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Review of the GLECAPREVIR PATENT LANDSCAPE: A scoping report

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This report was prepared by Haining Ji (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
RNA	ribonucleic acid
USPTO	United States Patent and Trademark Office

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. One compound of interest is AbbVie's investigational compound ABT-493, or glecaprevir.

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

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 key words, semantic searches, International Patent Classification (IPC) searches, chemical structure searches and combinations thereof.

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 Annex 1 represent those for which INPADOC data are available.

The searches were carried out in December 2016. The analysis of the identified patents and patent applications was undertaken on the basis of the international phase and the European phase prosecution unless otherwise indicated.

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 Haining Ji (Pharmathen) with input from Karin Timmermans (UNITAID). The patent searches were conducted by Haining Ji.

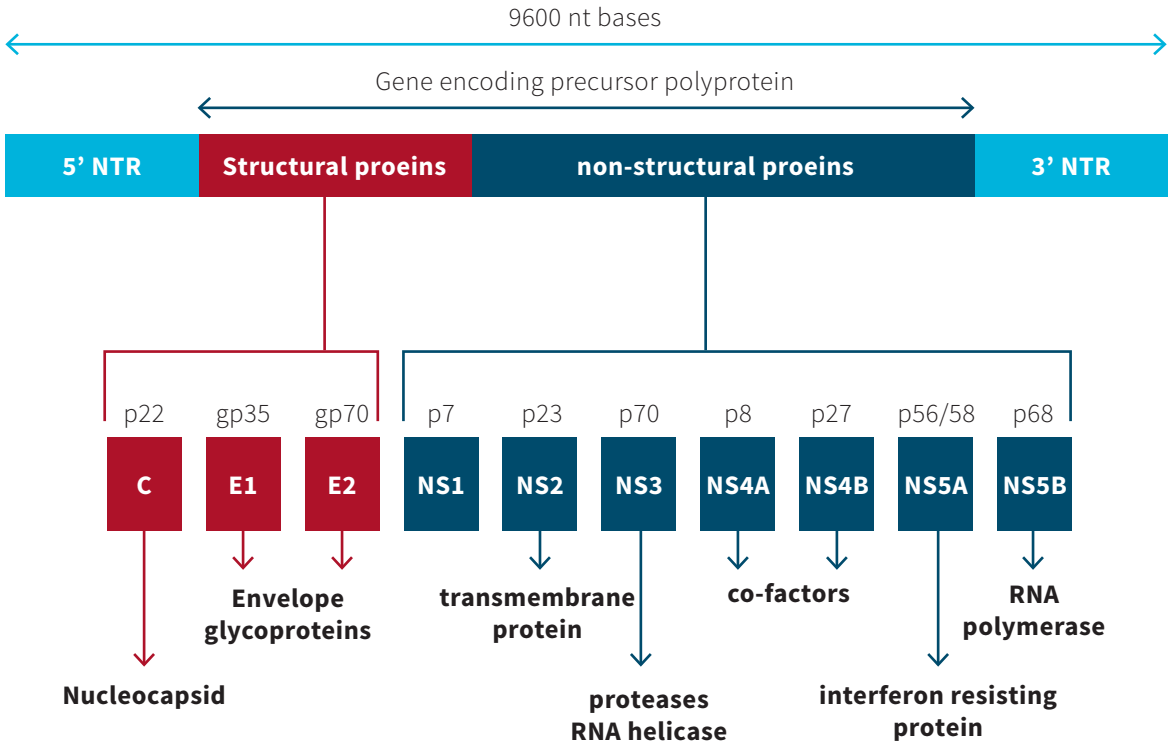
Peter Beyer and Pascale Boulet reviewed a draft version of this report, and provided valuable input and suggestions.

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 glecaprevir.

In September 2016, the US Food and Drug Administration (FDA) granted breakthrough therapy designation to AbbVie's investigational, pan-genotypic fixed-dose combination glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection who failed previous therapy with DAAs in genotype 1.[5] In January 2017, the European Medicines Agency reportedly granted accelerated assessment for glecaprevir/pibrentasvir.[6]

5. Enanta Pharmaceuticals announces AbbVie's investigational HCV regimen receives U.S. FDA breakthrough therapy designation. Business Wire. 30 September 2016.

