledipasvir acetone solvate is removed during the manufacturing of the film-coated tablets.

Ledipasvir acetone solvate is 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]-1H-benzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl]-3-methyl-1-oxobutan-2-yl]carbamate propan-2-one (1:1). The molecular formula is C₅₂H₆₀F₂N₈O₇ and the molecular weight 947.08.

Ledipasvir acetone solvate is a white to tinted (tan, yellow, or pink) powder, practically insoluble in water and freely soluble in ethanol. The drug substance physical properties have been appropriately characterised. The synthesis is described in satisfactory detail.

Control of Drug Substance

The drug substance specification covers appearance, identification assay, related substances by HPLC, residual solvents and heavy metals. Impurities have been evaluated and found to be acceptable for a drug substance at this stage of development. Acceptable analytical results of five batches of the active substance are included. The control of drug substance can be accepted.

Stability

The drug substance is stored in double polyethylene bags. A retest period of 12 months is proposed for ledipasvir acetone solvate at the recommended storage condition of 25 °C and protected from light. Stability data for one batch over 12 months at long-term conditions 25 °C/60% RH and accelerated stability data at 40 °C/75%RH is available. The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Drug Product

Pharmaceutical Development

The drug product is described as orange, diamond-shaped, film-coated tablets, debossed with "GSI" on one side and "7985" on the other side, packed in white HDPE bottles. The excipients are commonly used in drug development.

Adventitious Agents

Neither the excipients nor the active substances are derived from human or animal origin with the exception of lactose monohydrate. It is certified that lactose monohydrate conforms to BSE- and TSE-free requirements.

Manufacture of the Product

The drug product is manufactured by a standard manufacturing process. In-process controls are made during key steps of the manufacturing process.

Product Specification

The specification presented is considered appropriate at this stage of development and covers appearance, identity, content uniformity, assay, degradation product content, dissolution, water content and microbiological examination. The analytical procedures are described and appropriately validated. Batch analysis results from seven batches are included. The batch analyses conform to the specification. The impurity profile of the drug product is consistent with the impurity profile observed in the drug substance.

Stability of the Product

Stability data is presented for two batches of ledipasvir/sofosbuvir film-coated tablets. Long-term stability results are available up to 12 months at 25 °C/60% RH and 6 months accelerated stability results at 40 °C/75% RH. The parameters covered in the stability program are appearance, assay, degradation products content, dissolution and water content.

No trend in degradation can be seen. A shelf-life of 24 months is proposed when stored at 25 °C, excursions permitted from 15-30 °C. The stability data and proposed shelf-life can be accepted.

Long-term stability testing will continue to ensure that the clinical batches of drug product continue to meet the drug product specifications throughout their use in the clinic. Commitment is provided that if on testing, product does not meet the specification acceptance limits, the Competent Authorities will be notified and appropriate regulatory action taken through the submission of a substantial amendment.

Overall assessment on Quality

The overall assessment has taken into consideration the purpose of compassionate use. The fixed-dose combination of ledipasvir/sofosbuvir has previously been approved for use in clinical studies. Relevant information on development, manufacture and control of the active substance and finished product has in most parts been presented in a satisfactory manner. The results indicate acceptable consistency and uniformity of all the important quality characteristics of the product. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. The Quality documentation can be accepted and is not expected to have a negative impact on the Benefit Risk balance of the product.

3.3 Non-clinical aspects

Introduction

This article 83 application concerns ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of

adults infected with chronic hepatitis C with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.

Based on the currently available data the recommended treatment regimen, for subjects that would be eligible for early access to therapy under the proposed Article 83 usage, will be up to 24 weeks of treatment with the LDV/SOF FDC with or without RBV.

Pregnant or nursing women are excluded.

Data submitted-Ledipasvir-Sofosbuvir

Non-clinical data for the individual compounds have been summarised in the Investigator's Brochure, Edition 3, dated 18 October 2013.

Pharmacology

The pharmacology of sofosbuvir has been adequately described, characterised by activity against HCV genotype 1 to 6 replicon RNA replication, without significant cytotoxicity or mitochondrial toxicity. The active triphosphate form of sofosbuvir inhibited recombinant NS5B RNA-dependent RNA polymerase (RdRp) activity and the native HCV replicase activity, but did not inhibit human RNA polymerase II. DNA polymerases did not appear inhibited by sofosbuvir.

In vitro selection studies with SOF identified S282T in NS5B as a primary resistance mutation in genotypes 1 to 6.

Secondary pharmacology studies did not indicate any off target activity for sofosbuvir or the major *in vivo* metabolite.

Safety pharmacology studies did not suggest any remarkable effects of sofosbuvir on the nervous, cardiovascular, or respiratory systems.

Data indicates that the anti-HCV activity of sofosbuvir did not interfere with efficacy of nucleoside or nucleotide analogues used to treat HIV infection. In combination with ribavirin a minor synergistic interaction was reported.

Ledipasvir is proposed to inhibit HCV replication through NS5A. The mechanism of action has not been possible to biochemically confirm since NS5A has no known enzymatic function, however indirect evidence is consistent with ledipasvir targeting the HCV NS5A protein. Ledipasvir inhibitory activity *in vitro* was characterised by EC₅₀ (nM) of 0.031, 0.004, 10.8, 10.1 and 0.045 against GT1a, GT1b, GT2a, GT31 and GT4a, respectively. *In vitro* ledipasvir selected L31V and Y93H as signature mutants in NS5A. Ledipasvir has antiviral activity against signature HCV protease or NS5B polymerase mutants.

In *in vitro* radioligand binding assays ledipasvir showed inhibition (IC₅₀ of 0.21 µM) at the sodium channel, site 2 and at the L-type (dihydropyridine) calcium channel (IC₅₀ of 3.47 µM).

In safety pharmacology studies conducted in rat and dog given oral doses of up to 100 mg/kg (rat) and 30 mg/kg (dog) no significant effects were reported on parameters reflecting central nervous system function and respiratory and cardiovascular function. Ledipasvir was tested up to its limit of solubility (0.5 µM) in the cloned hERG potassium channels expressed in HEK cells and no effects were reported.

Combination ledipasvir and sofosbuvir

Additive antiviral activity was reported *in vitro* with the combination ledipasvir and sofosbuvir. No cross-resistance *in vitro* was evident.

No studies on secondary pharmacology or safety pharmacology with the combination were conducted.

