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Innovation in Global Health

Review of the
VOXILAPREVIR
PATENT LANDSCAPE:
A scoping report

March 2017

This report was prepared by Andrew Brown and Amel Garbi (Pharmathen) with input from Karin Timmermans (UNITAID).

CONTENTS

ABBREVIATIONS

DAA	direct-acting antiviral
EPO	European Patent Office
HCV	hepatitis C virus
HIV	human immunodeficiency virus
NS	non-structural
PCT	Patent Cooperation Treaty
PEG-interferon	Pegylated interferon
RNA	ribonucleic acid

1. 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 per cent and 30 per cent of HCV cases worldwide. Together, genotypes 2, 4 and 6 represent around 23 per cent of HCV cases, while genotype 5 accounts for less than 1 per cent.[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 per cent. Some combination regimens may have pan-genotypic efficacy, which would simplify treatment and monitoring. One compound of interest is Gilead's investigational compound GS-9857, or voxilaprevir.

In view of its potential role in future treatment, this report explores the patent landscape of voxilaprevir.

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).
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.

II. METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, namely: SciFinder, PatBase, TotalPatent and Google Patents. Searches were carried out using keywords, semantic searches, International Patent Classification (IPC) searches, chemical structure searches and combinations thereof.

For each of the most relevant patent and/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 Annex 1 represent those for which data are available.

The searches were performed in December 2015. Information for Patent 1 was complemented with data from Form 3 submitted to the Indian Patent Office in April 2016. Searches for Patents 2 and 3 were updated in February 2017.

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 and Amel Garbi (Pharmathen), with input from Karin Timmermans (UNITAID). The patent searches were conducted by Amel Garbi. Pascale Boulet updated the searches for Patent 2 and 3.

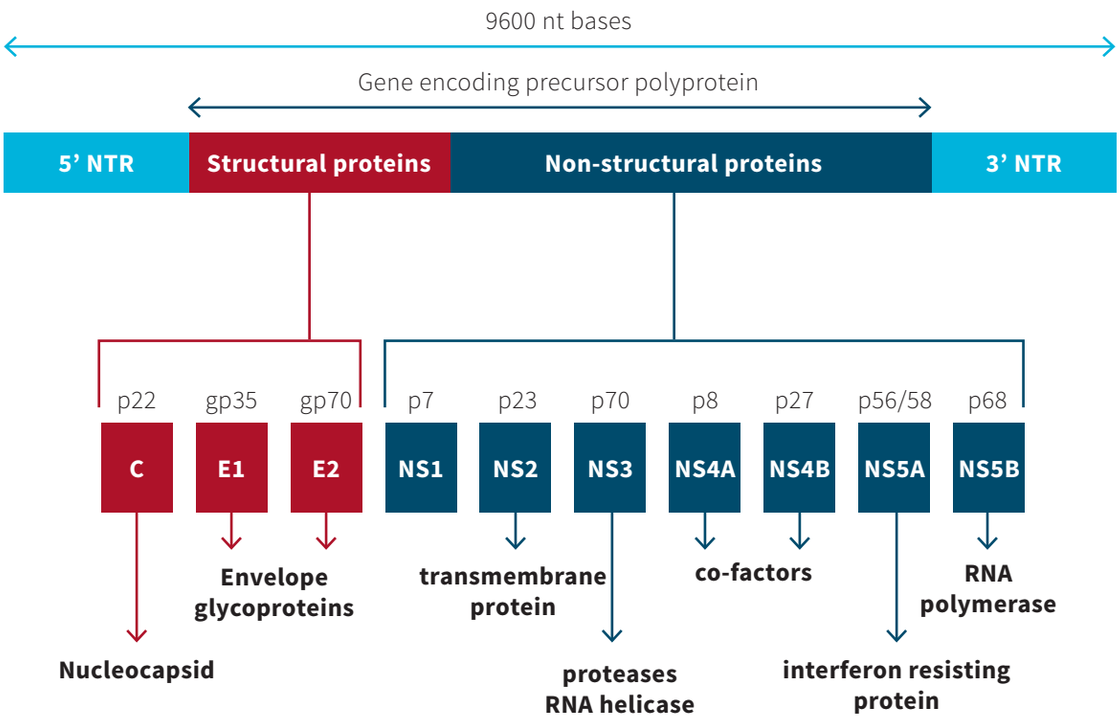
Peter Beyer and Pascale Boulet reviewed a draft version of this report, and provided valuable input and suggestions.

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).

HCV NS3 (serine) protease is one of the most, if not the most, intensively studied anti-HCV targets, possibly because it is one of the best-characterized HCV enzymes but also because of the successful use of protease inhibitors as anti-HIV agents. NS3/4A protease inhibitors work by blocking a viral enzyme (protease) that enables the hepatitis C virus to survive and replicate in host cells.

Several inhibitors of HCV NS3/4A protease have been identified and developed. The first-generation protease inhibitors (boceprevir and telaprevir) were approved for administration in combination with PEG-interferon and ribavirin. Cure rates for boceprevir or telaprevir with PEG-interferon and ribavirin were higher than those of PEG-interferon and ribavirin, but side-effects could be severe and some patients were obliged to stop the treatment.

Second-wave and second-generation HCV protease inhibitors appear to hold promise as they prove to be more potent, less prone to resistance, more convenient (most are once-daily) and more tolerable than the earlier drugs in this class. One of these newer protease inhibitors is voxilaprevir.

In December 2016, Gilead submitted a new drug application to the US Food and Drug Administration for the fixed-dose combination sofosbuvir/velpatasvir/voxilaprevir for treatment of HCV genotypes 1–6.[5] In January 2017, the European Medicines Agency reportedly granted accelerated assessment for sofosbuvir/velpatasvir/voxilaprevir.[6]

5 Gilead submits new drug application to U.S. Food and Drug Administration for the investigational single tablet regimen sofosbuvir/velpatasvir/voxilaprevir. Business Wire. 8 December 2016.