6. AbbVie. European Medicines Agency grants accelerated assessment, validates marketing authorization application for AbbVie's investigational regimen of glecaprevir/pibrentasvir (G/P) for the treatment of chronic hepatitis C in all major genotypes (GT1-6). PRNewswire. 24 January 2017.

7. Alcorn K. AbbVie pangenotypic combination cures almost all hard-to-treat people with HCV genotype 3. InfoHep, 16 November 2016 (quoting studies presented at the 2016 AASLD).

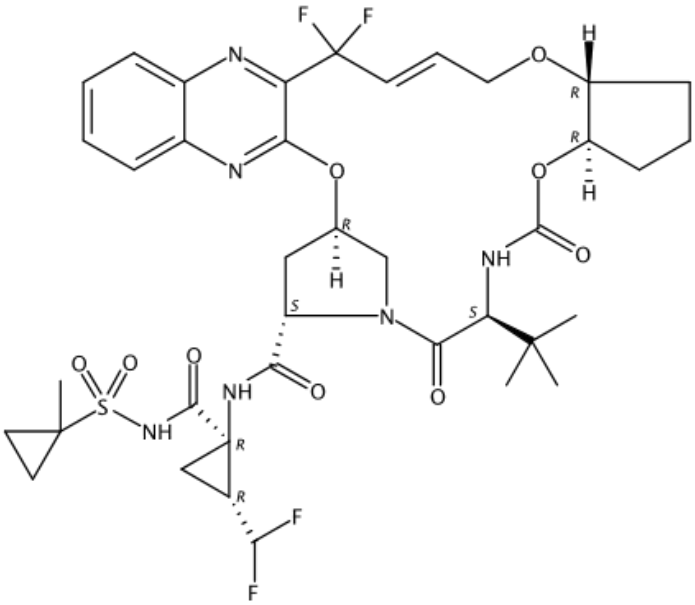
Glecaprevir

Glecaprevir (formerly known as ABT-493) is an HCV NS3/4A protease inhibitor. It is active against all genotypes of hepatitis C.

Glecaprevir is reported to be more potent against genotype 3 than many other HCV protease inhibitors.

The chemical structure of glecaprevir is shown in Figure 2.

Figure 2. Structure of glecaprevir



Chemical name:
(3aR, 7S, 10S, 12R, 21E, 24aR)-7-tert-butyl-N-((1R,2R)-2-(difluoromethyl)-1-((1-methyl cyclopropane-1-sulfonyl)carbamoyl)cyclopropyl)-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8, 11,12,20,23,24a-dodecahydro-1H,10H-9,12-methanocyclopenta(18,19) (1,10,17,3,6) trioxadiazacyclononadecino(11,12-b)quinoxaline-10-carboxamide.

Molecular formula:
$C_{38}H_{46}F_4N_6O_9S$.

Molecular weight:
838.9 g/mol.

CAS registry number:
1365970-03-1.

IV. OVERVIEW OF GLECAPREVIR PATENTS

Eight patents and/or patent applications related to glecaprevir appear to be the most relevant. These patents/applications, and divisional patents/applications thereof, include the patents/applications covering the compound per se, various solid forms of the compound, formulations and combinations that include it, and methods of use in the treatment of HCV infection.

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

Patents 2 to 6 relate to methods of treatment for HCV and comprise administration of at least two DAAs including glecaprevir and/or pibrentasvir.

Patent 4 relates to the use of glecaprevir to treat an infection with HCV genotype 2, 3, 4 or 6, where the genotype has not been established.

Patent 7 relates to crystalline forms of glecaprevir.

Patent 8 relates to combination therapy for HCV.