Pharmacokinetics

Sofosbuvir is well absorbed in nonclinical species and sufficient exposure levels were achieved in species chosen for assessment of toxicology. Oral administration resulted in high exposure to its major metabolites GS-566500 and GS-331007 across species tested. The oral bioavailability of sofosbuvir was 9.07%, reflecting a fraction absorbed of 36.4% and hepatic extraction of 74%, following oral administration to portal vein cannulated dogs. Higher esterase levels in the plasma from mice and rats limited sofosbuvir exposure, but levels of its major circulating metabolites remained high in these species.

Following oral administration of radioactive compound to rats, high concentrations of label were observed in the organs of absorption and excretion and the lymphatic system. Liver-to-plasma concentration ratios were approximately 15:1 at plasma T_{max} and were ≥ 20 at 24 hours post-dose. Sofosbuvir was primarily excreted in urine as metabolites in rats and dogs, with urinary recovery accounting for 72% and 81%, respectively, of the administered radiolabeled material. Low levels of radioactivity were reported in the brain and CNS. Tissue distribution in pigmented and non-pigmented rats was similar.

Extensive metabolism of sofosbuvir occurs mediated by esterase activity leading to high relative exposure to the metabolites GS-566500 and GS-331007 across species. The predominant circulating metabolite in rat and dog after oral doses was GS-331007. This metabolite was also the predominant metabolite in bile in rats and in urine and faeces in both species. The intracellular activation pathway of sofosbuvir involves sequential hydrolytic steps catalyzed by CatA, CES1, and HINT1 are followed by efficient phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Incubation of hepatocytes from across species showed formation of the pharmacologically active nucleoside analogue triphosphate *in vitro*. The triphosphate $t_{1/2}$ in dog liver was 17.8 hours after oral administration.

In general the distribution, metabolism, and elimination of sofosbuvir in selected animal species were consistent with those observed in humans during clinical studies. Sofosbuvir had no relevant interactions with CYP enzymes. Sofosbuvir is a substrate but not an inhibitor of Pgp and BCRP, and its absorption may be decreased by coadministration with inducers of the expression of these transporters.

Non-clinical pharmacokinetics showed good bioavailability of ledipasvir in rat, dog and monkey. After single oral doses in rat an approximately dose proportional increase in exposure with dose from 10 to 30 mg/kg was evident while exposure was less than dose proportional at doses of 30 to 300 mg/kg.

Ledipasvir showed very high *in vitro* protein binding (>99.8%) in all species. The volume of distribution at steady state was greater than body water volume and distribution was wide. In male rats ledipasvir radioactivity after oral doses of 10 mg/kg was widely distributed with highest concentrations, excluding the gastrointestinal tract, in liver, adrenal gland, urinary bladder, kidney and pancreas. No selective association with melanin rich tissues was reported in pigmented rats. Low levels of radioactivity were found in testes and brain in mouse. Mean residence time was long. The terminal half-life ranged from 4.7 hours in the rat to 10.3 hours in monkey.

Rate of metabolism of ledipasvir was slow in *in vitro* systems. The unchanged parent compound was the major circulating compound in both rat and dog, accounting for up to 95% of radioactivity. The unchanged parent compound was also the major component in bile and faeces of rat and dog. The only quantifiable metabolite in dog plasma was identified as oxy-ledipasvir, accounting for about 5% of circulating radioactivity. N-decarboxy-methyl ledipasvir was identified in rat bile and faeces and in dog bile.

Ledipasvir was primarily excreted as unchanged parent compound via bile with only trace amounts (less than 0.9%) in urine. In bile duct cannulated dogs given an intravenous dose of 0.25 mg/kg approximately 71% of the total dose was found in bile as the unchanged compound.

Ledipasvir had little or no inhibitory effect on CYP isozymes and weakly activated the pregnane X receptor. Ledipasvir was a moderate to weak inhibitor of Pgp and BCRP.

Combination ledipasvir and sofosbuvir

No specific non-clinical PK studies with the combination ledipasvir and sofosbuvir have been presented.

Toxicology

The nonclinical toxicologic profile of sofosbuvir has been characterized in single- and repeat-dose toxicity studies up to 39 weeks in duration and genetic toxicity, developmental and reproductive toxicity, and local tolerance studies. Studies up to 3 months in the mouse, 6 months in the rat, and 9 months in the dog were conducted. In 7-day toxicity studies with GS-9851, very high doses of GS-9851 resulted in adverse liver findings in dogs, and in adverse gastrointestinal (GI) and cardiac effects in both rats and dogs at doses of 2000 mg/kg/day and 1500 mg/kg/day, respectively. In chronic toxicity studies in rats (26-weeks) and dogs (39-weeks), the only observed effects were in high dose dogs (500 mg/kg/day) and were GI-related clinical signs (soft faeces and emesis) and a slight decrease (10%) in mean erythron mass. The NOAELs were 500 mg/kg/day and 100 mg/kg/day in the rats and dogs, respectively, at exposures that were 9 and 13 fold above the clinical exposure of sofosbuvir at 400 mg.

The primary target organ toxicities observed at high doses were in the cardiovascular, hepatobiliary, GI, and hematopoietic (erythroid) systems. Sofosbuvir was not genotoxic and did not result in developmental or reproductive toxicity. Sofosbuvir was considered a non-irritant to skin and a non-severe irritant to eyes and was negative in a delayed-type hypersensitivity study. Carcinogenicity studies in mice and rats are ongoing. At NOAELs in the 26- and 39-week studies in rats and dogs, the margins of exposure for GS-331007 at the clinical dose of 400 mg were 9 and 13, respectively (based on the mean GS-331007 AUC_{tau} of 7.20 µg h/mL from HCV subjects at 400 mg given once daily).

Ledipasvir was tested in repeated dose toxicity studies of up to 26 weeks duration in rat and 39 weeks in dog. In rat, the high dose, 100 mg/kg was proposed as the NOAELs and similarly in dog the dose of 30 mg/kg was presented as the NOAEL. At the dose of 100 mg/kg in rat only slight effects such as increased cholesterol, decreased reticulocytes, and changes in adrenal and liver weight were reported and these were not considered adverse. Some potentially treatment related histopathological findings in high dose males consisted of minimal paracortical lymphocyte hyperplasia in the mesenteric lymph nodes and an increase in the incidence of prostatic inflammation, however, these effects were not present at week 26. In the 39 week dog study there were 3 deaths, but 2 were determined to be gavage related and 1 due to bacterial infection. In a 2 week dog study decreased body weight and food consumption was recorded at the high dose of 30 mg/kg.

