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Innovation in Global Health

Review of the VELPATASVIR PATENT LANDSCAPE: A scoping report

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ABBREVIATIONS

API	active pharmaceutical ingredient
DAA	direct acting antiviral
EPO	European Patent Office
HCV	hepatitis C virus
HIV	human immunodeficiency virus
PCT	Patent Cooperation Treaty
RNA	ribonucleic acid

I. INTRODUCTION

Hepatitis C is a major global health problem; some 130–150 million people worldwide are chronically infected with the hepatitis C virus (HCV). It is estimated that, worldwide, 2.9 million people are coinfected with HIV and HCV. Each year, approximately 700 000 people die of HCV-related liver disease, and evidence indicates that the HCV burden is increasing.[1,2,3] While the HCV epidemic is global in scope, the HCV burden varies considerably between countries.

The virus has six primary genotypes. Genotypes 1 and 3 are the most prevalent, accounting respectively for 46% and 30% of HCV cases worldwide. Together, genotypes 2, 4 and 6 represent around 23% of HCV cases, while genotype 5 accounts for less than 1%.[4]

Efforts to treat HCV have historically been hampered by suboptimal and inadequate treatments. However, the development of direct-acting antivirals (DAAs) has dramatically improved the prospects for HCV treatment and has altered the standard of care. Several new DAAs that do not require Pegylated interferon (PEG-interferon) have been launched since late 2013, and a number of other DAAs are in development.

These DAAs generate cure rates that approach or exceed 90%. Some combination regimens may have pan-genotypic efficacy, which would simplify treatment and monitoring. In this context, velpatasvir is one of the compounds of interest. UNITAID published a report exploring the patent landscape of velpatasvir in July 2015.[5] The current report is an update of that report.

1. Hepatitis C factsheet. Geneva: World Health Organization; July 2016 (http://www.who.int/mediacentre/factsheets/fs164/en/, accessed 29 January 2017).
2. Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization; 2016.
3. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(117–71).Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77–87.
4. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77–87.
5. UNITAID. Review of the velpatasvir patent landscape: a scoping report. July 2015.

II. METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, namely: PatBase, TotalPatent, SciFinder and Google Patents. Searches were carried out using keywords, semantic searches and structure searches.

For each of the most relevant patents or applications, the equivalents were identified (INPADOC family) and the legal status of each of the equivalents was checked on the websites of the relevant patent offices. The countries listed in Annexes 1 and 2 represent those for which INPADOC data are available.

The searches were originally carried out in January 2015 and were updated in August 2016. Information for Patent 2 was complemented with data from Form 3, submitted to the Indian Patent Office.

Caveat: It is important to note that the patent status of a given product in a given country may change and that data may therefore become outdated. It is advisable always to check with the relevant national or regional patent office for the most up-to-date information on the status of a given patent or patent application.

This report was prepared by Andrew Brown, Amel Garbi and Haining Ji (Pharmathen), with input from Karin Timmermans (UNITAID). The patent searches were conducted by Amel Garbi and Haining Ji.

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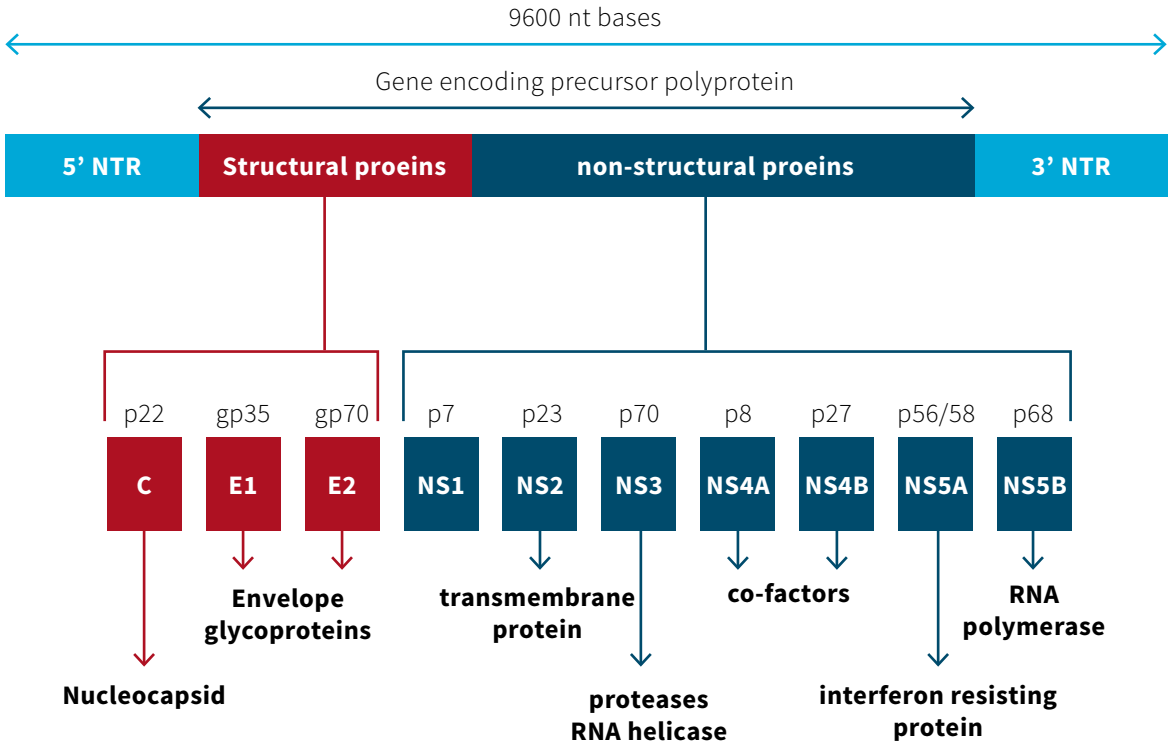
III. BACKGROUND

Hepatitis C virus

The hepatitis C virus is a small (55–65 nm), enveloped, positive-sense single-stranded RNA virus of the Flaviviridae family. The virus consists of three structural proteins (core, E1 and E2), the ion channel protein p7 and six non-structural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) (see Figure 1). Each of these proteins plays a role in HCV entry, infection, replication or maturation and is therefore a potential target for medicines.

Figure 1. Hepatitis C virus RNA



Adapted from Graham Colm.

DAAs block viral production by directly inhibiting one or more steps of the HCV replication cycle. DAAs can be divided into categories – notably NS3/NS4A serine protease inhibitors, NS5A complex inhibitors and NS5B RNA polymerase inhibitors (both nucleoside and non-nucleoside).

NS5A is a 447 amino acid, zinc-binding phosphoprotein that is believed to play a key role in HCV RNA replication. NS5A exists in two forms: a hypophosphorylated p56 and a hyperphosphorylated p58 based on electrophoric mobility. NS5A is essential to HCV genome replication.

Velpatasvir is an NS5A inhibitor. A once-daily, fixed-dose combination (FDC) tablet of sofosbuvir (400 mg) with velpatasvir (100 mg) received marketing approval in the United States in June 2016. Gilead is furthermore developing a triple-drug combination of sofosbuvir, velpatasvir and voxilaprevir (GS-9857).

5 Gilead announces data for investigational, all-oral, pan-genotypic three-drug regimen of sofosbuvir, GS-5816 and GS-9857 for chronic hepatitis C. Business Wire, 23 April 2015

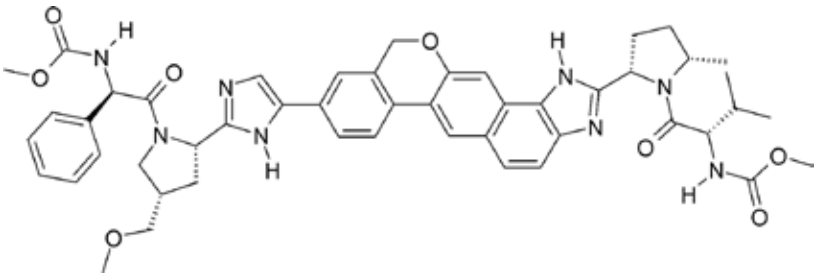
Velpatasvir

First-generation HCV NS5A inhibitors such as ledipasvir are attractive because of the low dose required to inhibit HCV replication, but they show a low barrier to resistance and have little or no antiviral effect on some common NS5A polymorphs and NS5A-inhibitor resistance-associated variants.