Non-sponsor patents

As of December 2016, there was competition for patents related to glecaprevir. Patents that have been filed by other entities include:

- Glaxo (WO2016/075584): targeting a long-acting parenteral pharmaceutical composition comprising a compound of formula IIA or IIB with glecaprevir (ABT-493).
- Medivir (WO2016/140615): targeting a combination of a compound of formula (IA) with glecaprevir (ABT-493).

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

Table 1. Overview of key patents on glecaprevir

	PCT application number	Applicants	Filing date	Comments
PATENT 1	**WO2012/040167**	Enanta Pharmaceuticals	20 September 2011	Compound patent; claims glecaprevir. Likely to constrain generic market entry where it is in force.
PATENT 2	**WO2014/152514**	AbbVie	14 March 2014	Claims an interferon- and ribavirin-free treatment for HCV, which comprises administration of glecaprevir and pibrentasvir.
PATENT 3	**WO2014/152635**	AbbVie	14 March 2014	Claims a method of treatment for HCV, which comprises administration of glecaprevir, pibrentasvir and ribavirin.
PATENT 4	**WO2015/061742**	AbbVie	24 October 2014	Claims glecaprevir to treat infection with HCV genotype 2, 3, 4 or 6, where the genotype is not established.
PATENT 5	**WO2015/153792**	AbbVie	01 April 2015	Claims a method of treatment for HCV, comprising administration of ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.
PATENT 6	**WO2015/153793**	AbbVie	01 April 2015	Claims an interferon- and ribavirin-free treatment for HCV, comprising administration of at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.
PATENT 7	**WO2015/188045**	AbbVie	05 June 2015	Claims crystalline forms of glecaprevir.
PATENT 8	**WO2016/134058**	AbbVie	17 February 2016	Combination therapy for HCV.

V. ANALYSIS OF GLECAPREVIR PATENTS/APPLICATIONS

PATENT 1

Title: Macrocyclic proline derived HCV serine protease inhibitors
WO 2012/040167 (Enanta pharmaceuticals, filed 20 September 2011)

Summary

This is the basic compound patent covering glecaprevir. It discloses and claims glecaprevir as well as pharmaceutical compositions comprising it.

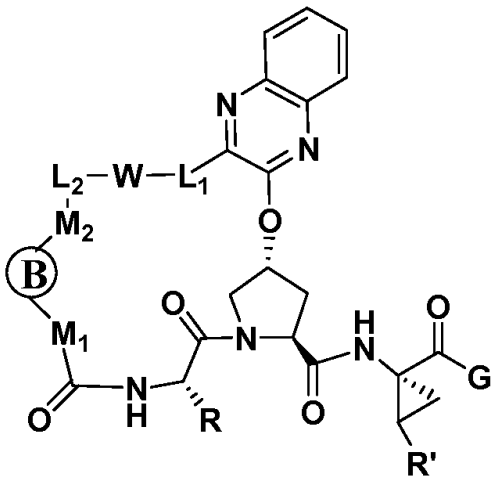
This patent would be likely to block generic market entry in the countries where it is in force.

Description

The PCT application discloses compounds, including glecaprevir, that are useful as inhibitors of the HCV NS3/4A protein. The NS3/4A protease is responsible for cleaving four sites on the viral polyprotein. Consequently, the disclosed compounds interfere with the life cycle of HCV and are useful as antiviral agents.

The PCT application discloses compounds of general formula (VIII).

Glecaprevir falls within the scope of this general structure, in which Ⓑ is  , M_1 and M_2 are both –O-, L_2–W-L_1 is a  , R is  , R' is , R'' is H and G is  .



(VIII)

Example 6 of compounds of Formula (VIII) corresponds to glecaprevir.

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.

Methods of using said compounds and pharmaceutical compositions containing them that are used to treat HCV infections are also disclosed.

Claims

This PCT application has 26 claims, of which claims 1, 16, 17 and 19 are independent.

The original PCT application discloses glecaprevir, but does not claim it. See however under “observations” below.

The application also claims pharmaceutical compositions comprising the claimed compounds (claim 16 and its dependent claims).

Also claimed are methods of treating HCV infection (claims 17 and 19, and their dependent claims).