The high doses in rat and dog studies corresponded to approximately x6 to x7 estimated ledipasvir clinical exposure in combination with sofosbuvir. No specific target organ toxicity was evident and the rationale for the selection of the high dose is not clear. This could indicate that the full toxicological profile of ledipasvir has not been sufficiently investigated or has not been possible to investigate.

No effects on fertility were reported in a standard fertility study in rat. However, mean corpora lutea and implantations were decreased at the high dose at Caesarean sectioning and a statistically non-significant reduction of average number of viable embryos was reported at the high dose. The high dose in this study was 100 mg/kg. In embryofetal toxicity studies in rat and rabbit given daily oral doses of up to 100 mg/kg (rat) and 180 mg/kg (rabbit) no adverse effects were reported. Ledipasvir

seemed devoid of any significant reproductive, embryo/foetal toxicity, but also in these studies the NOAEL was the high dose and exposure margins to a clinical dose of 90 mg ranged from 1.4 to 4-fold. The dose of 100 mg/kg in rat was, however, considered maternally toxic based on decreased maternal body weight gain and food consumption.

Standards tests on genotoxicity included the Ames test, chromosomal aberration test and a rat bone marrow micronucleus assay. Overall data showed that ledipasvir had no genotoxic potential.

The combination of ledipasvir and sofosbuvir

No non-clinical data on potential toxicity has been generated with the combination ledipasvir and sofosbuvir. Sofosbuvir has shown toxic effects in the gastrointestinal tract, liver and heart at high doses while no specific target organ toxicity of ledipasvir was reported. The repeated dose toxicity studies with ledipasvir may be considered not sufficient in that the high dose selected did not provide exposure that permitted evaluation of toxic effects and the rationale for the selection of the high dose is not clear.

Discussion on non-clinical aspects

The non-clinical data presented for ledipasvir includes a range of primary pharmacological and toxicological studies. The rationale for the selection of the high dose, that provided exposure levels x6 to x7 the expected clinical exposure, and also corresponded to the NOAEL with no specific evidence of target organ toxicity, is not clear. The potential for additive or synergistic toxicity in combination with sofosbuvir is uncertain. Nevertheless, considering the margins of exposure a concern for enhanced toxicological reactions due to combination treatment may likely be of lower significance also in view of the intended treatment groups.

The information relevant to non-clinical aspects presented in the Applicant's proposal for recommendations for health professionals is considered acceptable.

Overall conclusion on non-clinical aspects

From the non-clinical point of view there are no issues that specifically need to be further considered when ledipasvir is used at the proposed dose, duration and administration route in combination with sofosbuvir in the compassionate use programme.

3.3 Clinical aspects

Pharmacokinetics

- Absorption

The relative bioavailability of LDV/SOF FDC was compared in a crossover design to the coadministered individual tablet formulations of SOF (400 mg) and LDV (90 mg) in healthy subjects. Similar plasma exposures of SOF, its metabolites GS-566500 and GS-331007 (predominant circulating nucleoside metabolite), and LDV were achieved upon administration of LDV/SOF FDC and SOF+LDV coadministered as individual components. The lower bounds of the 90% confidence intervals (CIs) for the primary PK parameters (AUC and C_{max}) of SOF, GS-566500, and LDV were greater than 70%. The 90% CIs of the geometric-least squares mean (GLSM) ratios for all GS-331007 primary PK parameters were contained within bioequivalence bounds of 80% to 125%.

The effect of food on the single-dose PK of LDV/SOF was evaluated in 30 healthy subjects in Cohort 2 of Study GS-US-337-0101. The effect of a high fat meal on the PK of sofosbuvir and GS-331007 was in line with the results from administration of Sofosbuvir alone. Similar ledipasvir plasma exposure was achieved upon administration of LDV/SOF under fasted or fed conditions.

- Distribution

Ledipasvir is highly protein bound in plasma (> 99.8% bound). It is a P-glycoprotein (P-gp) substrate.

Sofosbuvir is approximately 85% bound to human plasma proteins while protein binding of GS-331007 is minimal in human plasma.

- Metabolism

Ledipasvir is metabolised to a low degree. Following administration of [14C]LDV, systemic exposure was almost exclusively to the parent drug (more than 98%). Ledipasvir was the major species in feces accounting for a mean of 70% of the administered dose, followed by the known oxidative metabolite M19 (Oxy-LDV-3, 2.2%).

Sofosbuvir is extensively metabolised in the liver to form the pharmacologically active nucleoside analogue triphosphate GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. After a single 400 mg oral dose of [14C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and >90% of drug-related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively.

- Elimination and Excretion

Ledipasvir

Study GS-US-256-0108 investigated the absorption, metabolism, and excretion of LDV following administration of a single oral dose containing 100 µCi[14C]LDV (equivalent to 1.65 mg LDV and 88.35 mg non-radiolabeled LDV) to 8 healthy male subjects. The total combined mean recovery of [14C]-radioactivity in faeces and urine was approximately 87%, with most of the radioactive dose recovered from the faeces (approximately 86%). Renal excretion of LDV was a minor pathway for elimination; approximately 1% of the administered dose was present in the urine as metabolites with no unchanged parent drug detected in the urine. Excretion of unchanged parent in bile is a major route of LDV elimination in preclinical species.

Sofosbuvir

Following a single 400 mg oral dose of [14C]-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 median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours respectively.

- Drug-Drug Interactions

Ledipasvir

Ledipasvir is an inhibitor of P-gp and Breast cancer resistance protein (BCRP).

The effect of LDV 90 mg once daily on the PK of a representative oral hormonal contraceptive medication, norgestimate 0.180 mg/0.215 mg/0.25 mg/ ethinyl estradiol 0.025 mg (Ortho Tri-Cyclen Lo; OC) was determined in 15 healthy female subjects. The effect of OC on the PK of LDV was also assessed. Similar plasma exposures of norelgestromin (NGMN), a major active metabolite of norgestimate, were achieved upon coadministration of OC and LDV 90 mg relative to OC administration alone. A 40% increase in C_{max} of ethinyl estradiol was seen but no significant change in AUC. Ledipasvir systemic exposure was similar to historical data.

The effects of a triple combination of DAAs, ledipasvir (LDV) 90 mg once daily + vedroprevir (VDV) 200 mg once daily + tegobuvir (TGV) 30 mg twice daily on organic anion transporting polypeptide(OATP), BCRP, sodium-taurocholate cotransporting polypeptide (NTCP), and Pgp using phenotypic probes (pravastatin, rosuvastatin or digoxin, respectively) were investigated in healthy subjects (Study GS-US-248-0125). In addition, the drug-drug interaction potentials between DAAs and a Pgp inducer (rifampin), a Pgp inhibitor (verapamil sustained-release [SR]), and a mixed OATP/MRP2/Pgp inhibitor (cyclosporine) were assessed.