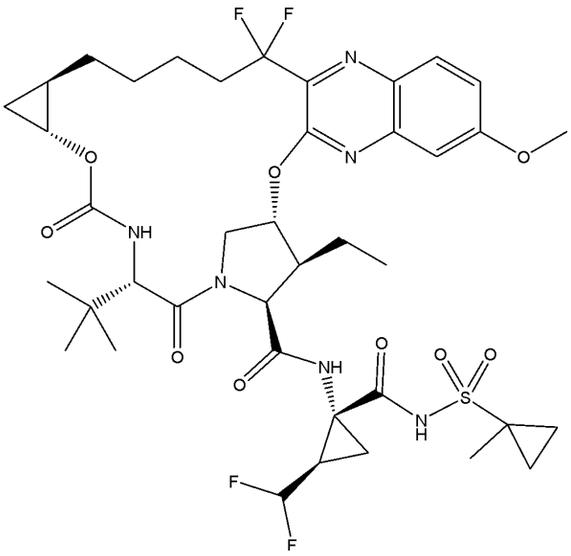
6 European Medicines Agency Validates Gilead's Marketing Authorization Application for Investigational Chronic Hepatitis C Therapy Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX). Business Wire. 20 January 2017.

Voxilaprevir

Voxilaprevir (formerly known as GS-9857) is a novel, fluorinated macrocyclic HCV NS3/4A protease inhibitor in clinical development that is showing efficacy against all genotypes. It also appears to have an improved resistance profile compared to other HCV protease inhibitors (PIs).[7]

The chemical structure of voxilaprevir is shown in Figure 2.

Figure 2. Structure of voxilaprevir



Chemical name:
(1aR,5S,8S,9S,10R,22aR)-5-tert-butyl-N-{(1R,2R)-2-(difluoromethyl)-1-{[(1-methylcyclopropyl) sulfonyl]carbamoyl}cyclopropyl}-9-ethyl-18,18-difluoro-14-methoxy-3,6-dioxo-1,1a,3,4,5 ,6,9,10,18,19,20,21,22,22a-tetradecahydro-8H-7,10-methanocyclopropa [18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoxaline-8-carboxamide.

Molecular formula:
$C_{40}H_{52}F_4N_6O_9S$.

Molecular weight:
766.9034 g/mol.

CAS registry number:
1535212-07-7.

7 Gilead Sciences. Evaluation of transporter and cytochrome P450-mediateddrug-drug interactions with the pan-genotypic HCV NS3/4A protease inhibitor voxilaprevir (GS-9857) or sofosbuvir/velpatasvir/voxilaprevir and phenotypic probe drugs. Presentation at the 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, June 2016, Washington DC, quoting Taylor JG et al., EASL 2015, poster 899.

IV. OVERVIEW OF VOXILAPREVIR PATENTS

Four patents and/or patent applications related to voxilaprevir 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 improved processes for the preparation of voxilaprevir and key intermediates, to new crystalline form(s) of voxilaprevir and their use in compositions, and to combinations and methods of use.

Patent 1 is the compound patent. It would be likely to block the production, import, marketing and use of generic versions of voxilaprevir in countries where it is in force.

Patents 2 and 3, which respectively relate to crystalline forms of voxilaprevir and to processes for the preparation of voxilaprevir and key intermediates, are not considered as constraining patents, provided that generic manufacturers are able to use a different crystalline form and/or prepare voxilaprevir via a different synthetic route using different intermediates.

Patent 4 relates to methods of treating hepatitis C virus infection in a subject with cirrhosis by administering to the subject an effective amount of sofosbuvir. In various methods, sofosbuvir can be concomitantly administered with at least one additional anti-HCV agent. Non-limiting examples include velpatasvir and voxilaprevir.

This application should be monitored because some claims may become constraining after amendments and depending on the country.

At the time of writing, the majority of the patents/applications identified, with the exception of Patent 1, were Patent Cooperation Treaty (PCT) patent applications that had not yet entered national phases.

Patent 1 had entered several national phases; the INPADOC family members are listed in Annex 1. All applications were still under examination; they should be monitored.

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 voxilaprevir

	PCT application number	Applicants	Filing date	Comments
PATENT 1	**WO2014/008285**	Gilead Sciences (USA)	02 July 2013	Broad compound patent; claims voxilaprevir generically and specifically. Likely to be constraining for generic entry.
PATENT 2	**WO2015/100144**	Gilead Sciences (USA)	18 December 2014	Crystalline forms of voxilaprevir. Provided that generic manufacturers source a different form, this patent will not constrain generic entry.
PATENT 3	**WO2015/100145**	Gilead Sciences (USA)	18 December 2014	Process for the preparation of voxilaprevir and key intermediates. Provided that generic manufacturers prepare voxilaprevir by a different synthetic route, via different intermediates, this patent will not constrain generic entry.
PATENT 4	**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).