Second-generation NS5A inhibitors display improved potency. Velpatasvir (formerly known as GS-5816) demonstrates potent activity against genotypes 1–6 in early studies, displaying low EC50 values (6–130 pM).[6] A once-daily, fixed-dose combination tablet of sofosbuvir (400 mg) with velpatasvir (100 mg) received marketing approval for all 6 genotypes of HCV in the United States in June 2016. The European Medicines Agency approved sofosbuvir/velpatasvir in July 2016.

The chemical structure of velpatasvir is shown in Figure 2.

Figure 2. Structure of velpatasvir



Chemical name:
methyl{(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-4-yl}-1,11-dihydro[2] benzopyrano[3',4':6,7] naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.

Molecular formula:
$C_{49}H_{54}N_8O_8$

Molecular weight:
883 g/mol.

CAS registry number:
1377049-84-7.

6 Report by Gilead Sciences, USA. Conference report of the 48th Annual Meeting of the European Association for the Study of the Liver, 24–28 April 2013, Amsterdam, Netherlands.

IV. OVERVIEW OF VELPATASVIR PATENTS

Eight patents and/or patent applications related to velpatasvir appear to be the most relevant. These patents/applications include the patent/application covering the compound per se. Patents/applications have also been identified that relate to processes for preparing velpatasvir or covering formulations and combinations that include it.

Patent 1 is a broad compound patent. It may be able to block the production, import, marketing and use of generic versions of velpatasvir, depending on the claims allowed/granted.

Patent 2 is the main patent. It would be likely to block the production, import, marketing and use of generic versions of velpatasvir in countries where it is in force.

Patent 3 appears to have been abandoned.

Patent 4 relates to the combination sofosbuvir/velpatasvir. Generic companies would have to develop a different formulation in countries where it is in force.

Patent 5 relates to a solid dispersion of velpatasvir. In most jurisdictions, it appears that this patent family is not being pursued.

Patent 6 relates to crystalline forms of velpatasvir. It may present challenges for generic production; where enforceable, generic companies would have to find another stable solid form of velpatasvir that is suitable to be used in the manufacture of a pharmaceutical product.

Patent 7 relates to synthetic routes that can be used to produce velpatasvir.

Patent 8 relates to methods of treatment. This application needs to be monitored, as some claims might become constraining after amendments and depending on the country.

Table 1 gives a brief overview of the most relevant patents and/or applications. More extensive information on the scope of protection is provided in section V and Annex 1.

Table 1. Overview of key patents on velpatasvir

	Application/ patent number	Applicant	Filing date	Comments
PATENT 1	**WO2012/068234**	Gilead Pharmasset LLC (USA)	16 November 2011	Broad compound patent (Markush formula). Likely to constrain generic market entry where velpatasvir is covered.*
PATENT 2	**WO2013/075029**	Gilead Pharmasset LLC (USA)	16 November 2012	Basic compound patent; claims the API. Likely to constrain generic market entry where it is in force.
PATENT 3	**WO2014/185995**	Gilead Pharmasset LLC (USA)	30 January 2014	Combination sofosbuvir/ velpatasvir with or without another anti-HCV agent.
PATENT 4	**WO2015/030853**	Gilead Pharmasset LLC (USA)	30 January 2014	Combination sofosbuvir/ velpatasvir (with velpatasvir in solid dispersion and sofosbuvir in substantially crystalline form).
PATENT 5	**WO2015/030854**	Gilead Pharmasset LLC (USA)	30 January 2014	Solid dispersion of velpatasvir
PATENT 6	**WO2015/191431**	Gilead Pharmasset LLC (USA)	08 June 2015	Crystalline forms of velpatasvir and its salts, hydrates and solvates
PATENT 7	**WO2015/191437**	Gilead Pharmasset LLC (USA)	08 June 2015	Processes for the preparation of velpatasvir and intermediates thereof.
PATENT 8	**WO2015/084741**	Gilead Pharmasset LLC (USA)	01 December 2014	Methods of treating HCV infection in subjects with cirrhosis, comprising administration of sofosbuvir (1–48 weeks) (100–800 mg) + optionally at least one additional anti-HCV agent (e.g. velpatasvir, voxilaprevir).

* Note: In the European phase, the claims of the PCT application of Patent 1 were amended and limited to a category of compounds that does not include velpastavir. Thus, in the European Patent Organisation Member States, this application is not relevant for velpatasvir.

In other countries, it will be important to check at the national level whether and how the claims of the original PCT application may have been amended. This would be particularly important in countries where Patent 2 has not been filed or has not been granted since, in these countries, Patent 1 may, or may not, be the blocking patent, depending on the actual claims.

V. ANALYSIS OF VELPATASVIR PATENTS/APPLICATIONS

PATENT 1

Title: Antiviral compounds
WO 2012068234 (Gilead Pharmasset (US), filed 16 November 2011)

Summary

The PCT application is for a broad compound patent that claims compounds of Markush formula (I). This Markush formula pertains to five different classes of compounds. The first class includes velpatasvir.

This patent would likely block generic market entry in the countries where it is in force.

Description

The PCT application relates to heterocyclic compounds of general formula (I) or a pharmaceutically acceptable salt thereof for use as antiviral agents in treatment of HCV.

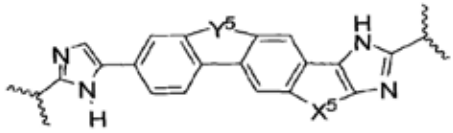
(I) E^{1a}-V^{1a}-C(=O)-P^{1a}- W^{1a}-P^{1b}-C(=O)- V^{1b}- E^{1b}

The compounds falling within the scope of the claims for which protection is sought have the following structural feature: a core W^{1a} which contains at least 2 hetero rings, and is selected from formulas A, B, C, D and E. The core W^{1a} links 2 moieties E^{1a}-V^{1a}-C(=O)-P^{1a}- and E^{1b}-V^{1b}-C(=O)-P^{1b}-.

Thus, a wide range of compounds, falling in five classes, is claimed.

The first class consists of antiviral compounds of formula (I) wherein W^{1a} is of formula A:

A



in which Y^5 is -O-CH_2- or -CH_2-O- and X^5 is -CH_2-CH_2- or -CH=CH-.

Such compounds have a pentacyclic ring system linked to an imidazole ring. Both the pentacyclic ring system and the imidazole ring are substituted by a substituted pyrrolidine.

Velpatasvir falls within the scope of this claimed class of compounds in which Y^5 is –CH_2-O- and X^5 is –CH=CH-. Velpatasvir is specifically claimed at claim 41 of the PCT application (8th compound, p. 1311, within a list of 23 compounds characterized by their chemical structure).

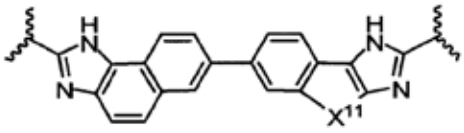
The PCT application has 324 claims, of which 19 are independent.

The claims encompass a large number of compounds and, according to the international preliminary report on

patentability, the number of alternative compounds falling within the scope of the present claims is such that it is unlikely that all of them possess the claimed activity. The claims should represent a reasonable generalization of the examples given in the description and in the examples section. According to the international preliminary report, the applicants failed to provide supporting evidence that all the compounds can be used for the claimed activity.

In the European phase, the compounds claimed were limited to the second class of compounds covered by the original PCT application – i.e. the compounds of invention 2, the subject matter of original claim 3: compounds where W^{1a} is of formula B and in which one or both pyrrolidine groups have a methoxymethyl substituent (amended claim of 14.01.2014).

B



Additionally, the terms alkyl and cycloalkyl have been redefined in accordance with the meaning given in the description (i.e. C_{1-18} alkyl and C_{3-7} alkyl).

As a result of these amendments, the European application no longer covers velpatasvir.

The European examiner found that, after these amendments, the claimed compounds are novel vis-à-vis the prior art, but lack an inventive step.

In a second round of amendments (dated 24.07.2014), the applicants argued that the modification of the pyrrolidine ring can impact on the antiviral activity of the compounds, as supported by biological assays used to analyse the antiviral potency (EC_{50}) of the said compounds.

The application is still under examination.

In another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent and a pharmaceutically acceptable carrier or excipient. The therapeutic agent used in combination with the claimed compound can be interferons, ribavirin and analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants and non-nucleoside inhibitors of HCV.