Administration of LDV+VDV+TGV with an OATP substrate pravastatin resulted in a modest increase of approximately 2.7- to 2.8-fold in AUC and C_{max} of the probe drug, as compared to pravastatin administration alone. Coadministration of rosuvastatin and LDV+VDV+TGV resulted in increases of approximately 8- to 9-fold in rosuvastatin AUC and approximately 18-fold increase in rosuvastatin C_{max}. The contribution of LDV on OATP1B1/1B3 cannot be assessed as it was administered in combination with other agents.

Modestly higher digoxin (AUC: approximately 1.3- to 1.6-fold higher; C_{max}: 1.2-fold higher) exposures were observed when administered with LDV+VDV+TGV.

Ledipasvir AUC was approximately 56% to 59% lower and C_{max} was approximately 35% lower, upon coadministration with rifampicin.

Coadministration of LDV+VDV+TGV with verapamil resulted in approximately 1.5- to 1.7-fold higher AUC of LDV. The pharmacokinetic parameters of Ledipasvir as well as Cyclosporin A were not significantly changed by coadministration of the two. Ribavirin and ledipasvir does not appear to interact pharmacokinetically.

The drug-drug interaction potential of a triple DAA combination of LDV 90 mg once daily + VDV 200 mg once daily + TGV 30 mg twice daily and efavirenz (EFV) 600 mg/ emtricitabine (FTC) 200 mg/ tenofovir (TFV) 300 mg once daily (administered as Atripla, ATR) was evaluated in healthy subjects. Ledipasvir exposure was decreased by approximately 30% when coadministered with ATR. TFV exposure was increased by approximately 35% when coadministered with LDV+VDV+TGV.

Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentrations. According to the company proton-pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF or up to 2 hours after taking LDV/SOF. Proton-pump inhibitors should not be taken before LDV/SOF

Sofosbuvir

Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Medicinal products that are potent P-gp inducers in the intestine (e.g. rifampicin, St. John's wort, carbamazepine and phenytoin) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect.

LDV/SOF

The effect of LDV (90 mg) on the PK of SOF (400 mg) and its metabolites was evaluated in 17 healthy subjects. Sofosbuvir plasma exposures (C_{max} and AUC) were increased by approximately 2.2- to 2.3-fold by LDV. Similarly, GS-566500 AUC and C_{max} were increased by approximately 1.8-fold by LDV. GS-331007 exposure was unaffected by LDV. Similarly, addition of SOF did not impact the PK of LDV.

- Special Populations

Hepatic impairment

Ledipasvir

Single dose PK of LDV was investigated in 11 subjects with severe hepatic impairment (HI) and 10 healthy matched controls. The majority (80%) were white male subjects. Inclusion criteria for the severe hepatic impairment group was Child-Pugh-Turcotte (CPT) score ≥ 10 at screening, without evidence of worsening clinical and/or laboratory signs of hepatic impairment during the screening period and without active HCV infection. A single oral dose of LDV (1 \times 90-mg tablet) was administered with a moderate fat meal and PK sampling was performed up until 168 hours post dose.

Mean(CV%) AUC_(0-inf) was 9567.2(67.7) ng*h/mL and 7615.7(30.9) ng*h/mL in severe HI subjects and healthy controls, respectively. Ledipasvir C_{max} was approximately 35% lower and terminal t_{1/2} was prolonged (median 84.25 hours vs 45.72 hours) in subjects with severe HI. The geometric mean ratio (90% CI) of AUC_(0-inf) (severe HI/normal controls) was 107.68 (70.06 to 165.49).

The steady-state PK of LDV+VDV with and without TGV in subjects with normal and moderately impaired hepatic function (Classification B as determined by the Child-Pugh-Turcotte classification) was evaluated. Ledipasvir steady-state plasma exposure parameters (AUC_{tau}, C_{max}, and C_{tau}) were similar in subjects with moderate hepatic impairment and in subjects with normal hepatic function who received a combination of LDV+VDV. Ledipasvir plasma exposures were approximately 34% to 36% decreased in hepatically impaired subjects relative to subjects with normal hepatic function who received a combination of LDV+VDV+TGV. Of note, the exposure in normal subjects was 40% higher in the LDV+VDV+TGV group compared to the LDV+VDV group. The plasma protein binding of ledipasvir was not seen to be different comparing normal subjects and subjects with moderate hepatic impairment.

Sofosbuvir

The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV infected subjects with moderate and severe hepatic impairment (CPT class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC₀₋₂₄ was 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC₀₋₂₄ was 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic impairment.

Renal impairment

Ledipasvir

The pharmacokinetics of ledipasvir has not been determined in subjects with renal impairment. A study to evaluate the pharmacokinetics of ledipasvir in subjects with severe renal impairment is currently ongoing.

Sofosbuvir

Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73 m²), the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment, while the GS-331007 AUC_{0-inf} was 55%, 88% and 451% higher, respectively. In subjects with end stage of renal disease (ESRD), relative to subjects with normal renal function, sofosbuvir AUC_{0-inf} was 28% higher when sofosbuvir was dosed 1 hour before haemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after haemodialysis. The AUC_{0-inf} of GS-331007 in subjects with ESRD could not be reliably determined. However, data indicate at least 10-fold and 20-fold higher exposure to GS-331007 in ESRD compared to normal subjects when Sovaldi was administered 1 hour before or 1 hour after haemodialysis, respectively.

No dose adjustment of Sovaldi is required for patients with mild or moderate renal impairment. The safety and appropriate dose of Sovaldi have not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) or ESRD requiring haemodialysis

Overall conclusion on Clinical Pharmacokinetics

Ledipasvir increases the exposure to sofosbuvir but not to GS-331007. Similar exposure of ledipasvir and sofosbuvir is obtained with the fixed dose combination compared to the individual tablet formulations. Ledipasvir exposure is reduced when given alone with a high fat meal, but in the fixed combination LDV/SOF this effect is not seen. The fixed combination can be administered without regard to food.

A clinically relevant interaction between ledipasvir and rosuvastatin cannot be ruled out and rosuvastatin should therefore not be administered with LDV/SOF. Ledipasvir does not appear to influence the pharmacokinetics of Cyclosporin A nor Ribavirin and vice versa. Ledipasvir solubility is pH dependent and bioavailability could be impacted by proton pump inhibitors.