Observations

The PCT application was filed on 20 September 2011 and published for the first time on 29 March 2012.

According to the written opinion of the International Searching Authority (USPTO), none of the claims as originally filed involve an inventive step in view of the documents cited in the international search report.

The PCT application discloses glecaprevir, but does not claim it. When entering the national phase, new claims directed to compounds of Formula VIII may be added that include glecaprevir. This way, glecaprevir may be claimed in the national phase and Patent 1 then becomes the compound patent.

This is for example the case in AU2011305695 (claims 12 and 13).

Similarly, when the PCT application entered the European phase, a new set of claims was filed. A supplementary search report was drawn up by the International Searching Authority (EPO). Both novelty and inventive step are acknowledged and the application was granted as EP2618831. Glecaprevir is specifically claimed in claim 23.

The PCT application has also entered a number of other national phases (see Annex 1).

PATENT 2

Title: Combination of two antivirals for treating hepatitis C.
WO 2014/152514 (AbbVie, filed 14 March 2014)

Summary

This PCT application relates to an interferon- and ribavirin-free treatment for HCV, comprising administration of at least two DAAs including glecaprevir and pibrentasvir.

Description

This PCT application is based on the unexpected finding that an interferon-free and ribavirin-free treatment using a combination of glecaprevir and pibrentasvir, for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treatment for HCV infection, which comprises administration of at least two DAAs – including glecaprevir and pibrentasvir – wherein the administration of interferon and/or ribavirin to the subject is excluded during the treatment. Thus, the side-effects associated with interferon and/or ribavirin are avoided.

Optionally, the treatment may also include another anti-HCV agent. Each DAA can be administered at the same dosing frequency or at different ones, at around the same time or at different times. The treatment duration is preferably no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 24 claims, directed to a method of treatment for HCV infection, which comprises administration of at least two DAAs, including glecaprevir and pibrentasvir, wherein neither interferon nor ribavirin is administered during the treatment.

Observations

The PCT application was filed on 14 March 2014 and was published for the first time on 25 September 2014.

According to the international preliminary report on patentability, none of the claims as originally filed involve an inventive step in view of the documents cited in the international search report.

The PCT application entered the European phase as EP 2968301. A set of amended claims has been filed before examination. The new claims contain one independent claim which protects a combination of at least two DAAs comprising glecaprevir and pibrentasvir for use in a method for treatment of HCV infection, wherein neither interferon nor ribavirin are administered during the treatment. The new claims are currently intended to be granted.

PATENT 3

Title: Combination of direct-acting antiviral agents and ribavirin for treating HCV patients

WO 2014/152635 (AbbVie, filed 14 March 2014)

Summary

This PCT application relates to an interferon-free treatment for HCV infection, comprising administration of ribavirin and at least two DAAs including glecaprevir and pibrentasvir.

Description

This PCT application is based on the unexpected finding that an interferon-free treatment using a combination of ribavirin and at least two DAAs including glecaprevir and pibrentasvir, for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treatment for HCV infection, which comprises administration of ribavirin, including its pro-drugs, and at least two DAAs including glecaprevir and pibrentasvir, without administration of interferon.

Optionally, the treatment may also include another anti-HCV agent (except interferon). Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration is preferably no more than 12 weeks, or no more than 8 weeks.

Claims

The PCT application contains a total of 24 claims, directed to a method for treatment for HCV infection, which comprises administration of ribavirin and at least two DAAs, including glecaprevir and pibrentasvir, without administration of interferon.

Observations

The PCT application was filed on 14 March 2014 and was published for the first time on 25 September 2014. Both novelty and inventive step have been acknowledged in the preliminary examination.

PATENT 4

Title: Methods for treating HCV
WO 2015/061742 (AbbVie, filed 24 October 2014)

Summary

This PCT application relates to a method of treatment for HCV infection, comprising administration of glecaprevir to a patient infected with HCV genotype 2, 3, 4 or 6, where the genotype has not been established.