Finally, the invention also relates to general methods of making the claimed compounds and intermediates thereof.

Observations

The PCT application covers velpatasvir, which is specifically claimed in claim 41 of the PCT application (velpatasvir is structure 8 in a list of 23 compounds characterized by their chemical structure).

However, in the European phase, the applicants have subsequently limited the compounds claimed to only one of the five classes of compounds in the PCT application. As a result, in Europe this application no longer concerns velpatasvir.

The pending or granted claims in countries outside the European Patent Organisation Member States will need to be monitored and checked in order to determine whether or not the application/patent in a given country covers velpatasvir.

PATENT 2

Title: Condensed imidazolylimidazoles as antiviral compounds.
WO 2013/075029 (Gilead Pharmasset, filed 16 November 2012)

Summary

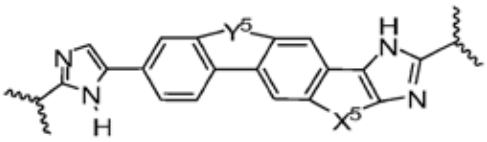
This is the basic compound patent covering velpatasvir. The patent claims velpatasvir (the API) as well as pharmaceutical compositions comprising it and its combination with other HCV agents.

This patent would likely block generic market entry in the countries where it is in force.

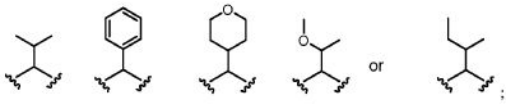
Description

The claimed compounds are a selection from the first class of compounds of formula (I) of PCT application WO-A-2012/068234 (Patent 1). They correspond to the first class of antiviral compounds of Patent 1.

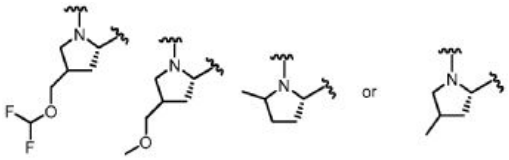
The PCT application provides a compound of formula (I): E^{1a}-V^{1a}-C(=O)-P^{1a}-W^{1a}-P^{1b}-C(=O)-V^{1b}-E^{1b} in which W^{1a} is:



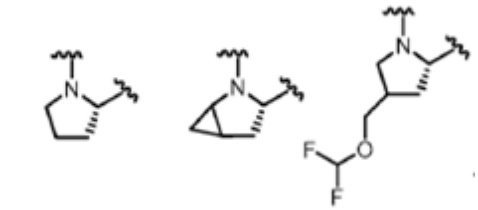
and is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl or cyano; and in which Y^5 is -O-CH_2- or -CH_2-O-; X^5 is -CH_2-CH_2- or -CH=CH-; E^{1a} is -N(H)(alkoxycarbonyl), N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1a}-V^{1a} taken together are R^{9a}; E^{1b} is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1b}-V^{1b} taken together are R^{9b}; V^{1a} and V^{1b} are each independently selected from:

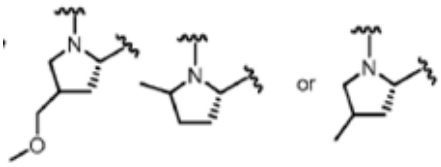


P^{1a} is selected from:

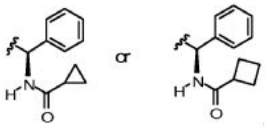


P^{1b} is selected from:





R^{9a} and R^{9b} are each independently:

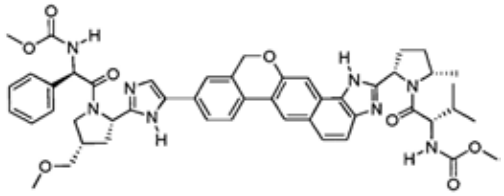


The compounds possess a pentacyclic ring system linked to an imidazole ring, and both the pentacyclic ring system and the imidazole ring are linked to a substituted pyrrolidine.

The International Searching Authority acknowledged the novelty and inventiveness of the claimed subject matter. However, it was found that the claims cover a large number of compounds and the description does not provide enough evidence that all of them possess the claimed function.

On entry into the European phase, the applicants filed an amended set of claims where the compounds claimed were limited to the specific compound or salt thereof of pending claim 12: velpatasvir.

The application has received an intention to grant (09.01.2015).



The present application also provides a pharmaceutical composition comprising claimed compounds or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. Additionally, the present application also discloses a pharmaceutical composition for use in treating HCV. In a further embodiment, the composition comprises at least one additional therapeutic agent for treating HCV; the said therapeutic agent being selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof.

In a preferred embodiment, the compound of formula (I) is methyl{(2S)-1-[(2S,5S)-2-(9-{2-[(2s,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxy methyl) pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7}naphtha [1,2-d]imidazole-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (GS-5816, velpatasvir) and the inhibitor is sofosbuvir.

Finally, the invention discloses general methods of making the claimed compounds and the intermediates thereof.

Observations

Divisional applications have been filed in a number of countries in relation to this PCT application, including in Australia, Canada, China, the European Patent Office, Japan and the Republic of Korea.

PATENT 3

Title: Hepatitis C treatments with sofosbuvir
WO 2014/185995 (Gilead Pharmasset, filed 30 January 2014)

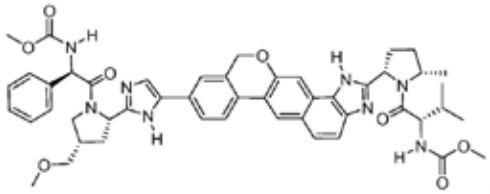
Summary

This application relates to combinations of specific compounds for treating hepatitis C virus, including the combination sofosbuvir/velpatasvir and sofosbuvir/ledipasvir.

Description

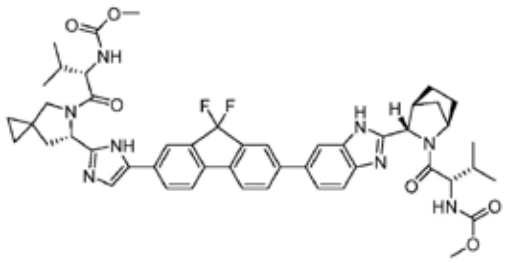
This application relates to methods for treating hepatitis C in a patient, comprising administration of an effective amount of sofosbuvir and an effective amount of a compound selected from the group consisting of Compound I, Compound II, Compound III, Compound IV and Compound V, or combination thereof.

Compound I is a selective inhibitor of non-structural protein 5A (NS5A), velpatasvir (GS-5816) of below formula.



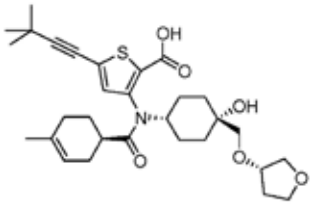
(I)

Compound II is a selective inhibitor of non-structural protein 5A (NS5A), ledipasvir of below formula.



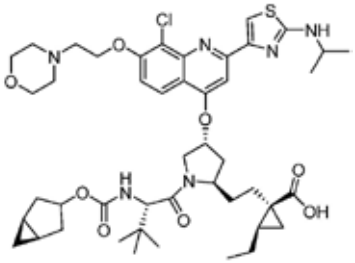
(II)

Compound III is a selective inhibitor of non-structural protein 5B (NS5B), GS-9669 (radalbuvir) of below formula.



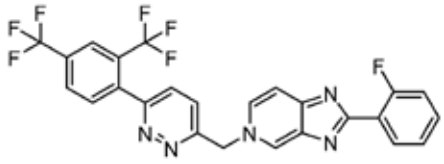
(III)

Compound IV is a selective inhibitor of non-structural protein 3 (NS3), GS-9451 (vedroprevir) of below formula.



(IV)

Compound V is a selective inhibitor of non-structural protein 5B (NS5B), GS-9190 (tegobuvir) of below formula.



(V)

It was observed that when co-administrated with one or more of compounds I–V, the dose of sofosbuvir needed for treating hepatitis C may be reduced (compared to using sofosbuvir alone). This could be due to the following reasons:

Compounds I–V were shown to increase the absorption of sofosbuvir by inhibiting its efflux; they also were shown to inhibit P-glycoprotein 1 (permeability glycoprotein or P-gp) transporter for which sofosbuvir is a substrate; and additionally, sofosbuvir exhibits increased exposure in vivo when administered along with one or more of the compounds I–V.

