PATENT SITUATION OF KEY PRODUCTS
FOR TREATMENT OF HEPATITIS C

SOFOSBUVIR

WORKING PAPER

Prepared for the
World Health Organization (WHO) by
Thomson Reuters

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World Health Organization

This report was prepared for the WHO Department of Essential Medicines and Health Products by Thomson Reuters. It is available for free download: http://www.who.int/phi/en/. If you have questions or feedback, please write to phidepartment@who.int.

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INTRODUCTION

The World Health Organization's (WHO) 2014 *Guidelines for the screening, care and treatment of persons with hepatitis C infection* state that worldwide more than 185 million people are infected with the hepatitis C virus (HCV). Of these people, 350 000 to 500 000 die each year. An estimated one third of those who become chronically infected develop liver cirrhosis or hepatocellular carcinoma. HCV infection can be cured, but most people infected with the virus are unaware of their infection and so do not seek timely treatment. Furthermore, treatment remains unavailable for many who have been diagnosed. Several medicines are available to treat HCV, including pegylated interferon and ribavirin but treatment duration is long, involves weekly injections, and side effects are considerable. With the development of new direct-acting antivirals, the treatment landscape is rapidly changing. These new antivirals are expected to reach cure rates of more than 90% in persons with HCV infection across different genotypes, with fewer side effects and a shorter duration of treatment.[1] Several new compounds have recently been approved in the United States and Europe and some (simeprevir and sofosbuvir) are recommended by the new WHO treatment guidelines. Many others are in various stages of development.

Resolution WHA67.6 adopted by the Sixty-Seventh World Health Assembly, requested the Director-General "to work with national authorities, upon their request, to promote comprehensive, equitable access to prevention, diagnosis and treatment for viral hepatitis" and "to assist Member States to ensure equitable access to quality, effective, affordable and safe hepatitis B and HCV treatments and diagnostics, in particular in developing countries". Ensuring access to new treatments is a challenging task. In order for countries to identify ways of increasing access and affordability of new HCV medicines, they need clarity about patent status. To assess whether a medicine is patent protected in a certain country requires expert knowledge and access to specialized databases that are not easily available. The WHO Global strategy and plan of action on public health, innovation and intellectual property provides WHO with a mandate to support efforts to determine the patent status of health products (element 5.1c). Despite the possibility of filing patents under the World Intellectual Property Organization (WIPO) Patent Cooperation Treaty (PCT) in 148 jurisdictions, there is no such thing as a worldwide patent. Patents are granted individually under each jurisdiction, depending on the national patent law and the outcome of the examination process. National patents that relate to the same basic patent (i.e. the same invention) are called family members and together build a patent family. In the present study, patent families are based on the Derwent World Patent Index (DWPI).[2]

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[1] Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en, April 2014).

[2] The Derwent World Patents Index (or DWPI) is a database containing patent applications. Each patent family is grouped around a basic patent, which is usually the first published example of the invention.

The WHO Secretariat has mandated Thomson Reuters to carry out an analysis of the patent situation of seven new hepatitis treatments[3]:

International nonproprietary name	**Sponsor**
daclatasvir	Bristol-Myers Squibb Company
dasabuvir	AbbVie Inc.
ledipasvir	Gilead Sciences, Inc.
ombitasvir	AbbVie Inc.
paritaprevir	AbbVie Inc.
simeprevir	Janssen Pharmaceutical Companies of Johnson & Johnson
sofosbuvir	Gilead Sciences Inc.

The draft reports were shared with the respective sponsor companies before publication.

OBJECTIVE

The objective of the patent working papers was to:

(1) identify the most relevant patents with respect to the medicines
(2) identify in which countries these patents have been filed and granted

One will often find numerous patents relating to one medicine. These patents will cover different aspects and innovations around the same product. Not all however are equally relevant, as many will cover variations or production processes but would not prevent somebody else to produce the medicine, e.g. by using a different process.

These patent working papers identify the most relevant patents for each medicine. The patents are categorized in primary and secondary patents. The patent publication covering the base compound is considered the “primary patent” and patents on specific pharmaceutical formulations, method of use, product derivatives, and processes are considered “secondary patents”. Secondary patents are generally easier to circumvent (“to invent around”), meaning to make the medicine without infringing the secondary patents. For example, a patent on the aqueous solution would not prevent competitors to produce a

[3] Initially two additional candidate medicines were included in the project (faldaprevir and deleobuvir), but development of these has been discontinued and thus the patent landscapes were not finalized.

tablet, and a combination patent would not prevent competitors to produce the combined products separately.