Description

The PCT application is based on the surprising discovery that glecaprevir is effective in inhibiting a wide array of HCV genotypes and variants, such as HCV genotypes 1, 2, 3, 4, 5 and 6. Therefore, the treatment can be initiated without establishing the specific HCV genotype.

The PCT application describes methods of treatment comprising administration of an effective amount of glecaprevir to a patient infected with HCV, regardless of the specific HCV genotype(s). Optionally, glecaprevir is co-administered with another anti-HCV agent.

Preferably, glecaprevir is formulated in a solid composition comprising glecaprevir in amorphous form, a pharmaceutically acceptable hydrophilic polymer and, optionally, a pharmaceutically acceptable surfactant.

The composition employed in the invention can be prepared by a variety of techniques such as melt-extrusion, spray-drying, co-precipitation, freeze-drying or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage form.

Each treatment regimen can be both interferon-free and ribavirin-free; however, if necessary, administration of interferon and/or ribavirin can be included. Each treatment regimen may also optionally include administration of one or more other anti-HCV agents.

The treatment duration is preferably no more than 24 weeks, or no more than 12 weeks.

Claims

This PCT application contains a total of 26 claims.

Claims 1–19 are directed to a method of treatment for HCV infection comprising administration of an effective amount of glecaprevir to a patient who is infected with HCV genotype 2, 3, 4, 5 or 6 and where the genotype has not been established.

Claims 20–26 are directed to a method of treatment for HCV infection comprising administration of an effective amount of glecaprevir to a patient who is infected with HCV genotype 2, 3, 4, 5 or 6.

Observations

The PCT application was filed on 13 February 2013 and was published for the first time on 30 April 2015. No international search report has been established for any of the claims, because the claims relate to a method of treatment of the human body by therapy (PCT Rule 43 bis. 1(b), Rule 67.1 (iv)).

The PCT application entered European phase as EP3060216. A new set of claims has been filed. The new claims contain one independent claim and 14 dependent claims. Claim 1 is directed to glecaprevir for use in treatment of HCV infection, where the patient is infected with HCV genotype 2, 3, 4 or 6 and where the genotype has not been established.

PATENT 5

Title: Methods for treating HCV
WO 2015/153792 (AbbVie, filed 01 April 2015)

Summary

This PCT application relates to an interferon-free treatment for HCV infection, comprising administration of ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.

Description

This PCT application is based on the unexpected finding that a combination therapy of glecaprevir and pibrentasvir, in the absence of interferon and for duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method for treating HCV infection, which comprises administration of at least two DAAs selected from glecaprevir, pibrentasvir and an HCV polymerase inhibitor. The method does not include administration of interferon. The HCV polymerase inhibitor is preferably sofosbuvir.

Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration should preferably be no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 17 claims directed to a method for treating HCV infection, which comprises administration of ribavirin and at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir, without administration of interferon.

Observations

The PCT application was filed on 13 February 2013 and was published for the first time on 08 October 2015.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 6

Title: Methods for treating HCV
WO 2015/153793 (AbbVie, filed 01 April 2015)

Summary

This PCT application relates to interferon- and ribavirin-free treatments for HCV infection, which comprise administration of at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir.

Description

This PCT application is based on the unexpected finding that a combination therapy of glecaprevir and pibrentasvir, in the absence of interferon and ribavirin and for a duration of no more than 12 weeks, can achieve significant sustained virological response.

This PCT application describes a method of treating HCV infection, which comprises administering at least two DAAs selected from glecaprevir, pibrentasvir and a HCV polymerase inhibitor without administration of either interferon or ribavirin. The HCV polymerase inhibitor is preferably sofosbuvir.

Each DAA can be administered independently at the same or different dosing frequencies. The treatment duration should preferably be no more than 12 weeks, or no more than 8 weeks.

Claims

This PCT application contains a total of 17 claims, directed to a method for treating HCV infection, which comprises administration of at least two DAAs selected from glecaprevir, pibrentasvir and sofosbuvir, without administration of either interferon or ribavirin.

Observations

The PCT application was filed on 13 February 2013 and was published for the first time on 08 October 2015.