V. ANALYSIS OF VOXILAPREVIR PATENTS/APPLICATIONS

PATENT 1

Title: Inhibitors of hepatitis C virus
WO 2014/008285 (Gilead Sciences (USA), filed 02 July 2013)

Summary

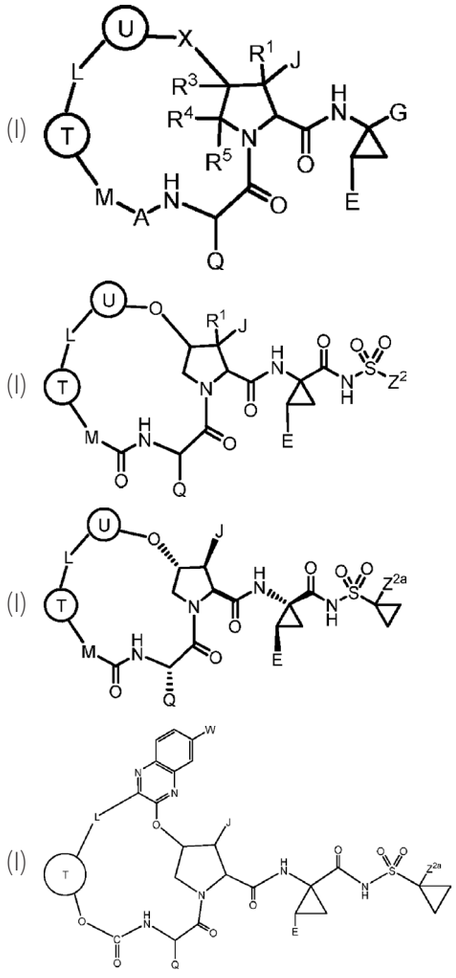
The PCT application, a broad compound patent, claims compounds of Markush formula (I), and the selection compounds of general formulae (II), (III) and (IV), and pharmaceutically acceptable salts thereof.

Voxilaprevir falls within the scope of compounds of general formula (IV). It is generically claimed at claim 1 of the PCT application and is specifically claimed at claims 21 and 22.

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

Description

The PCT application relates to compounds of Markush formula (I) and the selection compounds of general formulae (II), (III) and (IV), or stereoisomer, mixture of stereoisomers, or pharmaceutically acceptable salts thereof, depicted below.



The disclosed compounds are claimed to be useful as inhibitors of the HCV NS3 protease, and thus useful for the prophylactic or therapeutic treatment of HCV infection, either as compounds or as pharmaceutical composition ingredients.

A large number of compounds has been tested and has been shown to inhibit multiple genotypes of the virus.

The PCT application has 84 claims, of which 18 are independent.

The claims are directed to compounds (I), (II), (III) and (IV) or stereoisomers, or mixtures of stereoisomers or pharmaceutically acceptable salts thereof (claims 1, 29, 37 and 42).

Compounds which are selections of the compounds of Markush and general formulae are specifically claimed (claims 21–28 and claim 76 [list of 97 compounds]).

Voxilaprevir falls within the scope of compounds of general formula (IV), compounds comprising a quinoxaline heterocycle, which is connected to the proline moiety through the carbocyclic part of the fused heterocycle.

Voxilaprevir is generically claimed at claim 1 of the PCT application, and specifically claimed at claims 21 and 22. Claim 21 refers to voxilaprevir or a stereoisomer or mixture of stereoisomers or salts thereof (no stereochemistry mentioned); voxilaprevir as a single stereoisomer is claimed at claim 22.

Also claimed are pharmaceutical compositions comprising a compound of any of the claims 1–76, or salts thereof, and a pharmaceutically acceptable excipient (claim 77).

As pharmaceutical composition ingredients, these compounds, or salts thereof, may be the primary active therapeutic agent and, when appropriate, may be combined with at least one additional therapeutic agent including, but not limited to, another HCV antiviral (e.g. interferon, ribavirin analog, HCV NS3 protease inhibitor, NS4B inhibitor, NS5A inhibitor, NS5B inhibitor, alpha-glucosidase inhibitor, a non-nucleoside inhibitor), a hepatoprotectant or another drug for treating hepatitis C virus infection (claim 83).

A method for treating HCV infection comprising administration of a therapeutically effective amount of the compounds of any of claims 1–76 or a salt thereof or pharmaceutical compositions of claim 77 are also claimed (claim 78).

The application finally claims the use of the claimed compounds and pharmaceutical compositions for the prophylactic or therapeutic treatment of hepatitis C virus (claim 81), and for the manufacture of a medicament for treating hepatitis C virus infection (claim 82).

Processes for the preparation of the claimed compounds and their key intermediates are disclosed. General and specific schemes, procedures and examples are provided describing the synthesis of the claimed compounds as well as the intermediates used to prepare the compounds.

Observations

Some of the claimed compounds, namely the ones covered by the scope of claims 1 and 21–28, were considered novel and inventive by the International Searching Authority (European Patent Office, or EPO) as none of the prior art discloses any compounds which are structurally close to these compounds.

According to the International Searching Authority, the compounds that fall within the scope of claims 29–75 lack novelty over the prior art (i.e. WO 2007/016441 A1 [Merck, filed 28 July 2006]) and are not adequately supported by the description.

Upon entry into the European phase (17 December 2014), and following the comments made by the International Searching Authority (20 January 2015), the applicants submitted a set of amended claims (23 March 2015). The amended claims have been limited to the subject matter of original claims 1–28 for which both novelty and inventive step were conceded by the examiner.

After these amendments, the application still covers voxilaprevir per se, pharmaceutical compositions comprising it – either as a sole active ingredient or, when appropriate, combined with at least one additional therapeutic agent, including but not limited to, other HCV antivirals – and its methods of use.

The application is still under examination and should be monitored.

This patent, when granted, would be likely to block generic market entry in the countries where it is in force.

PATENT 2

Title: Crystalline forms of a macrocyclic HCV NS3 inhibiting tripeptide
WO 2015/100144 (Gilead Sciences (USA), filed 18 December 2014)

Summary

This PCT application relates to crystalline forms of voxilaprevir.

This patent is not considered as constraining for generic market entry, provided that the generic manufacturer uses a different crystalline form.