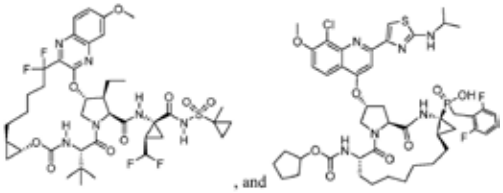
Based upon the above observations, the application claims pharmaceutical compositions comprising a compound selected from compounds I–V, or combination thereof, and an effective amount of sofosbuvir, wherein the amount of sofosbuvir is about 350 mg or less (claim 7).

The application also claims method for treating HCV comprising the administration of an effective amount of compound I–V, or a combination thereof, and an effective amount of sofosbuvir, wherein the amount of sofosbuvir is about 350 mg daily or less (claim 1).

The administration period is usually not longer than about 8 weeks, preferably for a period of about 2 weeks to about 6 weeks and even more preferably for a period of about 4 weeks to about 6 weeks.

In a further embodiment, the methods and pharmaceutical compositions disclosed and claimed can further comprise the administration of another therapeutic agent for treating HCV, and other conditions such as HIV infections. Non-limiting examples of suitable additional therapeutic agents include one or more of: interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers etc.

In a specific embodiment, the additional therapeutic agent used in combination with the pharmaceutical compositions as described is a HCV NS3 protease inhibitor. Non-limiting examples include one or more compounds selected from the group consisting of:



The structure at the left is voxilaprevir (designated in the application as Compound X-7 (see pp. 21-22 [description] of the PCT application)), the structure at the right is GS-9256 (designated in the application as Compound X-9 (see p. 22 [description] of the PCT application)).

Although disclosed, the combination of voxilaprevir with the pharmaceutical composition comprising a compound selected from compound I–V and sofosbuvir as described herein is not claimed.

Observations

According to the written opinion of the International Searching Authority (the EPO) (published 16 November 2015), the combinations of sofosbuvir + Compound III (GS-9885) and sofosbuvir + Compound IV (GS-9451) were already disclosed in WO 2013/059630 A1 (Abbvie, filed 19

October 2012) and the combination of sofosbuvir + Compound II was disclosed in WO 2013/040492 A2 (Gilead Sciences, filed 14 September 2012); thus, these are novelty destroying for the combinations of sofosbuvir with Compound II, Compound III and Compound IV.

However, the combination of sofosbuvir + Compound I (velpatasvir) and combination of sofosbuvir + Compound V could potentially get granted.

The combination of Compound I and sofosbuvir seems novel and inventive, the closest prior art being WO 2012/068234 A2 (Gilead Sciences, filed 16 November 2011), disclosing the use of Compound I alone for treating hepatitis C.

WO 2013/075029 (Gilead Sciences, filed 16 November 2012), which was cited by the examining division, discloses Compound I and its possible co-administration with sofosbuvir, but was published after the priority date of the present application and, thus, was considered as not relevant for the assessment of novelty.

This patent application covers the combination sofosbuvir/velpatasvir and would likely block the production, import, marketing and use of generic versions of sofosbuvir/velpatasvir.

The application has entered European phase (European application N°: 14704266.7).

However, it appears that this patent family is not being pursued.

PATENT 4

Title: Combination formulation of two antiviral compounds
WO 2015/030853 (Gilead Pharmasset, filed 30 January 2014)

Summary

This application relates to the combination sofosbuvir/velpatasvir. In particular, it relates to a combination of sofosbuvir and velpatasvir wherein velpatasvir is substantially amorphous and wherein sofosbuvir is substantially crystalline.

This PCT application, together with Patent 6 in the present report, may present difficulties for generic market entry.

Description

This application relates to a composition comprising a solid dispersion in which velpatasvir is dispersed within a polymer matrix. The starting material of the solid dispersion can be a variety of forms of velpatasvir including crystalline forms, amorphous form, salts thereof, solvates thereof and free base. Substantially amorphous solid of velpatasvir free base is preferred. The polymer matrix is formed by a pharmaceutically acceptable polymer. Preferably, it is a hydrophilic polymer. Most preferably, the polymer is selected from hypromellose, copovidone, povidone or Soluplus®.

Techniques suitable for preparing such solid dispersion include, but are not limited to, melt-extrusion, spray-drying, lyophilizaiton and solution evaporation. Spray dried solid dispersions of velpatasvir provide improved in vivo and in vitro performance. Also, spray drying out of ethanol resulted in high yields across a wide range of spray-drying outlet temperatures, with no material accumulation on the spray dry chamber. Furthermore, velpatasvir demonstrated good chemical stability in the ethanolic feed solution.

The composition also comprises effective amount of sofosbuvir wherein the sofosbuvir is substantially crystalline. Crystalline forms, namely forms 1-6, of sofosbuvir are known from prior art. The most preferred form is the Form 6 as described in US2011/251152, which may be referred to as From 2 by the US Food and Drug Administration.

The pharmaceutical composition may be formulated for immediate release or sustained release dosage forms. The preferred dosage form is tablets. The tablets may be coated to provide a dosage form affording the advantage of prolonged action or to protect from the acid conditions of the stomach. The tablets may also comprise a film coating useful for limiting photolytic degradation.

The tablets may be formulated into monolayer or bilayer tablets. Monolayer tablets comprise the active ingredients co-mixed in a single uniform layer. Bilayer tablets comprise the active ingredients in separated layers, each layer comprising a different active ingredient.

The pharmaceutical composition is effective in treating HCV infected patients. Advantageously, the pharmaceutical composition is pangenotypic, meaning it is useful across all genotypes.

Also disclosed is a combination therapy, comprising the administration of the pharmaceutical composition of the invention and another therapeutic agent for treating HCV and other conditions such as HIV infections.

Finally, the PCT application provides examples on the preparation of the pharmaceutical composition, the drug-drug interaction PK studies, the food effect on the pharmaceutical composition and the safety and efficacy of the interferon-free, ribavirin-free treatment with genotype 1-6 HCV infection.

The PCT application contains 59 claims of which only claim 1 is independent.

Claim 1 is directed at a pharmaceutical composition comprising velpatasvir in substantially amorphous form and sofosbuvir in substantially crystalline form.

Claims 2–46 cover various preferred embodiments of the pharmaceutical composition according to claim 1.

Claims 47–59 cover a method of the use of the pharmaceutical composition according to claim 1.

Observations

The PCT application was filed on 30 January 2014 and published for the first time on 05 March 2015.

The International Searching Authority (EPO) identified Patent 1 as the closest prior art to the subject-matter of claim 1. According to the International Searching Authority, none of the claims involve an inventive step.

The PCT application has entered a number of national phases. No national patent has been granted yet.

PATENT 5

Title: Solid dispersion formulation of an antiviral compound
WO 2015/030854 (Gilead Pharmasset, filed 30 January 2014)

Summary

This PCT application relates to solid dispersion comprising velpatasvir wherein velpatasvir is dispersed within a polymer matrix.

Description

This application relates to a solid dispersion in which velpatasvir is dispersed within a polymer matrix. The starting material of the solid dispersion can be a variety of forms of velpatasvir including crystalline forms, amorphous form, salts thereof, solvates thereof and free base. Substantially amorphous solid of velpatasvir free base is preferred. The polymer matrix is formed by a pharmaceutically acceptable polymer. Preferably, it is a hydrophilic polymer. Most preferably, the polymer is copovidone or Soluplus®.

Spray dried solid dispersions of velpatasvir provide improved in vivo and in vitro performance. Also, spray drying out of ethanol resulted in high yields, across a wide range of spray-drying outlet temperatures, with no material accumulation on the spray dry chamber. Furthermore, velpatasvir demonstrated good chemical stability in the ethanolic feed solution.

A pharmaceutical composition incorporating such solid dispersion of velpatasvir is prepared in a manner well known in the pharmaceutical art. Such pharmaceutical composition may be formulated for immediate release or sustained release dosage forms. The preferred dosage form is tablets. The tablets may be coated to provide prolonged action or to protect from the acid conditions of the stomach. The tablets may also comprise a film coating useful for limiting photolytic degradation.

The PCT application contains 44 claims of which only claim 1 is independent.

Claim 1 is directed at a solid dispersion comprising velpatasvir, which is dispersed within a polymer matrix.

Claims 13–38 relate to pharmaceutical composition comprising the solid dispersion according to claim 1.