According to the international preliminary report on patentability, none of the claims as originally filed involves an inventive step in view of the documents cited in the international search report.

PATENT 7

Title: Crystal forms
WO 2015/188045 (AbbVie, filed 05 June 2015)

Summary

This PCT application relates to four crystalline forms of glecaprevir, methods for preparing the crystalline compounds and pharmaceutical compositions comprising them.

Description

This PCT application describes four crystalline forms of glecaprevir, namely hydrate, trimethanol solvate, dimethanol monohydrate and desolvate.

Processes for using one or these crystalline forms to make a composition are also described.

Claims

This PCT application contains a total of 8 claims.

Claims 1–6 are directed to four crystalline forms of glecaprevir, notably the hydrate, trimethanol solvate, dimethanol monohydrate and desolvate.

Claim 7 is directed to a pharmaceutical composition comprising any of the claimed crystalline forms of glecaprevir.

Claim 8 is directed to a process for making a pharmaceutical composition comprising glecaprevir using one of the claimed crystalline forms.

Observations

The PCT application was filed on 13 February 2013 and published for the first time on 10 December 2015.

Both novelty and inventive step have been acknowledged in the written opinion of the International Searching Authority.

PATENT 8

Title: Combinations useful to treat hepatitis C virus
WO 2016/134058 (AbbVie, filed 05 June 2015)

Summary

This PCT application relates to a pharmaceutical composition comprising two or more therapeutic agents that are useful for treating HCV, including a nucleoside/nucleotide-based NS5B inhibitor (A-1 to A-6) and pibrentasvir (or ombitasvir). The composition may further contain glecaprevir.

Description

This PCT application describes methods for treating HCV using a combination of a therapeutic agent A selected from:

A-1: (2R)-isopropyl 2-(((((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl) methoxy(phenoxy)phosphoryl)amino) propanoate,

A-2: (R)-isopropyl 2-(((S)-(((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino) propanoate,

A-3: (R)-isopropyl 2-(((R)-(((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy)phosphoryl)amino) propanoate,

A-4: ((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl dihydrogen phosphate,

A-5: ((2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl trihydrogen phosphate,

A-6: (2R, 3R, 4R, 5R)-5-(2, 4-dioxo-3, 4-dihydropyrimidin-1(2H)-yl)-3, 4-dihydroxy-4-methyltetrahydrofuran-2-yl)methyl trihydrogen phosphate

and a therapeutic agent B selected from (B-1) ombitasvir and (B-2) pibrentasvir. The method may further comprise a therapeutic agent selected from (C-1) paritaprevir and (C-2) glecaprevir.

Claims

This PCT application contains a total of 20 claims, of which claims 1, 2 and 11 are independent.

Claim 1 is directed to a pharmaceutical composition comprising a therapeutic agent A selected from compounds (A-1) to (A-3) and a therapeutic agent B selected from ombitasvir and pibrentasvir.

Claim 2 and its dependent claims are directed to a method for treating HCV using the combination comprising a therapeutic agent A selected from compounds (A-1) to (A-3) and a therapeutic agent B selected from ombitasvir and pibrentasvir. Dependent claim 9 is directed to the same method, further comprising administration of a therapeutic agent C, selected from paritaprevir and glecaprevir.

Claim 11 and its dependent claims are directed to a method for treating HCV using the combination comprising a therapeutic agent A selected from compounds (A-1) to (A-6) and a therapeutic agent B selected from ombitasvir and pibrentasvir. Dependent claim 15 is directed to the same method, further comprising administration of a therapeutic agent C selected from paritaprevir and glecaprevir.

Observations

The PCT application was filed on 05 June 2015 and was published for the first time on 25 August 2016.

The examiner found that the chemical names of compounds A-1 to A-6 (on p14 of the PCT application) do not correspond to the structures in the claims (see the written opinion of the International Searching Authority).

The International Searching Authority (EPO) acknowledged novelty for all claims 1–20. However, none of the claims are acknowledged as involving an inventive step due to lack of data with respect to the antiviral effect of the compounds A-1 to A-6 or of combinations comprising the same.