Description

The PCT application discloses:

- 17 crystalline voxilaprevir solvate forms (such as the ethyl acetate, isopropyl acetate, ethanol, isopropanol, methanol, tetrahydrofuran, 2-methyl tetrahydrofuran, toluene, methyl tert-butyl ether, dimethyl acetamide and dimethylformamide, but also the hydrates [hemihydrate, dihydrate, tetrahydrate]);
- 4 crystalline voxilaprevir anhydrous forms; and
- 14 crystalline forms of salts or co-crystals of voxilaprevir (such as the sodium, potassium, meglumine, piperazine, choline, dimethyl aminoethanol, 1-(2-hyrdoxyethyl) pyrrolidine, lysine and arginine).

These crystalline forms are characterized by peaks from the X-ray powder diffractogram, as determined on a diffractometer using Cu-Kα radiation. In addition to the X-ray powder diffraction patterns, the differential scanning calorimetry (DSC) curves, the thermogravimetric analysis (TGAs) and the dynamic vapour sorptions (DVS) of the disclosed forms are given.

The application discloses crystalline forms I–XXI, but only crystalline forms I–XII are claimed. As mentioned above, the PCT application also discloses crystalline forms of salts or co-crystals of voxilaprevir but does not claim them.

Another embodiment of the invention is directed to a composition comprising one or more of voxilaprevir forms I–XXI together with one or more pharmaceutically acceptable carriers or excipients. Additionally, a method for treating a subject suffering from hepatitis C virus comprising administration to the subject of a therapeutically effective amount of any one of voxilaprevir forms I–XXI is provided.

Pharmaceutical compositions comprising a compound selected from the claimed crystalline forms (i.e. forms I–XII only) and a pharmaceutically acceptable excipient are claimed (claim 33).

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a voxilaprevir crystalline form, selected from disclosed forms I–XXI, in combination with at least one additional therapeutic agent. The

additional therapeutic agent includes, without limitation, one or more of the following: interferons, ribavirin and analogs, NS3 protease inhibitors, NS5A inhibitors, NS5B inhibitors, alpha-glucosidase-1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, nucleosides analogs and other drugs for treating HCV infection. The additional antiviral agent should preferably not be an interferon, ribavirin or a ribavirin analog. Even more preferably, the pharmaceutical composition should include voxilaprevir crystalline form and one or more of an NS5A inhibitor and/or an NS5B inhibitor.

A method of treating a subject with HCV infection is claimed (claim 34) comprising administration to the subject of a therapeutically effective amount of one of the claimed crystalline forms and a pharmaceutically acceptable excipient. This method can, optionally, further include the administration to the subject of at least one further anti-HCV agent (claim 35).

Finally, processes for making the claimed crystalline forms I–XII are claimed (claims 36–47).

Observations

The PCT application has not yet entered any national phase.

The PCT application has 47 claims, of which 26 are independent.

The written opinion of the International Searching Authority (EPO), published on 02 July 2015, found that all claims were novel and involve an inventive step.

The International Searching Authority noted that the application suffers from lack of clarity, chiefly because the claimed crystalline forms are defined by only three or four peak positions. This is insufficient for a person skilled in the art; the 10 strongest reflections are generally required for complete characterization of a given polymorph.

This patent is not considered as constraining for generic market entry provided that the generic manufacturer uses a different crystalline form.

PATENT 3

Title: Synthesis of a macrocyclic HCV NS3 inhibiting tripeptide
WO 2015/100145 (Gilead Sciences (USA), filed 18 December 2014)

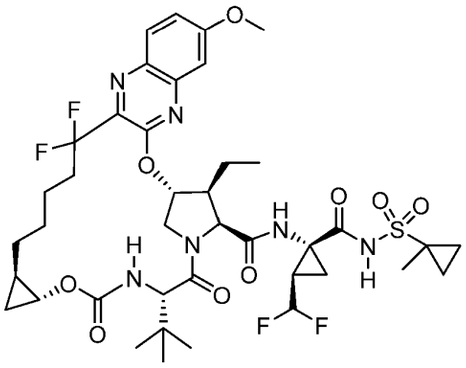
Summary

The PCT application provides and claims processes for the preparation of voxilaprevir. The application also provides and claims compounds and processes for the preparation of key intermediates.

This patent is not considered as constraining for generic market entry, provided that the generic producer manufactures voxilaprevir using different key intermediates and a different synthetic route for the preparation of voxilaprevir.

Description

The application provides, in a first embodiment, a process for making compound (I) (voxilaprevir), or a co-crystal or salt thereof, according to Route I (claim 5 of the PCT application):

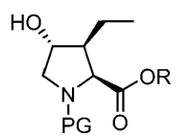


I

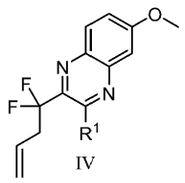
Route I:

The process for the preparation of voxilaprevir, or a co-crystal or a salt thereof, comprises:

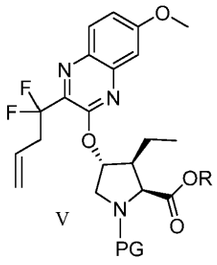
(a) contacting a compound (III), or a co-crystal or salt thereof, with a compound (IV) or a co-crystal or salt thereof under O-arylation conditions to provide a compound (V) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl, PG is a protective group and R^1 is a leaving group;



III

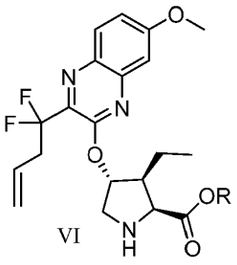


IV



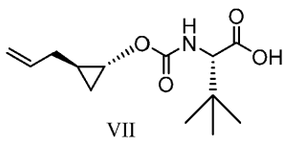
V

(b) subjecting compound (V), or a co-crystal or salt thereof, to N-deprotection conditions to provide compound (VI) or a co-crystal or salt thereof;