Exposure to ledipasvir in subjects with severe hepatic impairment following a single 90 mg dose was variable but on average not seen to differ from healthy controls.

Clinical efficacy

Ledipasvir is an investigational NS5A inhibitor that is being developed in combination with SOF for the treatment of chronic HCV infection. Sofosbuvir is a nucleotide NS5B polymerase inhibitor and a marketing application to support SOF, in combination with other agents for the treatment of chronic HCV infection, has recently been approved in the US and Europe (under the tradename of Sovaldi).

As individual components, both LDV and SOF displayed potent inhibition of HCV replicon RNA replication. Ledipasvir demonstrated picomolar potency in HCV genotypes 1a and 1b, with mean EC₅₀ values of 0.031 and 0.004 nM, respectively. In addition, LDV had various levels of antiviral activity against genotypes 2 to 6, with EC₅₀ values ranging from 0.15 to 530 nM. Sofosbuvir demonstrated potent activity against all HCV genotypes with a range of activities observed in replicon assay (14–241 nM) depending on the genotype and testing method used. The combination of LDV and SOF has been shown to exhibit additive antiviral activity in vitro.

The compassionate use of LDV/SOF FDC is primarily supported by three studies conducted in patients with genotype 1 infection (LONESTAR, ION-1, ION-2). Furthermore, the applicant has submitted preliminary data from a study of patients with genotype 3, to support the widening of the indication beyond genotype 1 (ELECTRON 2). These are not presented in this report for reasons of data confidentiality.

LONESTAR

This is an ongoing Phase 2, randomized, open-label study. The study assessed the safety, tolerability, and antiviral efficacy of LDV/SOF administered with and without RBV for 8 or 12 weeks. The study had 2 parallel cohorts.

Study design

In Cohort 1, non-cirrhotic treatment-naive (TN) subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups:

- LDV/SOF 8 Week TN group (Group 1): LDV/SOF 90 mg/400mg (1 tablet) once daily for 8 weeks in treatment-naive subjects

- LDV/SOF+RBV 8 Week TN group (Group 2): LDV/SOF 90 mg/400 mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg (5 × 200-mg tablets) or 1200 mg for subjects weighing ≥ 75 kg (6 × 200-mg tablets) administered in a divided daily dose for 8 weeks in treatment-naive subjects
- LDV/SOF 12 Week TN group (Group 3): LDV/SOF 90 mg/400mg (1 tablet) once daily for 12 weeks in treatment-naive subjects

In Cohort 2, cirrhotic and non-cirrhotic subjects who had previously failed PI+Peg-IFN+RBV (treatment experienced, TE) therapy were randomized in a 1:1 ratio to 1 of 2 treatment groups:

- LDV/SOF 12 Week TE group (Group 4): LDV/SOF 90 mg/400 mg (1 tablet) once daily for 12 weeks in treatment-experienced subjects
- LDV/SOF+RBV 12 Week TE group (Group 5): LDV/SOF 90 mg/400mg (1 tablet) once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg (5 × 200-mg tablets) or 1200 mg for subjects weighing ≥ 75 kg (6 × 200-mg tablets) administered in a divided daily dose for 12 weeks in treatment-experienced subjects

Efficacy outcomes

A total of 97 of 100 subjects achieved SVR12 across all groups; individual group proportions of subjects who achieved SVR12 ranged from 94.7% to 100%. Of note, 21 of the 22 cirrhotic subjects who had previously failed treatment with a PI-based regimen achieved SVR12.

ION-1

This ongoing Phase 3, randomized, open-label, international, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-naive subjects with chronic genotype 1 HCV infection.

Study design

Following screening and confirmation of eligibility by the investigators, approximately 800 subjects were randomized (1:1:1:1) to 1 of the following 4 treatment groups:

- LDV/SOF 24 Week group (Group 1): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks
- LDV/SOF+RBV 24 Week group (Group 2): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided twice daily [BID]) for 24 weeks
- LDV/SOF 12 Week group (Group 3): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- LDV/SOF+RBV 12 Week group (Group 4): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Randomization was stratified by HCV genotype (1a, 1b, or mixed 1a/1b) and cirrhosis status (presence or absence) at screening. Enrollment was managed so that approximately 20% of randomized subjects had cirrhosis.

Study Population

Eligible subjects were males or non-pregnant/non-lactating females ≥ 18 years of age with chronic genotype 1 HCV infection who had screening HCV RNA levels ≥ 10⁴ IU/mL, were HCV treatment naive, had documentation of the presence or absence of cirrhosis, and had a body mass index (BMI) ≥ 18 kg/m². Subjects were enrolled across 100 sites in the US, Germany, France, United Kingdom, Spain, and Italy.

A total of 870 subjects were randomized in approximately equal proportions across the 4 groups. A total of 865 subjects received at least 1 dose of study drug and were included in the safety and full analysis sets. In the total population, 136 patients had compensated cirrhosis.

Efficacy Results

SVR12 data have been presented for patients randomized to 12 week treatment arms

The primary efficacy endpoint was SVR12 (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after discontinuation of all study drugs) in the full analysis set (FAS).

A total of 97.7% of subjects (209 of 214) in the LDV/SOF 12 Week group and 97.2% of subjects (211 of 217) in the LDV/SOF+RBV 12 Week group achieved SVR12. The addition of RBV to the LDV/SOF regimen did not impact the SVR rate. No subject in either 12-week treatment group had on-treatment virologic failure (ie, breakthrough, rebound, or nonresponse). There was no effect on SVR12 or relapse rates when subjects took LDV/SOF with or without food.

The table below presents the virologic outcomes (SVR and non-SVR) for subjects in the FAS following 12 weeks of treatment with LDV/SOF±RBV (Groups 3 and 4).

In the LDV/SOF 12 Week group, 5 subjects (2.3%) did not achieve SVR12.

	LDV/SOF 12 Weeks (N = 214)	LDV/SOF+RBV 12 Weeks (N = 217)
SVR12	209/214 (97.7%)	211/217 (97.2%)
Overall Virologic Failure	1/214 (0.5%)	0/217

Note: HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.

ION-2

This ongoing Phase 3, randomized, open-label, multicenter study assessed the antiviral efficacy, safety, and tolerability of 12 or 24 weeks of LDV/SOF±RBV treatment in treatment-experienced subjects with chronic genotype 1 HCV infection.