Claim 39 is directed at a method of treating hepatitis C comprising administering effective amount of a solid dispersion according to claim 1.

Claims 40–44 relate to a method of making the solid dispersion according to claim 1.

Observations

The PCT application was filed on 30 January 2014 and published for the first time 05 March 2015.

According to the International Searching Authority, none of the claims involve an inventive step.

In most jurisdictions, it appears that this patent family is not being pursued.

PATENT 6

Title: Solid forms of an antiviral compound
WO 2015/191431 (Gilead Pharmasset, filed 08 June 2015)

Summary

This application relates to a number of crystalline solid forms of velpatasvir and its salts, hydrates and solvates.

This PCT application, together with Patent 4 in the present report, may present difficulties for generic market entry.

Description

This PCT application describes stable solid forms screens. A number of crystalline solid forms of velpatasvir and its salts, hydrates and solvates have been selected and their PXRD, DSC, TGA and some other physical properties are displayed.

These solid forms may be used in the manufacture of a medicament for treating hepatitis C or a hepatitis C associated disorder.

The PCT application contains 80 claims of which claims 1, 6, 11, 16, 21, 26, 31, 34, 39, 44, 47, 52, 57, 60, 63, 66, 71, 74, 79 and 80 are independent.

Each one of the independent claims is directed at a crystalline form of velpatasvir or the dihydrobromide, dihydrochloride, phosphate, D-tartrate or L-tartrate salt of velpatasvir.

Observations

The PCT application was filed on 08 June 2015 and published for the first time on 17 December 2015.

According to the written opinion of the International Searching Authority, all claims 1-80 are novel. In assessment of the inventive step, Patent 2 in the present report is considered to represent the closest prior art. The International Searching Authority points out that it would be obvious for a person skilled in the art to screen further crystalline forms of a given compound to provide alternative forms, and notes that “in the absence of any substantiated unexpected property of the claimed solid dispersion, no inventive step can be acknowledged”. Therefore, none of the claims are acknowledged to involve an inventive step.

According to Patent 4, the starting material of the solid dispersion can be a variety of forms of velpatasvir including crystalline forms, amorphous form, salts thereof, solvates thereof and free base. Patent 6 together with Patent 4 may present difficulties for generic companies. Where these patents are granted and enforceable, generic companies would have to look for another stable form suitable to be used as the starting material of the solid dispersion.

PATENT 7

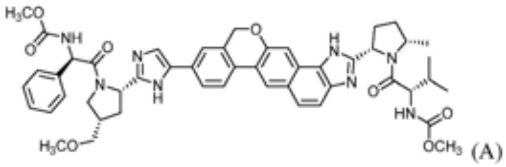
Title: Processes for preparing antiviral compounds
WO 2015/191437 (Gilead Pharmasset, filed 08 June 2015)

Summary

This application relates to processes for the preparation of velpatasvir and compounds that are synthetic intermediates. Processes for the preparation of the synthetic intermediates are also provided.

Description

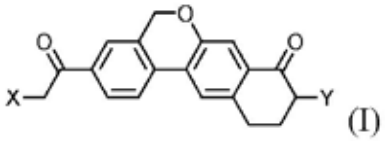
This PCT application discloses processes for making velpatasvir of formula (A):



(A)

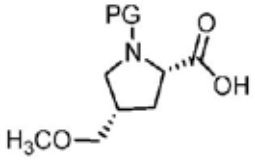
or a salt or solvate thereof, comprising steps of:

(1) Contacting a compound of formula (I), stereoisomer thereof, or mixture of stereoisomer thereof:



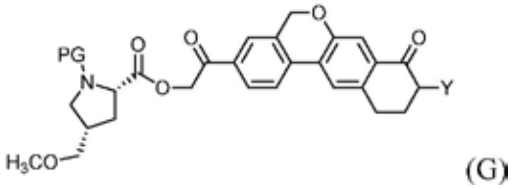
(I)

with a compound of formula (J) or a salt thereof:



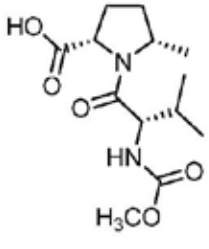
(J)

under conditions sufficient to yield a compound of formula (G) , stereoisomer thereof, or mixture of stereoisomer thereof:



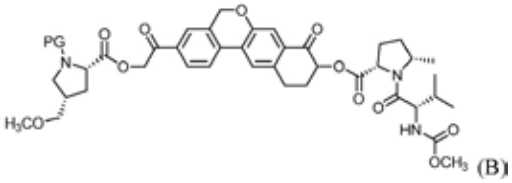
(G)

(2) Contacting the compound of formula (G) with a compound of formula (H) or a salt thereof:



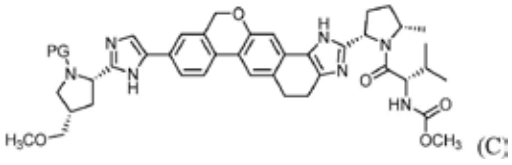
(H)

under conditions sufficient to yield a compound of formula (B), stereoisomer thereof, or mixture of stereoisomer thereof:



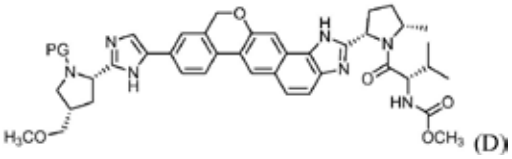
(B)

(3) Cyclizing compound of formula (B) under conditions sufficient to yield a compound of formula (C):



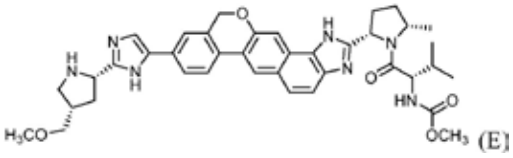
(C)

(4) Dehydrogenating the compound of formula (C) under condition sufficient to yield a compound of formula (D):



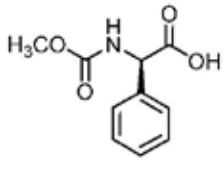
(D)

(5) Deprotecting the compound of formula (D) under conditions sufficient to yield a compound of formula (E) or a salt thereof:



(E)

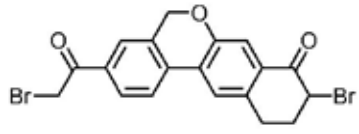
(6) Contacting the compound of formula (E) with a compound of formula (F):



(F)

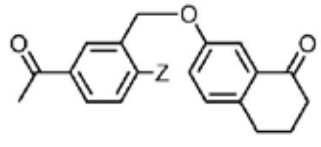
under conditions sufficient to yield a compound of formula (A), wherein PG is an amine protecting group, X and Y are each independently selected from the group consisting of halo, -OSO_2R-, -OP(O)OR and –$OP(O)(OR)_2$ and R is alkyl, haloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteraryl.

Also discloses is a process for the preparation of the starting material compound (I), wherein X is Br and Y is Br which is a compound of formula (I-a), comprising steps of:



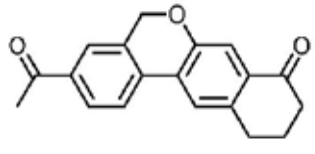
(I-a)

(i) Cyclizing a compound of formula (L):



(L)

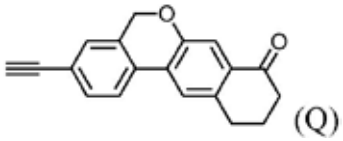
under conditions sufficient to yield a compound of formula (K); and



(K)

(ii) Brominating the compound (K) under conditions sufficient to yield a compound of formula (I-a).

Also discloses is a process for the preparation of earlier starting material of formula (K), comprising derivatizing a compound of formula (Q):

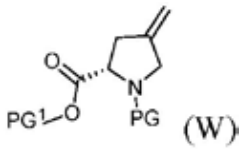


(Q)

under conditions sufficient to yield a compound of formula (K).