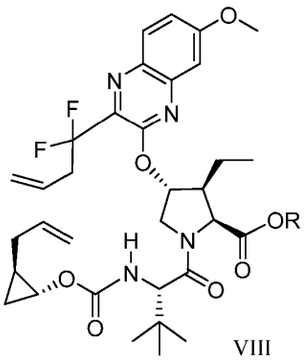


VI

(c) contacting compound (VI), or a co-crystal or salt thereof, with a compound (VII) or a co-crystal or salt thereof under amide coupling conditions to provide a compound (VIII) or a co-crystal or salt thereof;

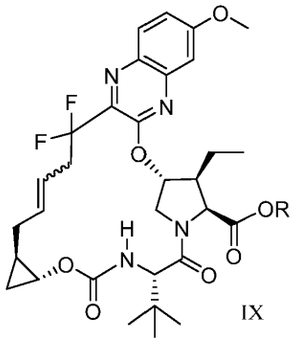


VII



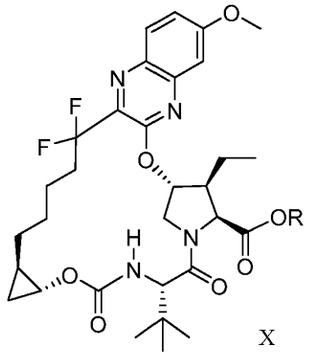
VIII

(d) performing ring closing metathesis of compound (VIII), or a co-crystal or salt thereof, to provide compound (IX) or a co-crystal or salt thereof;



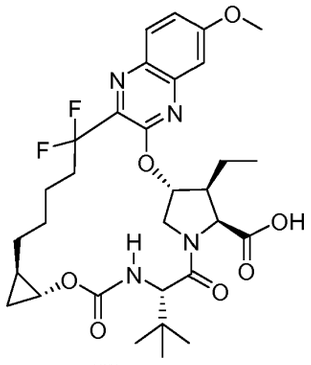
IX

(e) hydrogenating compound (IX), or a co-crystal or salt thereof, in the presence of a catalyst to provide a compound (X) or a co-crystal or salt thereof;



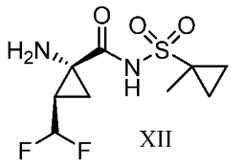
X

(f) hydrolysing compound (X), or a co-crystal or salt thereof, to provide compound (XI) or a co-crystal or salt thereof;



XI

(g) contacting compound (XI), or a co-crystal or salt thereof, with compound (XII) or a co-crystal or salt thereof under amide coupling conditions to provide voxilaprevir.



XII

In relation to Route I, the application additionally provides processes for the preparation of the key intermediates (V), (VI), (VIII) and (IX).

The process for the preparation of key compound (V), or a co-crystal or salt thereof, comprises contacting compound (III) or a co-crystal or salt thereof with a compound (IV) or a co-crystal or salt thereof under O-arylation conditions to provide compound (V) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl, PG is a protective group and R^1 is a leaving group (see step a of process Route I and claim 1).

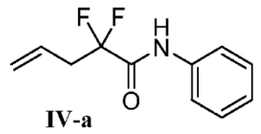
The process for the preparation of key compound (VI), or a co-crystal or salt thereof, comprises subjecting compound (V) or a co-crystal or salt thereof, to N-deprotection conditions to provide the compound (VI) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl and PG is a protective group (see step b of process Route I, and claim 2).

The process for the preparation of key compound (VIII), or a co-crystal or salt thereof, comprises contacting compound (VI) or a co-crystal or salt thereof with a compound (VII) or a co-crystal or salt thereof, under amide coupling conditions to provide compound (VIII) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl (see step c of process Route I and claim 3).

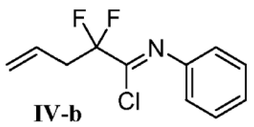
The process for the preparation of key compound (IX), or a co-crystal or salt thereof, comprises performing ring closing metathesis of compound (VIII) or a co-crystal or salt thereof to provide compound (IX) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl (see step d of process Route I and claim 4).

Key compounds (IV), (V), (VI), (VII) and (VIII) are claimed per se (claims 16, 17, 18, 19 and 20 respectively).

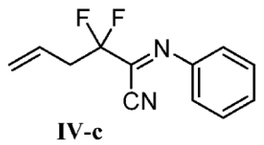
Additionally, key compounds (IV-a), (IV-b), (IV-c) and (IV-d), which are precursors of compound (IV), wherein R_1 is a leaving group (e.g. Cl), and compound M3, which is a precursor of compound (VII), are also claimed (claims 28, 29, 30, 31 and 32).



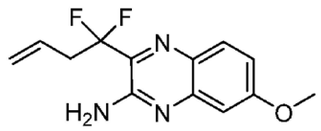
IV-a



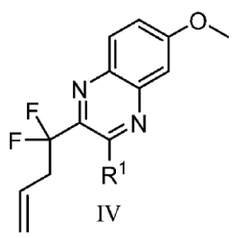
IV-b



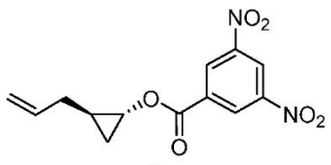
IV-c



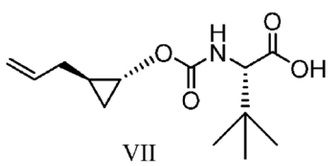
IV-d



IV

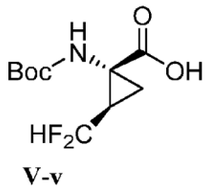


M3

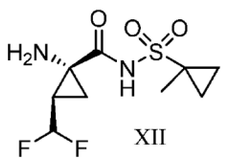


VII

Finally, a process for the preparation of compound (V-v), precursor of compound (XII), is claimed (claim 15).