Study design

Following screening and confirmation of eligibility by the investigator, approximately 400 subjects were randomized (1:1:1:1) to 1 of the following 4 treatment groups:

- LDV/SOF 24 Week group (Group 1): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 24 weeks
- LDV/SOF+RBV 24 Week group (Group 2): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 24 weeks
- LDV/SOF 12 Week group (Group 3): LDV/SOF FDC (90 mg/400 mg) tablet once daily for 12 weeks
- LDV/SOF+RBV 12 Week group (Group 4): LDV/SOF FDC (90 mg/400 mg) tablet once daily + RBV (1000 or 1200 mg/day divided BID) for 12 weeks

Randomization was stratified by HCV genotype (1a, 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. Enrollment was managed so that approximately 20% of randomized subjects had cirrhosis and approximately 50% of randomized subjects had failed prior treatment with a PI+Peg-IFN+RBV regimen at screening.

Study Population

Eligible subjects were males or non-pregnant/non-lactating females ≥ 18 years of age with chronic genotype 1 HCV infection who had screening HCV RNA levels ≥ 10⁴ IU/mL, had virologic failure to prior

treatment with a Peg-IFN+RBV regimen (including regimens containing nonstructural protein 3/4A [NS3/4A] PIs), had documentation of the presence or absence of cirrhosis, and had BMI \geq 18 kg/m². Subjects were enrolled across 64 sites in the US.

A total of 441 subjects were randomized in approximately equal proportions across the 4 groups. A total of 440 subjects received at least 1 dose of study drug and were included in the safety and full analysis sets: 109 subjects in the LDV/SOF 12 Week group; 111 subjects in the LDV/SOF+RBV 12 Week group; 109 subjects in the LDV/SOF 24 Week group; and 111 subjects in the LDV/SOF+RBV 24 Week group. One subject was randomized to the LDV/SOF 24 Week group but did not receive study drug, and was excluded from both the safety and full analysis sets.

Subjects who had discontinued their prior HCV therapy due to an AE were prohibited from enrolling in this study; therefore, all subjects in this study were prior virologic failures, classified as either relapse/breakthrough (55.7%) or nonresponse (44.3%). These treatment-experienced subjects had failed a prior Peg-IFN+RBV regimen, with approximately half having failed prior PI+Peg-IFN+RBV therapy (52.5%).

Of the 231 subjects who failed prior PI+Peg-IFN+RBV therapy (58.4% failed telaprevir; 29.4% failed boceprevir; 12.1% failed investigational PIs), 62.3% of subjects had relapse/breakthrough and 37.7% of subjects had nonresponse.

Of the 207 subjects who failed prior Peg-IFN+RBV therapy, 48.8% of subjects had relapse/breakthrough and 51.2% of subjects had nonresponse. The majority of these prior Peg-IFN+RBV non-responders (60.4%) were null responders (ie, subjects who did not achieve undetectable HCV RNA levels while on treatment and who had $< 2 \log_{10}$ reduction during the first 12 weeks of treatment), and 39.6% were partial responders.

88 patients had cirrhosis.

Efficacy Results

The primary efficacy endpoint was SVR12 (HCV RNA $<$ LLOQ 12 weeks after discontinuation of all study drugs) in the FAS.

The table below presents the virologic outcomes (SVR and non-SVR) for subjects in the FAS.

	LDV/SOF 12 Weeks (N=109)	LDV/SOF+RBV 12 Weeks (N=111)	LDV/SOF 24 Weeks (N=109)	LDV/SOF+RBV 24 Weeks (N=111)
SVR12	102/109 (93.6%)	107/111 (96.4%)	108/109 (99.1%)	110/111 (99.1%)
Overall Virologic Failure	7/109 (6.4%)	4/111 (3.6%)	0/109	1/111 (0.9%)

Note: HCV RNA analyzed using Roche TaqMan V 2.0 assay for use with High Pure system with limit of quantitation 25 IU/mL.

Discussion on clinical efficacy

Overall, the combination of ledipasvir and sofosbuvir has shown outstanding results in the treatment of genotype 1 infection, including a substantial number of patients with prior failure on telaprevir or boceprevir + pegIFN/RBV therapy, as well as a substantial number of patients with compensated cirrhosis. In the reported studies, SVR rates with 12 weeks of therapy, without ribavirin has yielded SVR rates above 93%. There are generally no viral breakthroughs in adherent patients, and the recorded relapses are few. In the ION-2 study, extending therapy from 12 to 24 weeks led to higher

point estimates for SVR (99.1%). The increment over 12 weeks of therapy, however, was modest. Of note, no relapses were recorded in 220 treatment experienced patients getting 24 weeks of ledipasvir+sofosbuvir, with or without ribavirin.

The applicant remarks that the appropriate treatment strategy in patients with very advanced liver disease, including those with hepatic impairment or signs or history of clinical decompensation, has not been defined. Thus, the role of ribavirin in such patients is not known, nor whether the added benefit of treatment beyond 12 weeks in such patients would lead to a greater increment in SVR rates than those seen in the ION-2 trial.

To further explore the efficacy and appropriate treatment strategy with ledipasvir+sofosbuvir, the applicant is performing three studies in patients with very advanced liver disease (SOLAR-1, SOLAR-2 and SIRIUS). Data from these studies are anticipated to inform on the appropriate regimen to use in patients with very advanced liver disease; no outcome data, however, are presently available.

While there is limited evidence on the efficacy of ledipasvir+sofosbuvir in patients with hepatic impairment or decompensated liver disease, SVR rates in compensated cirrhotics are very high. Therefore, it is reasonable to believe that this drug combination, with or without ribavirin, will deliver substantial response rates also in patients with very advanced liver disease.

While it is recognised that the optimal treatment duration, and the value of adding ribavirin in such patients is unknown, it is understood that clinicians treating patients under compassionate use conditions, that are deemed to be at a high risk of decompensation or death within 12 months if left untreated, may wish to maximise the probability of SVR, as for such patients there may not be a second chance to reach the treatment goal. The applicant therefore suggests that "ledipasvir/sofosbuvir should be used for a duration of at least 12 weeks, up to 24 weeks, with or without ribavirin".