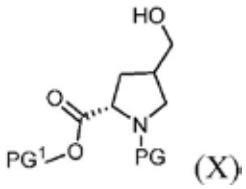
Also discloses is a process for the preparation of intermediate compound (J), comprising steps of:

(a) Contacting a compound of formula (W):



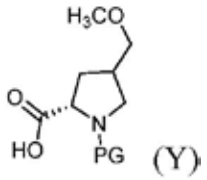
(W)

with a hydrobromation reagent under conditions sufficient to yield a compound of formula (X);



(X)

(b) Methylating the compound of formula (X) under conditions sufficient to yield a compound of formula (Y); and

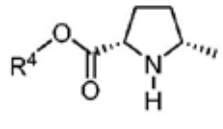


(Y)

(c) Resolving the compound of formula (Y) under conditions sufficient to yield a compound of formula (J), wherein PG is an amine protecting group and PG^1 is a carboxylic acid protecting group.

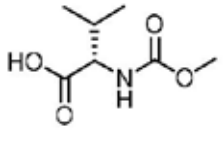
Also discloses is a process for the preparation of intermediate compound (H), comprising steps of:

(A) Contacting a salt of a compound of formula (R):



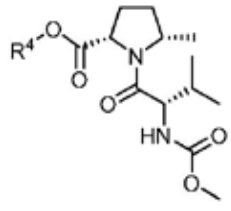
(R)

with a compound of formula (S):



(S)

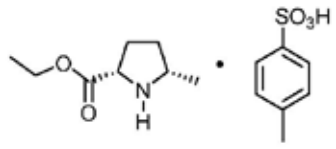
under conditions sufficient to yield a compound of formula (T); and



(T)

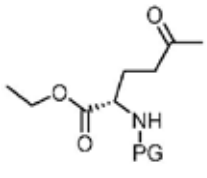
(B) Hydrolyzing the compound of formula (T) under conditions sufficient to yield a compound of formula (H).

Also discloses is a process for the preparation of a salt of intermediate compound (R), which is compound of formula (R-a), comprising the steps of:



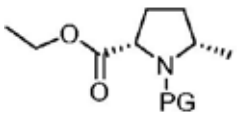
(R-a)

(i) Cyclizing a compound of formula (U'):



(U')

under conditions sufficient to yield a compound of formula (V'); and



(V')

(ii) Contacting the compound of formula (V') with para-toluenesulfonic acid, wherein PG is an amine protecting group, under conditions sufficient to yield the complex of formula (R-a).

The PCT application contains 138 claims of which claims 1, 27, 44, 56, 67, 87, 93, 110, 135 and 137 are independent.

Claim 1 is directed at a process for the preparation of velpatasvir, which is compound of formula (A), or a salt or solvate thereof.

The other independent claims relate to processes for the preparation of various intermediate compounds or starting materials.

Observations

The PCT application was filed on 08 June 2015 and published for the first time on 17 December 2015.

According to the written opinion of the International Searching Authority, Patent 2 is considered to represent the closest prior art and all claims 1–138 are novel and involve an inventive step.

PATENT 8

Title: Methods of treating hepatitis C virus infection in subjects with cirrhosis
WO 2015/084741 (Gilead Pharmasset (USA), filed 01 December 2014)

Summary

This application relates to methods of treating HCV infection in a subject with cirrhosis, comprising administration of an effective amount of sofosbuvir, alone or in combination with another anti-HCV agent.

The method may further include the concomitant administration of at least one additional anti-HCV agent; preferably selected from ribavirin, NS3 protease inhibitors (e.g. voxilaprevir), NS5A (e.g. velpatasvir) and NS5B inhibitors.

The claims to the combinations are only dependent claims.

This application may need to be monitored, as some claims might become constraining for generic market entry after amendments (depending on the country).

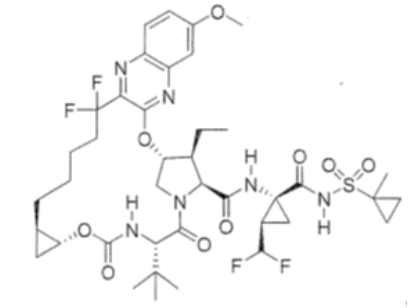
Description

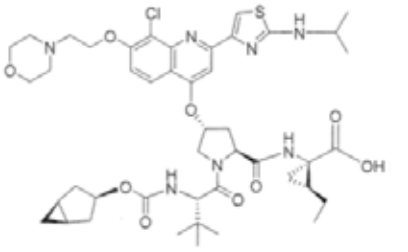
This application describes various methods of treating HCV infection in a subject with cirrhosis.

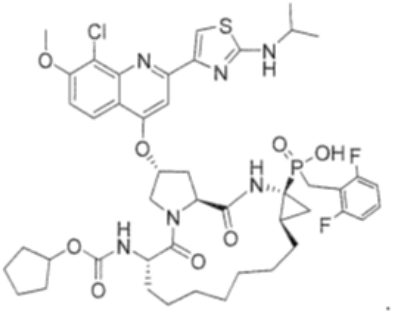
The first method for treating HCV infection in a subject with cirrhosis comprises the administration to the subject of an effective amount of sofosbuvir (claim 1). Sofosbuvir may be administered to the subject with cirrhosis for a duration ranging from about 1 week to about 48 weeks (preferably 4, 8, 12, 24 or 48 weeks).

In various methods, sofosbuvir can be concomitantly administered with at least one additional anti-HCV agent. Examples of additional anti-HCV agents are given; these include, without limitation, interferons and their analogues, ribavirin and its analogues, NS5A inhibitors (e.g. compound A.1: ledispavir; compound A.2: velpatasvir; compound A.4: ombitasvir), NS5B polymerase inhibitors (e.g. compound A.5: radalbuvir [GS-9669]), protease (NS3, NS3/4) inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers (see pp. 8–9 [description] of the PCT application).

In a preferred embodiment, the additional therapeutic agent used in combination is an HCV NS3 protease inhibitor; non-limiting examples including the following compounds:







The first structure corresponds to voxilaprevir (designated as Compound A.9 at [0051] in the description). The second structure corresponds to GS-9451 (vedroprevir) (designated as Compound A.10 at [0052] in the description), and the third structure corresponds to GS-9256 (designated as Compound A.11 at [0053] in the description).

Various methods are disclosed but only some of them are claimed. These include the methods of claim 1 or claim 11, further including administration of at least one additional anti-HCV agent to the subject (dependent claim 21), wherein the additional anti-HCV agent is selected from NS3 protease inhibitor, NS5A inhibitors and NS5B polymerase inhibitors (dependent claim 22), preferably Compound A.1: ledispavir (GS-5885) (dependent claim 23) or compound A.2: velpatasvir (GS-5816) (dependent claim 24), and wherein the subject has less than about 25 IU/ml of HCV RNA 2–24 weeks after the end of the treatment (dependent claim 25).

In other words, voxilaprevir is covered in general terms by dependent claims 21 and 22 but it is not specifically claimed.

Observations

During the search and substantive examination of the PCT procedure, the International Searching Authority (EPO) determined that the application lacked unity. The Authority considered that five inventions were covered by the claims, as follows:

1. Claims 6–10 (completely), 1–5 (partially) and 21–25 (partially): directed to a method of treating HCV infection in a subject with cirrhosis comprising the administration to the subject of an effective amount of Compound 1 (sofosbuvir); the method further includes concomitantly administering to the subject an effective amount of ribavirin.

2. Claims 11–20: directed to a method of treating HCV infection in a subject with cirrhosis comprising the provision to the subject of the 5'-mono-, di- or triphosphate metabolite of Compound 1 (sofosbuvir).

3. Claims 1–5, 21–23 and 25 (all partially): directed to a method of treating HCV infection in a subject with cirrhosis comprising administration to the subject of an effective amount of Compound 1 (sofosbuvir) and Compound A.1 (ledipasvir).

4. Claims 1–5, 21, 22 and 25 (all partially): directed to a method of treating HCV infection in a subject with cirrhosis comprising administration to the subject of an effective amount of Compound 1 (sofosbuvir) and Compound A.2 (velpatasvir).

5. Claims 1–5, 21, 22 and 25 (all partially): directed to a method of treating HCV infection in a subject with cirrhosis comprising administration to the subject of an effective amount of Compound 1 (sofosbuvir) and one additional anti-HCV agent other than ribavirin, Compound A.1 (ledpasvir) or Compound A.2 (velpatasvir).

Only the first invention was subjected to search and examination. According to the International Searching Authority, this first invention is not novel and lacks an inventive step in view of existing prior art.

The non-searched "inventions" (inventions 2–5) may be the subject of one or more divisional applications after the application has entered the regional phase before the EPO.