V-v



XII

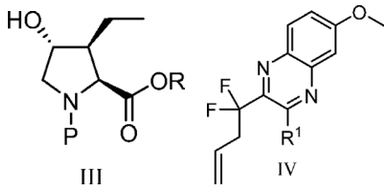
Route I differs from the prior art in that the ring-closing metathesis step occurs at a different position, providing higher efficiency and higher overall yield.

In another embodiment, the application provides a further process for making voxilaprevir, or a co-crystal or a salt thereof, according to Route II (claim 9 of the PCT application).

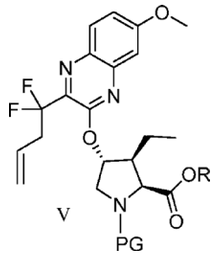
Route II:

The process for the preparation of voxilaprevir, or a co-crystal or salt thereof, comprises:

(a) contacting a compound (III), or a co-crystal or salt thereof, with a compound (IV) or a co-crystal or salt thereof under O-arylation conditions to provide compound (V) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl, PG is a protective group and R1 is a leaving group;

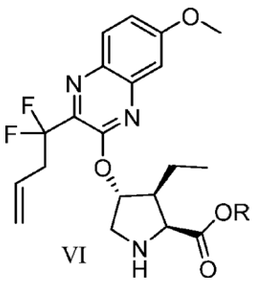


III IV



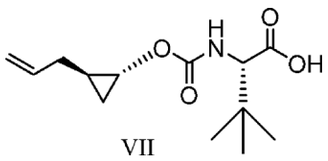
V

(b) contacting compound (V), or a co-crystal or salt thereof, with an acid under N-deprotection conditions to provide compound (VI) or a co-crystal or salt thereof;

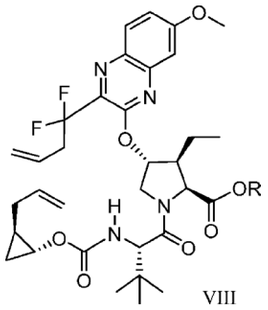


VI

(c) contacting compound (VI), or a co-crystal or salt thereof, with a compound (VII) or a co-crystal or salt thereof under amide coupling conditions to provide compound (VIII) or a co-crystal or salt thereof;

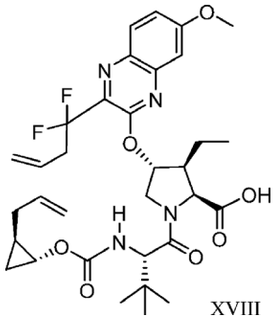


VII



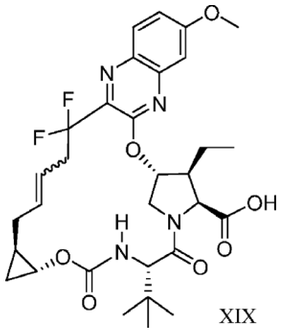
VIII

(d) hydrolysing compound (VIII), or a co-crystal or salt thereof, to provide compound (XVIII) or a co-crystal or salt thereof;



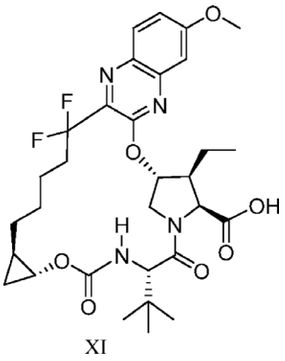
XVIII

(e) performing ring-closing metathesis of compound (XVIII), or a co-crystal or salt thereof, in the presence of a catalyst to provide compound (XIX) or a co-crystal or salt thereof;



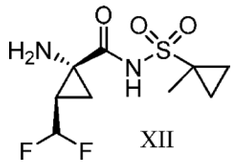
XIX

(f) hydrogenating compound (XIX), or a co-crystal or salt thereof, in the presence of a catalyst to provide compound (XI) or a co-crystal or salt thereof;

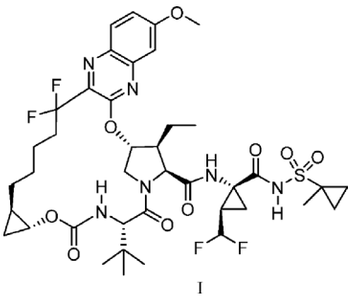


XI

(g) contacting compound (XI), or a co-crystal or salt thereof, with a compound (XII) or a co-crystal or salt thereof under amide coupling conditions to provide voxilaprevir or a co-crystal or salt thereof.



XII



I

In relation to Route II, the application additionally provides processes for the preparation of the key intermediates (XVIII), (XIX) and (XI).

The process for the preparation of key compound (XVIII), or a co-crystal or salt thereof, comprises hydrolyzing compound (VIII) or a co-crystal or salt thereof to provide compound (XVIII) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl (see step d of process Route II and claim 6).

The process for the preparation of key compound (IX), or a co-crystal or salt thereof, comprises performing ring-closure metathesis of compound (XVIII) or a co-crystal or salt thereof in the presence of a catalyst to provide compound (XIX) or a co-crystal or salt thereof (see step e of process Route II, and claim 7).

The process for the preparation of key compound (XI), or a co-crystal or salt thereof, comprises hydrogenating compound (XIX) or a co-crystal or salt thereof in the presence of a catalyst to provide compound (XI) or a co-crystal or salt thereof (see step f of process Route II and claim 8).

Key compounds (XVIII) and (XIX) are claimed per se (claims 26 and 27 respectively).

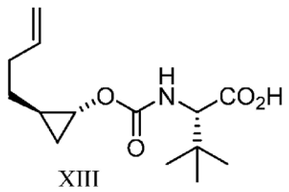
Route II differs from Route I in that steps (d), (e) and (f) are different. In Route I, compound (VIII) was first submitted to ring-closing metathesis, then to hydrogenation and then to hydrolization reactions; in Route II, compound (VIII) is first hydrolyzed to provide compound (XVIII) which is then subjected to ring-closure metathesis to give compound (XIX) which is hydrogenated to give compound (XI).