ANNEX 1. GLECAPREVIR PATENT SITUATION IN COUNTRIES

	Patent 1	Patent 2	Patent 3	Patent 4
Pub. No (Appl. No)	**WO2012040167A1 (PCT/US2011/052304)**	**WO2014152514A1 (PCT/US2014/027423)**	**WO2014152635A1 (PCT/US2014/027556)**	**WO2015061742A1 (PCT/US2014/062265)**
Applicants	Enanta Pharmaceuticals	AbbVie	AbbVie	AbbVie
Filing date	20 September 2011	14 March 2014	14 March 2014	24 October 2014
Title	Macrocyclic proline derived HCV serine protease inhibitors	Combination of two antivirals for treating hepatitis C	Combination of direct-acting antiviral agents and ribavirin for treating HCV patients	Methods for treating HCV
Subject matter	Basic compound patent – constraining for generic medicines where granted.	Combination of glecaprevir/pibrentasvir	Combination of glecaprevir / pibrentasvir and ribavirin	Use of glecaprevir to treat infection with HCV genotype 2, 3, 4 or 6, when genotype is not established
Priority data	US61/504,616: 05 July 2011 US61/385,058: 20 September 2010 US61/499,994: 22 June 2011	US61/783,376: 14 March 2013	US61/783,437: 14 March 2013	US61/895,945: 25 October 2013

Patent status

Argentina	Status N/A AR083052A1	–	–	–
Australia	Granted AU2011305695B2 Pending AU2016204491A1	Granted AU2014239563B2 Pending AU2016202823A1	Pending AU2014239322A	–
Bolivia	Status N/A SP2011-00292	–	–	–
Brazil	Status N/A BR112013006693	–	–	–
Canada	Pending CA2812261A1	Pending CA2942823	Pending CA2901818A	Pending CA2925328A
Chile	Status N/A CL2013000791A1	–	–	–

The INPADOC patent family members for patents/applications 1 to 8 are listed in the tables 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.

	Patent 5	Patent 6	Patent 7	Patent 8
Pub. No (Appl. No)	**WO2015153792A1 (PCT/US2015/023922)**	**WO2015153793A1 (PCT/US2015/023923)**	**WO2015188045A1 (PCT/US2015/034371)**	**WO2016134058A1 (PCT/US2016/018327)**
Applicants	AbbVie	AbbVie	AbbVie	AbbVie
Filing date	01 April 2015	01 April 2015	05 June 2015	17 February 2016
Title	Methods for treating HCV	Methods for treating HCV	Crystal forms	Combinations useful to treat hepatitis C virus
Subject matter	Combination comprising ribavirin and at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir	Combination comprising at least two of the DAAs selected from glecaprevir, pibrentasvir and sofosbuvir	Crystalline forms of glecaprevir	Combination therapy of HCV
Priority data	US61/973,930: 02 April 2014 US61/989,953: 07 May 2014 US62/016,460: 24 June 2014	US61/973,929: 02 April 2014 US61/989,951: 07 May 2014 US62/016,459: 24 June 2014	US62/008,786: 06 June 2014	US62/117,764: 18 February 2015 US62/133,005: 13 March 2015
Argentina	–	–	–	–
Australia	Pending AU2015240753A	Pending AU2015240754A	Pending AU2015269306A	–
Bolivia	–	–	–	–
Brazil	–	–	–	–
Canada	Pending CA2943054A	Pending CA2942823A	Pending CA2948902A	–
Chile	–	–	–	–