ANNEX 1. VELPATASVIR PATENT SITUATION IN COUNTRIES

	Patent 1	Patent 2	Patent 3
	WO2012068234A1 **Appl. N°: PCT/US2011/060966**	**WO2013075029A1** **Appl. N°: PCT/US2012/065681**	**WO2014185995A1** **Appl. N°: PCT/US2014/013947**
Applicants	Gilead Pharmasset (USA)	Gilead Pharmasset (USA)	Gilead Pharmasset (USA)
Filing date	16.11.2011	16.11.2012	30.01.2014
Title	Antiviral compounds	Condensed imidazolylimidazoles as antiviral compounds	Hepatitis C treatments with sofosbuvir
Subject matter	Generic compound patent – constraining for generic medicines where granted.	Basic compound patent – constraining for generic medicines where granted.	Sofosbuvir/velpatasvir combination with or without another anti-HCV compound
Priority data	US 61/414,818 – 17.11.2010 US 61/504,924 – 06.07.2011	US 61/560,654 – 16.11.2011	US 61/824,266 – 16.05.2013 US 61/919,108 – 20.12.2013

Patent status

African Regional Intellectual Property Organization *		Appl. N°: AP/P/2013/006877 Under examination	-
Argentina	Appl. N°: 2011PI04276 Publ. N°: 083711A Status not available	-	-
Australia	2011328980 B2 Ganted 2015243078A1 Under examination	2012318253 B2 Granted 2015252077A1 Under examination	-
Brazil		1120130120916 #	-
Canada	2817840A Under examination	2815082 C Granted Expiry: 16.11.2023	-
	-	2884712A1 (divisional) Under examination	-
Chile	-	Publ. N°: 2013001428A1 Status not available	-
China	-	Appl. N°: 201280004097 Publ. N°: 103328480 C Granted Publ. N°: CN105837584A Awaiting examination	-

The INPADOC patent family members for each of the patents/applications are listed in the tables below.

Anticipated expiry dates of Patent 2 have been provided for some jurisdictions. It may be noted that expiry dates can differ between countries due to differences in patent term or because the patent application was filed – on a different date – directly at the concerned office (instead of through the PCT route). The indicated expiry dates therefore should be checked in countries that offer patent term extension/restoration (such as the members of the European Union, Japan and the USA).

	Patent 4	Patent 5	Patent 6	Patent 7
	WO2015030853A1 Appl. N°: PCT/ US2014/013930	WO2015030854A1 Appl. N°: PCT/ US2014/013933	WO2015191431A1 Appl. N°: PCT/ US2015/034649	WO2015191437A1 Appl. N°: PCT/ US2015/034655
Applicants	Gilead Pharmasset (USA)	Gilead Pharmasset (USA)	Gilead Pharmasset (USA)	Gilead Pharmasset (USA)
Filing date	30.01.2014	30.01.2014	08.06.2015	08.06.2015
Title	Combination formulation of two antiviral compounds	Solid dispersion formulation of an antiviral compound	Solid forms of an antiviral compound	Processes for preparing antiviral compounds
Subject matter	Combination of velpatasvir and sofosbuvir	Solid dispersion comprising velpatasvir which is dispersed within a polymer matrix	Crystalline forms of velpatasvir	Processes for preparing velpatasvir and intermediate compounds
Priority data	US61/870,712 – 27.08.2013 US61/898,690 – 01.11.2013 US61/907,308 – 21.11.2013	US61/870,703 – 27.08.2013	US62/010,919 – 11.06.2014	US62/010,813 – 11.06.2014
Patent status				
African Regional Intellectual Property Organization*	-	-	-	-
Argentina	Publ. N°: AR095133A1 Status not available	Publ. N°: AR095132A1 Status not available	-	-
Australia	AU2014311827 Under examination	-	-	-
Brazil		-	-	-
Canada	CA2921160 Under examination	-	-	-
	-	-	-	-
Chile	-	-	-	-
China	Publ. N°: CN105517540 Under examination	-	-	-

	Patent 1	Patent 2	Patent 3
China, Hong Kong SAR	-	Publ. N°: HK1188989Granted	-
Colombia	-	Publ. N°: CO6791562 Granted	-
Costa Rica	-	20130231A Status not available	-
Ecuador	-	Appl. N°: 2013SP12790 Publ. N°: 13012790A Status not available	-
Egypt	-	833/2013 #	-
El Salvador	-	00069 # Appl./Publ. N°: 2013004461 # Granted # 2015004891 #	-
Eurasian Patent Office **	-	EA023644B1 Granted EA2015-91244 Status not available	-
European Patent Office ***	Appl. N°: 11791700 Publ. N°: 2640719A Under examination	2635588 # Appl. N°: 12798525 Publ. N°: 2635588B Expiry date: 16.11.2032	-
	-	Divisional: Appl. N°: 15156617 Publ. N°: 2907816A under examination	-
India	-	4351/DELNP/2013 Awaiting examination	-
Israel	226346 Under examination	226345 Granted 244122, 244123, 244124 Under examination	-
Japan	Appl. N°: 2013-539970A Publ. N°: 2013-542996A JP5905020 B2 Granted Publ. N°: 2016-106149 Under examination	Appl. N°: 2014-542523A Publ. N°: 2015-512860A Under examination	-
Malaysia	-	PI2014001415 #	-
Mexico	-	MX/a/2013/005575 Status not available	-
Moldova	-	Appl. N°: a 2013 0029 Publ. N°: MD4403 Granted Publ. N°: MD2015-0091 Under examination	-
Morocco	-	0034727 # Appl. N°: 20130036 Publ. N°: 34727B1 Granted #	-
New Zealand	Publ. N°: NZ610531 Abandoned Publ. N°: NZ710567 Under examination	Publ. N°: NZ610525 Under examination	-
Organisation Africaine de la Propriété Intellectuelle (OAPI) °	-	1201300262 #	-
Panama	-	90000-01 #	-

	Patent 4	Patent 5	Patent 6	Patent 7
China, Hong Kong SAR	-	-	-	-
Colombia	-	-	-	-
Costa Rica	-	-	-	-
Ecuador	-	-	-	-
Egypt	-	-	-	-
El Salvador	-	-	-	-
Eurasian Patent Office **	Publ. N°: EA201690473 Under examination	-	-	-
European Patent Office ***	Publ. N°: EP3038601 Under examination	-	-	-
	-	-	-	-
India	Appl. N°: IN201627008488 Under examination	-	-	-
Israel	Publ. N°: IL243988 Under examination	-	-	-
Japan	Publ. N°: JP2016538907 Under examination	-	-	-
Malaysia	-	-	-	-
Mexico	MX/a/2016/002185 Under examination	-	-	-
Moldova	-	-	-	-
Morocco	-	-	-	-
New Zealand	Publ. N°: NZ716840 Under examination	-	-	-
Organisation Africaine de la Propriété Intellectuelle (OAPI) °	-	-	-	-
Panama	-	-	-	-

	Patent 1	Patent 2	Patent 3
Peru	-	Appl. N°: 1207-2013/DIN Publ. N°: 1163-2014A Under examination	-
Philippines	-	PH/1/2013/500976 # Granted Appl. N°: 1-2015-502839 #	-
Republic of Korea	Appl. N°: 1020137015201 Publ. N°: 1020140033316A Under examination	Appl. N°: 1020137015198 Publ. N°: 1020140096239A Under examination	-
Russian Federation	-	EA023644 designated In force in RU	-
Serbia	-	Publ. N°: RS54207 Granted	-
Singapore	Appl. N°: 201303622 Publ. N°: 190785A Under examination Appl. N°: 201509456 Under examination	-	-
South Africa	-	2013/04829 # 2014/06307 #	-
Thailand	-	1301002526 #	-
Ukraine	-	Publ. N°: UA110354 C2 Granted	-
Uruguay	Appl. N°: 20110033735 Publ. N°: 33735A Status not available	-	-
USA	Appl. N°: 13/884,578 Publ. N°: 20140018313AUS9156823B2 Granted 20150299213A1 – 9221833B2 Publ. N°: 20150353529 A1 Under examination Publ. N°: 20160083394 A1 Under examination	20130177530A1 – 8575135B2 20130156732A1 – 8940718B2 20140112885A1 – 8921341B2 13/679,862 – 20130164260A1 Application abandoned (30.05.2014) 14/261,325 – 20140309432A1 US9051340B2 Granted Publ. N°: 20150141326 A1 Under examination	Appl. N°: 14/169,004 Publ. N°: 20140343008A Abandoned
Viet Nam	-	1-2013-01721 #	-

	Patent 4	Patent 5	Patent 6	Patent 7
Peru	-	-	-	-
Philippines	-	-	-	-
Republic of Korea	KR20160047522 Under examination	-	-	-
Russian Federation	-	-	-	-
Serbia	-	-	-	-
Singapore	-	-	-	-
South Africa	-	-	-	-
Thailand	-	-	-	-
Ukraine	-	-	-	-
Uruguay	UY35300 Status not available	UY35301 Status not available	-	-
USA	Publ. N°:US2015064253 Under examination	Publ. N°:US2015064252 Abandoned	Publ. N°:US2015361085 Under examination	Publ. N°: US2015361073 Under examination
Viet Nam	-	-	-	-

Notes: Cells with "–" indicate that no patent or patent application has been found in the INPADOC database. This may mean that no patent application was filed, that the application has not been found (e.g. in the case of clerical error), or the application had not been published at the time of the search. Information in this Annex should therefore always be checked at the relevant patent office.