The applicant proposes an indication for compassionate use that would encompass all genotypes. In support of this, the applicant has submitted interim data from the small ELECTRON 2 study, where ledipasvir+sofosbuvir are given with or without ribavirin for 12 weeks. As a further background to this study, it is notable that whereas the EC_{50} of ledipasvir against genotype 1a and -1b replicons are in the picomolar range (0.031 and 0.004 nM, respectively), the EC_{50} against a hybrid genotype 3a replicon is given as 35.1 nM (Ledipasvir IB). It is fully recognised that the clinical cut-off (the EC_{50} values where ledipasvir would be anticipated not to meaningfully contribute to sum regimen efficacy) is presently not well characterised, and the studies performed in genotypes other than 1 are encouraged and of considerable interest. Furthermore, the data presented are indicative of a contribution to regimen efficacy of ledipasvir in combination with sofosbuvir in genotype 3. However, the interim data presented do not support a clear cut indication for a CHMP recommendation on compassionate use in non-GT1 patients. This evaluation takes into account the anticipated efficacy of the presently approved interferon-free regimens, which are expected to be more efficacious against other genotypes than -1. It is recognised that physicians may, on a case to case basis, consider the use of ledipasvir+sofosbuvir also in patients with other genotypes than -1.

Overall conclusion on clinical efficacy

The combination of ledipasvir/sofosbuvir for 12-24 weeks, with or without ribavirin, has been shown to deliver very high SVR rates in phase III studies of patients with genotype 1 virus infection, including a substantial number of patients with compensated cirrhotics. The efficacy shown supports the compassionate use of ledipasvir+sofosbuvir in genotype 1 patients with very advanced liver disease. The optimal duration and the value of adding ribavirin has not been defined. It is anticipated that use in patients with very advanced disease will be informed by emerging data from relevant studies.

While early data on the efficacy of ledipasvir+sofosbuvir in genotype 3 are very interesting, they are presently not considered sufficiently solid for an Article 83 opinion. This is not only due to the scarcity of data, but also to the fact that presently approved interferon-free treatment options are anticipated to be more effective in genotype 3 than genotype 1.

Clinical safety

The safety of sofosbuvir has been extensively reviewed by the CHMP in the course of the MAA for Sovaldi. In conclusion, no characteristic side effect profile has emerged, and the tolerability of this drug is not clearly different from that of placebo.

According to the ledipasvir Investigator's brochure, as of 01 June 2013, a total of 2225 subjects have been administered LDV, of which 1261 were subjects with chronic HCV infection. Ledipasvir has been investigated in several different combinations, with and without peginterferon and ribavirin.

Here follows a summary of safety findings of the combination use of ledipasvir+sofosbuvir +/- ribavirin from the LONESTAR study:

Overall, the highest percentage of subjects with any AE was observed in the 2 RBV-containing groups (LDV/SOF+RBV 8 Week TN and LDV/SOF+RBV 12 Week TE groups [57.1% in both]), followed by the RBV-free groups (LDV/SOF 8 Week TN group [45.0%], the LDV/SOF 12 Week TN group [42.1%], and the LDV/SOF 12 Week TE group [36.8%]).

The 3 most frequently reported overall AEs were nausea, anemia, and upper respiratory tract infection. The LDV/SOF+RBV 12 Week TE group had the highest numbers of subjects with nausea, anemia, and upper respiratory tract infection (19.0%, 4 subjects; 28.6%, 6 subjects; 19.0%, 4 subjects; respectively); all other AEs were reported in ≤ 2 subjects in any group, with the exception of headache (14.3%, 3 subjects) in the LDV/SOF+RBV 8 Week TN group. Anemia was only reported in subjects receiving RBV.

Most AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 AEs were only reported in subjects receiving RBV. A total of 4 subjects (19.0%) in the LDV/SOF+RBV 8 Week TN group and 2 subjects (9.5%) in the SOF/LDV+RBV 12 Week TE group had a Grade 3 (severe) AE. Anemia was the only Grade 3 AE reported in > 1 subject; Grade 3 anemia was reported for 2 subjects (9.5%) in the LDV/SOF+RBV 12 Week TE group. No Grade 4 AEs were reported.

No deaths, pregnancies, or permanent study drug discontinuations due to AEs were reported during this study. A total of 5 SAEs were reported in 4 subjects on or after the first dose of study drug through the date of last dose of study drug plus 30 days. No SAEs were reported in the LDV/SOF 8 Week TN group on or after the first dose of study drug through the date of last dose of study drug plus 30 days. No trends in SAE type or onset time were observed, as no individual SAE was experienced by more than 1 subject. All SAEs were considered unrelated to study drug with the exception of anemia reported in 1 subject in the LDV/SOF+RBV 12 Week TE group.

All AEs leading to dose modifications led to modification of RBV only. The most frequently reported AE leading to modification or interruption of study drug was anemia, which was observed only in subjects treated with LDV/SOF+RBV (6 subjects [28.6%] in the LDV/SOF+RBV 12 Week TE group and 2 subjects [9.5%] in the LDV/SOF+RBV 8 Week TN group). Each of the other AEs that led to modification or interruption of study drug (dyspnea exertional, edema, and peptic ulcer) was reported in 1 subject only. One subject had LDV/SOF interrupted due to an SAE of peptic ulcer.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. Grade 3 laboratory abnormalities were reported in 2 subjects in each 12 Week TE group and in 1 subject in each 8 Week

TN group (none in the 12 Week TN group). Grade 4 laboratory abnormalities were only reported in the 12 Week TE groups (2 subjects in the LDV/SOF+RBV group and 1 subject in the LDV/SOF group).

Consistent with the expected safety profile of RBV, corresponding decreases in hemoglobin and elevations in reticulocytes, bilirubin, and platelets were observed in subjects who received RBV as a component of the treatment regimen for the duration of treatment. Regarding the LDV/SOF+RBV groups, 4 subjects had a Grade 3 (3 subjects) or 4 (1 subject) decrease in hemoglobin, and 8 subjects had post baseline hemoglobin values < 10 g/dL, of whom 2 had hemoglobin values < 8.5 g/dL; no subjects in the RBV-free groups met these criteria. Median hemoglobin, reticulocytes, bilirubin, and platelets returned towards baseline values within 4 weeks after the last dose of study drug.

Grade 3 chemistry laboratory abnormalities were reported for lipase and serum glucose (hyperglycemia and hypoglycemia). Grade 4 chemistry laboratory abnormalities were reported for serum glucose (hyperglycemia) and serum potassium (hyperkalemia). The most common Grade 3 or 4 chemistry laboratory abnormality was increased serum glucose; all such subjects with hyperglycemia had a medical history of diabetes (the subject with a Grade 3 decrease in serum glucose [hypoglycemia] also had a medical history of diabetes). All other Grade 3 and 4 laboratory abnormalities occurred in 1 subject across the groups.

No subject in any group had Grade 3 or 4 ALT or total bilirubin changes (increases) from baseline. Three subjects had bilirubin > 2 × ULN while on treatment, 2 who received LDV/SOF+RBV and 1 who received LDV/SOF (this subject had elevated bilirubin at baseline). No notable changes in total bilirubin values were observed in the other groups.