In yet another embodiment, the application provides a further process for making voxilaprevir, or a co-crystal or a salt thereof, according to Route III (claim 14 of the PCT application).

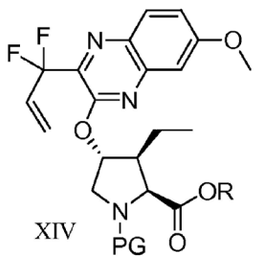
Route III:

The process for the preparation of voxilaprevir, or a co-crystal or a salt thereof, comprises:

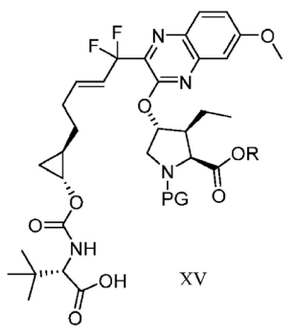
(a) contacting a compound (XIII), or a co-crystal or salt thereof, with a compound (XIV) or a co-crystal or salt thereof under cross-metathesis conditions to provide compound (XV) or a co-crystal or salt thereof, wherein R is C_{1-6} alkyl and PG is a protective group;



XIII

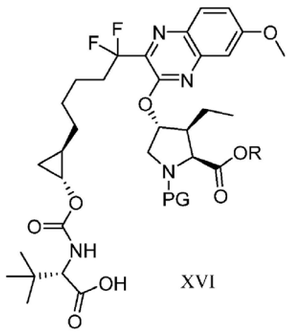


XIV



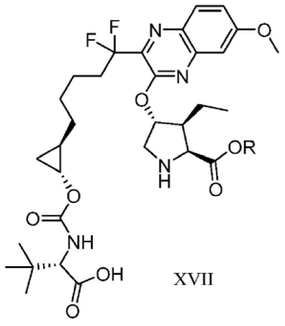
XV

(b) hydrogenating compound (XV), or a co-crystal or salt thereof, in the presence of a catalyst to provide compound (XVI) or a co-crystal or salt thereof;



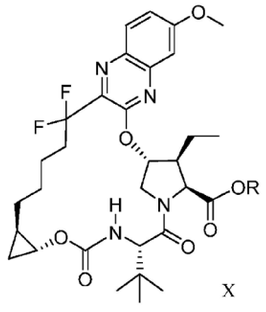
XVI

(c) subjecting compound (XVI), or a co-crystal or salt thereof, to N-deprotection conditions to provide compound (XVII) or a co-crystal or salt thereof;



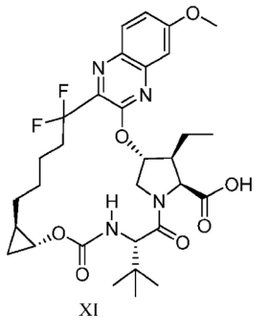
XVII

(d) contacting compound (XVII) with an amide coupling agent under lactamization conditions to give compound (X) or a co-crystal or salt thereof;



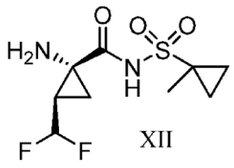
X

(e) hydrolysing compound (X), or a co-crystal or salt thereof, to provide a compound (XI) or a co-crystal or salt thereof;



XI

(f) contacting compound (XI), or a co-crystal or salt thereof, with compound (XII) or a co-crystal or salt thereof under amide coupling conditions to provide voxilaprevir or a co-crystal or salt thereof.



XII

In relation to Route III, the application additionally provides processes for the preparation of the key intermediates (XV), (XVI), (XVII) and (X).

Route III differs from Route I and Route II in that the process starts with different starting compounds (i.e compounds (XIII) and (XIV)) and thus proceeds via different intermediates until the preparation of key compound (XI), which at the final step is contacted with compound (XII) to provide the desired compound (voxilaprevir).

The process for the preparation of key compound (XV), or a co-crystal or salt thereof, comprises contacting a compound (XIII) or a co-crystal or salt thereof with a compound (XIV) or a co-crystal or salt thereof, wherein R is C1-6

alkyl and PG is a protective group, under cross-metathesis conditions to provide compound (XV) or a co-crystal or salt thereof (see step a of process Route III and claim 10).

The process for the preparation of key compound (XVI), or a co-crystal or salt thereof, comprises hydrogenating compound (XV) or a co-crystal or salt thereof in the presence of a catalyst to provide compound (XVI) or a co-crystal or salt thereof (see step b of process Route III, and claim 11).

The process for the preparation of key compound (XVII), or a co-crystal or salt thereof, comprises subjecting compound (XVI) or a co-crystal or salt thereof to N-deprotection conditions to provide compound (XVII) or a co-crystal or salt thereof (see step c of process Route III and claim 12).

The process for the preparation of key compound (X), or a co-crystal or salt thereof, comprises contacting compound (XVII) or a co-crystal or salt thereof with an amide coupling agent under lactamization conditions to give compound (X) or a co-crystal or salt thereof (see step d of process Route III and claim 13).

Key compounds (XIII), (XIV), (XV), (XVI) and (XVII) are claimed per se (claims 21, 22, 23, 24 and 25 respectively).

Observations

The PCT application has not yet entered any national phase.

The PCT application has 32 claims, all of which are independent.

As described above, the PCT application discloses and claims three different routes for the preparation of voxilaprevir. Additionally, the application discloses and claims novel key intermediates and processes for their preparation.