	Patent 1	Patent 2	Patent 3	Patent 4
China	Granted CN103209703 Pending CN104829688	Pending CN105073113A	Pending CN105007921A	Pending CN105658219A
China, Hong Kong SAR	Pending HK1186979	–	Pending HK1213191	–
Colombia	Status N/A CO6700835A	–	–	–
Costa Rica	Status N/A CR20130135A	–	–	–
Dominican Republic	Status N/A DOP2013000062A	–	–	–
Ecuador	Status N/A ECSP13012559A	–	–	–
Egypt	Status N/A 481/2013	–	–	–
Eurasian Patent Office*	Granted EA023009B1 Pending EA201500728A	Pending EA201591702	Pending EA201591701A	–
European Patent Office ****	Granted EP2618831B1 Pending EP3020723A1	Pending EP2968301A	Pending EP2968302A	Pending EP3060216A
Guatemala	Status N/A GT201300077A	–	–	–
Gulf Cooperation Council * **	Status N/A GCC2011/19330	–	–	–
India	Pending IN2891DELNP2013	–	–	–
Indonesia	Status N/A W00201301596	–	–	–
Israel	Pending IL225412	Pending IL240419	Pending IL240445	–
Japan	Granted JP5857053B2 Pending JP2016104756A	Pending JP2016-513695	Pending JP2016-513703	Pending JP2016526018
Malaysia	Pending MY2013-700450	–	–	–
Mexico	Pending MX/a/2013/003230	Pending MX/a/2015/012538	Pending MX/a/2015/012536	Pending MX/a/2016/005393
Mongolia	Status N/A MN5031	–	–	–

	Patent 5	Patent 6	Patent 7	Patent 8
China	–	–	–	–
China, Hong Kong SAR	–	–	–	–
Colombia	–	–	–	–
Costa Rica	–	–	–	–
Dominican Republic	–	–	–	–
Ecuador	–	–	–	–
Egypt	–	–	–	–
Eurasian Patent Office*	–	–	–	–
European Patent Office **	–	–	–	–
Guatemala	–	–	–	–
Gulf Cooperation Council ***	–	–	–	–
India	–	–	–	–
Indonesia	–	–	–	–
Israel	–	–	–	–
Japan	–	–	–	–
Malaysia	–	–	–	–
Mexico				
Mongolia				

	Patent 1	Patent 2	Patent 3	Patent 4
New Zealand	Granted NZ608720 Granted NZ703416	Granted NZ631155 Pending NZ719137	Pending NZ631789	–
Pakistan	Status N/A PK683/2011	–	–	–
Panama	Status N/A PA89436	–	–	–
Paraguay	Status N/A PY39984/2011	–	–	–
Peru	Status N/A PE2014-0015A1	–	–	–
Philippines	Pending PH/1/2013/500533	–	–	–
Republic of Korea	Pending KR1020130098369	Pending KR20150129032	Pending KR20150129035	–
Russian Federation	Granted EA023009B1 (designated) Pending EA201500728A	Pending EA201591702A	Pending EA201591701A	–
Singapore	Granted SG188618	Pending SG11201507364S	Pending SG11201507361Y	–
South Africa	Granted ZA201302317 Granted ZA201308655	Pending ZA2015/05880	Pending ZA2015/06031	–
Thailand	Pending TH139657	–	–	–
Ukraine	Pending UA2013-05119	–	–	–
Uruguay	Status N/A UY33617A	–	–	–
USA	Granted US8648037B2 Granted US9220748B2 Pending US2016145298A	Pending US20140275099A	Pending US2014274934A	Pending US2015119400A
Venezuela	Status N/A VE1241-11	–	–	–
Viet Nam	Status N/A VN1-2013-01552	–	–	–

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.

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

	Patent 5	Patent 6	Patent 7	Patent 8
New Zealand	–	–	–	–
Pakistan	–	–	–	–
Panama	–	–	–	–
Paraguay	–	–	–	–
Peru	–	–	–	–
Philippines	–	–	–	–
Republic of Korea	–	–	–	–
Russian Federation	–	–	–	–
Singapore	–	–	–	–
South Africa	–	–	–	–
Thailand	–	–	–	–
Ukraine	–	–	–	–
Uruguay	–	–	–	–
USA	Pending US2015283199 Pending US2016317603	Pending US2015283198A Pending US2016317602	Granted US9321807B2 Pending US2016220487	–
Venezuela	–	–	–	–
Viet Nam	–	–	–	–

** 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 & Herzegovina, Montenegro. Validation states: Moldova, Morocco, Tunisia.

*** 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.