*African Regional Intellectual Property Organization (ARIPO): Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, São Tomé and Príncipe, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

** Eurasian Patent Organization (EAPO): Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian Federation, Tajikistan, Turkmenistan.

*** European Patent Office (EPO): designated contracting states: Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia (former Yugoslav Republic of Macedonia), Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom; Extension states: Bosnia and Herzegovina, Montenegro. Validation states: Moldova, Morocco, Tunisia.

° Organisation Africaine de la Propriété Intellectuelle (OAPI): Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, Equatorial Guinea, Gabon, Guinea, Guinea Bissau, Ivory Coast, Mali, Mauritania, Niger, Senegal, Togo.

Data source: Form 3, submitted to the Indian Patent Office on 10 February 2016.

ANNEX 2. PATENT APPLICATION FILING DATES

Patent 1: EP-A-2640719 – WO-A-2012068234 (Gilead, filed 16.11.2011)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2012/068234	PCT filing: 16.11.2011	
EP-A-2640719	Filing date: 16.11.2011	Under examination
AR-A-083711	Filing date: 16.11.2011	Not available
AU2011-328980 B2	Filing date: 16.11.2011 National entry: 03.04.2013	Granted
AU-A-2015-243078	divisional	Under examination
CA-A-2817840	National entry: 13.05.2013	Under examination
IL-A-226346	National entry: 13.05.2013	Not yet examined
JP-A-2013-542996	Filing date: 09.07.2013	Granted
JP-A-2016-106149	divisional	Under examination
KR-A-20140033316 KR-A-1020137015201	Filing date: 13.06.2013	Not yet examined
NZ610531	Filing date: 16.11.2011	Abandoned
NZ710567	divisional	Under examination
PH/1/2013/500976	National entry: 15.05.2013	Granted
SG-A-190785	National entry: 10.05.2013	Under examination
US-A-2014-0018313 US-B-9156823	Filing date: 16.01.2014	Granted
US-B-9221833	Filing date: 24.04.2015	Granted
US-A-2015-0353529	Filing date: 30.07.2015	Under examination
US-A-2016-0083394	Filing date: 23.11.2015	Under examination
UY-A-33735	National entry: 16.11.2011	Not available

Notes: It will be important to check at the national level whether and how the claims of the original PCT application may have been amended. This would be particularly important in countries where Patent 2 has not been filed or has not been granted (for example, the Philippines) since, in these countries, Patent 1 may, or may not, be the blocking patent, depending on the actual claims.

Patent 2: EP-B-2635588 – WO-A-2013/075029 (Gilead Pharmasset, filed 16.11.2012)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2013/075029	WO 2013/075029	WO 2013/075029
EP-B-2635588	EP-B-2635588*	EP-B-2635588*
EP-A-2907816	EP-A-2907816	EP-A-2907816
AP/P/2013/006877	AP/P/2013/006877	AP/P/2013/006877
AU-A-2012-318253	AU-A-2012-318253	AU-A-2012-318253
AU-A-2015-252077	AU-A-2015-252077	AU-A-2015-252077
CA-A-2815082	CA-A-2815082	CA-A-2815082
CA-A-2884712	CA-A-2884712	CA-A-2884712
CL-A-2013-01428	CL-A-2013-01428	CL-A-2013-01428
CN-A-103328480	CN-A-103328480	CN-A-103328480
CN-A-105837584	CN-A-105837584	CN-A-105837584
HK1188989	HK1188989	HK1188989
CO6791562	CO6791562	CO6791562
CR-A-2013-0231	CR-A-2013-0231	CR-A-2013-0231
EA023644	EA023644**	EA023644**
EA-A-2015-91244	EA-A-2015-91244**	EA-A-2015-91244**
ECSP13012790	ECSP13012790	ECSP13012790
IL-A-226345	IL-A-226345	IL-A-226345
JP-A-2014-542523	JP-A-2014-542523	JP-A-2014-542523
KR-A-10-2014-0096239	KR-A-10-2014-0096239	KR-A-10-2014-0096239
MA-B-34727	MA-B-34727	MA-B-34727
MD4403	MD4403	MD4403
MD-A-2013-0029	MD-A-2013-0029	MD-A-2013-0029
MX/a/2013/005575	MX/a/2013/005575	MX/a/2013/005575
NZ-A-610525	NZ-A-610525	NZ-A-610525
PE-A-1163-2014	PE-A-1163-2014	PE-A-1163-2014
UA110354 C2	UA110354 C2	UA110354 C2
US-B-8575135	US-B-8575135	US-B-8575135
US-B-8921341	US-B-8921341	US-B-8921341
US-B-8940718	US-B-8940718	US-B-8940718
US-B-9051340	US-B-9051340	US-B-9051340
US-A-2013-0164260	US-A-2013-0164260	US-A-2013-0164260
US-A-2015/0141326	US-A-2015/0141326	US-A-2015/0141326

Patent 3: WO-A-2014/185995 (Gilead Pharmasset, filed 30.01.2014)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2014/185995	PCT filing: 30.01.2014	
US-A-2014-0343008	Filing date: 30.01.2014	Abandoned

Notes: This PCT no longer has any active national phase.

Patent 4: WO-A-2015/030853 (Gilead Pharmasset, filed 30.01.2014)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2015/030853	PCT filing: 30.01.2014	
EP-A-3038601	Filing date: 30.01.2014	Under examination
AR-A-095133	Filing date: 30.01.2014	Not available
AU-A-2014-311827	Filing date: 30.01.2014	Under examination
CA-A-2921160	Filing date: 30.01.2014	Under examination
CN-A-105517540	Filing date: 30.01.2014	Under examination
EA-A-2016-90473	Filing date: 30.01.2014	Under examination
IN201627008488	Filing date: 30.01.2014	Under examination
IL-A-243988	Filing date: 30.01.2014	Under examination
JP-A-2016-538907	Filing date: 30.01.2014	Under examination
MX/a/2016/002185	Filing date: 30.01.2014	Under examination
KR-A-2016-0047522	Filing date: 30.01.2014	Under examination
NZ-A-716840	Filing date: 30.01.2014	Under examination
US-A-2015-0064253	Filing date: 30.01.2014	Under examination
UY-A-35300	Filing date: 30.01.2014	Not available

Patent 5: WO-A-2015/030854 (Gilead Pharmasset, filed 30.01.2014)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2015/030854	PCT filing: 30.01.2014	
AR-A-095132	Filing date: 30.01.2014	Not available
US-A-2015-0064252	Filing date: 30.01.2014	Abandoned
UY-A-35301	Filing date: 30.01.2014	Not available

Patent 6: WO-A-2015/191431 (Gilead Pharmasset, filed 08.06.2015)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2015/191431	PCT filing: 08.06.2015	
US-A-2015-0361085	Filing date: 08.06.2015	Under examination

Patent 7: WO-A-2015/191437 (Gilead Pharmasset, filed 08.06.2015)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2015/191437	PCT filing: 08.06.2015	
US-A-2015-0361073	Filing date: 08.06.2015	Under examination

Patent 8: WO-A-2015/084741 (Gilead Pharmasset, filed 01.12.2014)

Legal status of the equivalents:

Patent/application number	Filing date	Legal status
WO 2015/084741	PCT filing: 01.12.2014	
US-A-2015-0150897		