No notable changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse) were reported during the study.

Discussion on clinical safety

The safety profile of sofosbuvir is well characterised and has been assessed by the CHMP during the MAA procedure leading to its approval. No specific side effect profile differing from placebo has emerged. Furthermore, the applicant has provided a summary of the safety profile seen in the phase II and III studies where ledipasvir, with or without ribavirin, was added to sofosbuvir. It is apparent that the combination of ledipasvir and sofosbuvir is well tolerated, with very few discontinuations due to side effects. Serious side effects and grade 3/4 laboratory abnormalities were uncommon with the use of ledipasvir+sofosbuvir. The addition of ribavirin had a negative impact on the safety profile, with typical side effects such as anaemia, hyperbilirubinemia, cough, dyspnoea, irritability and rash.

Overall conclusion on clinical safety

The safety profile of sofosbuvir in combination with ledipasvir appears favourable with few discontinuations, serious side effects or laboratory abnormalities. The addition of ribavirin adds to the side effect burden, as anticipated. No adverse effects in need of specific monitoring have been identified with ledipasvir+sofosbuvir in the absence of ribavirin; furthermore, no side effects that would preclude the use of ledipasvir+sofosbuvir in patients with very advanced liver disease, in urgent need of treatment, have been identified.

3.5 Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for ledipasvir/sofosbuvir fixed dose combination formulation as follows:

Conditions for safety monitoring to be implemented by the applicant

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 24(1) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the applicant will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

Conditions for safety monitoring to be implemented by the Member States

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 25 of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore the Member State(s) will ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3.6 Risk/benefit assessment and recommendation

Risk Benefit assessment

The combination of ledipasvir+sofosbuvir, with or without ribavirin, used for 12-24 weeks, has shown very high efficacy when treating patients with genotype 1 virus, including patients with compensated cirrhosis and patients with prior failure on boceprevir or telaprevir in combination with pegIFN+ribavirin. The regimen has been very well tolerated, apparently with no specific side effect profile emerging. There are no specified safety concerns to preclude the use of this combination in patients with hepatic impairment. Furthermore, PK of ledipasvir and sofosbuvir support that no dose adjustment is prompted in hepatic impairment. For these reasons, it is reasonable to assume that the compassionate use of ledipasvir+sofosbuvir in patients with very advanced liver disease and with an urgent need of successful therapy will provide meaningful rates of viral clearance.

In the notification to the CHMP of the potential compassionate use of ledipasvir in combination with sofosbuvir, the efficacy shown in patients with prior failure on NS3/4A inhibitors was particularly noted.

For patients that have previously failed boceprevir- or telaprevir based antiviral therapy, and do not tolerate interferon, there is presently no likely highly effective licensed treatment option. A subset of this population has advanced liver disease and is at a considerable short term risk of progression to decompensation or death. Furthermore, there are many patients that have advanced liver disease, as evidenced by signs and symptoms of portal hypertension, with or without past or present clinical decompensation. For such patients, interferon based treatment alternatives are at best ill tolerated with low effectiveness, or, in case of hepatic impairment/decompensation, outright contraindicated. These patients are in urgent need of effective therapy that can induce SVR.

Regarding the treatment history, the CHMP recognises that the urgent medical need extends also to patients with very advanced liver disease that have not been exposed to boceprevir or telaprevir, either because they did not have the opportunity, or because they were not able to tolerate the necessary interferon comedication. Therefore, the CHMP, in a recent similar procedure, proposed that the indication for compassionate use of sofosbuvir in combination with a NS5A inhibitor be extended to encompass patients with genotype 1 virus regardless of prior treatment experience, provided that there is an urgent medical need of viral clearance.

The applicant rightly noted that the aforementioned medical need extends also to patients infected with other viral genotypes than -1, and proposes the following indication for compassionate use of ledipasvir/sofosbuvir:

Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.

In practice, this would primarily encompass patients with signs or symptoms of portal hypertension, as well as those with present or past episodes of clinical decompensation/hepatic impairment.

The CHMP acknowledged that there are also patients with non-genotype 1 infection subject to the aforementioned medical urgency. For such patients, the anticipated effectiveness of available treatment options may differ on a case to case basis. Therefore, for patients with non-genotype 1 infection that are deemed unlikely to respond to or tolerate licensed and available treatment options, compassionate use of ledipasvir in combination with sofosbuvir and ribavirin, may also be relevant. However, available data are presently too scarce to evaluate the anticipated benefit of this combination in other genotypes than -1, when compared to other treatment options.

In this light, and in order to be consistent with other relevant procedures, the following addendum to the applicant suggestion has been made:

Ledipasvir/sofosbuvir fixed dose combination (with or without ribavirin), when used as part of a compassionate use programme, is indicated for the treatment of adults infected with chronic hepatitis C genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.

Studies in patients with hepatic impairment/decompensation are ongoing, and results are not yet available. For this reason, the optimal regimen in such patients has not been defined in terms of duration, and the possible benefit of adding ribavirin is not known. Adding ribavirin increases the side effect burden of the regimen, particularly due to haemolytic anemia. However, this in no way precludes the use in patients with very advanced liver disease.

While any incremental effect of adding ribavirin to the regimen, or of continuing therapy beyond 12 weeks, appears low to minimal in patients with compensated liver disease, it is unclear whether this pertains also to patients with hepatic impairment. For this reason, the applicant provisionally suggested that the recommended regimen is ledipasvir+sofosbuvir, *with or without ribavirin*, for at least 12 weeks, up to 24 weeks. This recommendation may be impacted by emerging data from relevant trials.

The applicant suggestion is deemed reasonable, not least as it is assumed that the compassionate use of ledipasvir+sofosbuvir in the target population would be managed by physicians that are expert in the field and who could make an individualised assessment of available data.

In summary, the benefit risk of Ledipasvir in combination with sofosbuvir, with or without ribavirin, when used for at least 12 weeks up to 24 weeks as part of a compassionate use programme, for the treatment adults infected with chronic hepatitis C genotype 1 virus with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated, is deemed positive.

The overall assessment of quality issues has taken into consideration the purpose of compassionate use. It can be reasonably concluded that the product should have a satisfactory and uniform performance in the clinic. The Quality documentation can be accepted and is not expected to have a negative impact on the Benefit Risk balance of the product.

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for Ledipasvir/sofosbuvir fixed dose combination available for compassionate use (see Appendix 1).

Superseded by Marketing Authorisation