The International Search Report, issued by the International Searching Authority (EPO), mentions lack of unity of invention; it considers that there are five (5) inventions:

1. claims 1–14, 16–18, 20 and 22–28;
2. claim 15, directed at the process for the preparation of compound V-v;
3. claims 19 and 21, directed at compounds VII and XIII per se;
4. claim 29, directed at compound M3 per se; and
5. claims 30–32 which are directed to compounds Iva, Iv-b and IV-c.

The written opinion of the International Searching Authority, published on 2 July 2015, has been established only with respect to invention 1 (i.e. claims 1–14, 16–18, 20 and 22–28). These claims were found to be novel, to involve an inventive step and to be industrially applicable.

This patent is not considered as constraining for generic market entry, provided that the generic supplier manufactures voxilaprevir by a route different from the claimed ones and via different key intermediates.

PATENT 4

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).

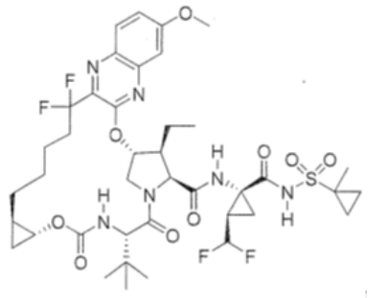
Description

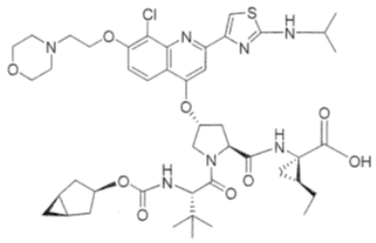
This application describes various methods of treating HCV infection in a subject with cirrhosis.

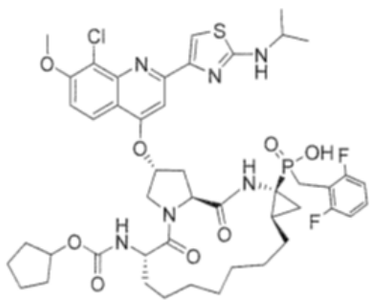
The first method for treating HCV infection in a subject with cirrhosis comprises the administration to the subject of an effective amount of sofosbuvir (claim 1). Sofosbuvir may be administered to the subject with cirrhosis for a duration ranging from about 1 week to about 48 weeks (preferably 4, 8,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

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

The equivalents were identified (INPADOC family) and, where possible, the legal status of each equivalent was checked on the websites of the relevant patent offices.

Expiry dates in countries that offer patent term extension should be checked. If voxilaprevir is approved for use, it is likely that the originator will apply for the patent term to be extended; countries that offer extension/ restoration of the patent term include the members of the European Union, Japan and the USA.

	Patent 1	Patent 2	Patent 3	Patent 4
	WO2014008285A Appl. N°: PCT/ US2013/049119	**WO2015100144A Appl. N°: PCT/ US2014/071310**	**WO2015100145A Appl. N°: PCT/ US2014/071319**	**WO2015084741A1 Appl. N°: PCT/ US2014/067965**
Applicants	Gilead Sciences (USA)	Gilead Sciences (USA)	Gilead Sciences (USA)	Gilead Pharmasset (USA)
Filing date	02 July 2013	18 December 2014	18 December 2014	01 December 2014
Title	Inhibitors of hepatitis C virus	Crystalline forms of a macrocyclic HCV NS3 inhibiting tripeptide	Synthesis of a macrocyclic HCV NS3 inhibiting tripeptide	Methods of treating hepatitis C virus infection in subjects with cirrhosis
Subject matter	Basic compound patent. Generic and specific compound claim.	Crystalline solvates, including the hydrates and anhydrous crystalline forms of voxilaprevir and processes for making them; compositions comprising them and method for treating HCV patient by administration of said crystalline forms either alone or in combination with at least one anti-HCV agent.	Processes for the preparation of key intermediates and for the preparation of voxilaprevir. New key intermediates compounds are claimed per se.	Methods of treating HCV infection in subjects with cirrhosis comprising administration of sofosbuvir plus, optionally, at least one additional anti-HCV agent (examples include velpatasvir and voxilaprevir).
Priority data	US61/667,806: 03 July 2012 US61/798,524: 15 March 2013	US 61/920,427: 23 December 2013	US 61/920,446: 23 December 2013	US 61/910,631: 02 December 2013

	Patent 1	Patent 2	Patent 3	Patent 4
Patent status				
African Regional Intellectual Patent Office*	201408166D0 Status not available	-	-	-
Argentina	091661A1 Under examination	-	-	-
Australia	2013286729B2 Granted Expiry: 02 July 2033	2014370124A1	2014370125A1	-
Bolivia	SP-00204-2013 #	-	-	-
Brazil	1120140330808 #	-	-	-
Canada	2877005A1 Request for examination (12 November 2015)	2934049A1	2934537A1	-
Chile	3634-2014 #	-	-	-
China	104540832A Request for examination (22 July 2015)	-	105849118A Request for examination (7 September 2016)	-
China, Hong Kong SAR		-	-	-
Colombia	7160104A2 Status not available	-	-	-
Costa Rica	2015-0045A status not available	-	-	-
Eurasian Patent Office**	201492214A1 Under examination Published with search report in October 2015.	-	201691031A1	-
Ecuador	2015-2066 #	-	-	-
Egypt	2100/2014 #	-	-	-
El Salvador	20150017587 #	-	-	-
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Notes: Cells with "–" indicate that no patent or patent application has been found in the INPADOC database. This may mean that no patent application has been filed, that the patent application has not been found (e.g. in the case of clerical error), or the patent 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, Tanzania, Uganda, Zambia, Zimbabwe.

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° The Patent Office of the Cooperation Council for the Arab States of the Gulf (Gulf Cooperation Council or GCC) includes the following countries: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates.

°° 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 26 April 2016.