The following are different types of patents:

Product patents claim the chemical molecule/the active pharmaceutical ingredient. Product patents are usually the strongest patents as the patent holder can use product claims to prevent others from making, selling, or importing the chemical product.

Product-by-process patents define the product by its process of preparation.

Process patents claim a (new) production process for an active pharmaceutical ingredient.

Formulation patents relate to the specific dosage form (e.g. coated tablet, soft gel capsule, syrup etc.).

Combination patents claim the combination of new or existing medicines.

Patents on product derivatives claim a specific form or derivative, e.g. a salt of an existing compound.

Patents containing Markush claims refer to a chemical structure with multiple alternatives in a format such as "chemical compound A wherein X^1 is selected from a group consisting of a, b and c".

This list is simplified and not exhaustive. Detailed explanations can be found in Philip Grubb, Peter Thomsen, *Patents for Chemicals, Pharmaceuticals, and Biotechnology*, 5th Edition Oxford 2010 as well as in the patenting guidelines of the respective national or regional patent offices.

Interpretation of patentability criteria varies, in particular with respect to the so-called secondary patents. Some jurisdictions are more restrictive to prevent a proliferation of secondary patents covering minor modifications of existing medicines. In those jurisdictions, for example India and Argentina, many of the secondary patents may not be granted as they do not fulfil their specific requirements. Further information can be found in the draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* which provides detailed information on the different forms of patents in the pharmaceutical sector (www.who.int/phi/publications/category/en/).

HOW TO USE THIS WORKING PAPER?

The working papers identify the relevant patents and provide data where these patents have been filed or granted. They allow countries to carry out a first assessment on whether a medicine is patent protected and to assess their possibilities for rendering the new treatments more affordable. The data is also essential to allow WHO to fulfil its mandate under Resolution WHA67.6 which requests WHO to assist Member States in ensuring equitable access to quality, effective, affordable and safe HCV treatments. Assisting countries in accessing the new hepatitis treatments at an affordable price requires

knowledge about the patent situation in the respective jurisdictions as this determines the various options countries have.

The working papers can also help other interested parties to negotiate transfer of technology or license agreements, research ways to enhance or improve the current drug or treatment modality, and facilitate the development of generics.

Although being public domain information, patent information in many countries is difficult to retrieve, as is reflected by the gaps in the Annex. N/A indicates that no information could be retrieved for the relevant patents in the databases that were used in this working paper. This can either mean that the information in the databases is not up-to-date or complete, or that the patents were not filed in these jurisdictions. While the latter may often be the case, certainty can only be achieved by checking the information with the local patent office. This can be done by using the patent numbers provided in this report, as they allow retrieval of information through national patent offices and/or national patent registries. The following WIPO page provides links to all national online patent search tools to search national patent registries:

http://www.wipo.int/branddb/portal/portal.jsp

LIMITATIONS

While endeavours have been made to make the content of this study accessible to the non-expert, the highly technical nature of the subject matter and the singularities of the patent system require a certain expertise to make full use of this study.

Every effort has been made to obtain comprehensive and accurate information, including on the legal status of the patents. However, in many countries patent information is not readily available or not updated on a regular basis. In addition, some patent applications may have been published only after the searches were conducted and thus may not be included in this study. As this study endeavours to identify the most relevant patents, it does not include the many additional patents and application filed by the Sponsor and other entities that also relate to sofosbuvir, some of them are included in the draft license agreement (see under section License Agreements).

It should also be noted that this study is not a freedom-to-operate analysis. The information provides useful guidance, but only reflects the situation at a particular point in time. Neither WHO nor Thomson Reuters accept any responsibility for the accuracy of data, nor guarantee that it is complete or up-to-date. Users are advised, before taking any investment or other legally relevant decision, to consult a local patent expert to provide a full assessment of the patent situation in a given country.

METHODOLOGY

The initial study set out relevant patents and patent applications in the countries included as of March 2014. Relevant patents and patent applications were identified initially by searching patent and non-patent databases, comprising Thomson Innovation, Newport, Thomson Pharma, Questel, Scientific Technology Network (STN) and Cortellis. Additional bibliographic details were collected from publicly available databases, comprising the United States Patent and Trademark Office (USPTO), Espacenet, and relevant national patent office websites. This publication has been updated in March 2015 to reflect the current patent status for the patents that were identified previously. The data stems from Espacenet, The Lens, online registries of national and regional patent offices, data contained in the draft licence agreement referred to below and national patent offices. The annex includes information directly retrieved or received from the following patent offices: ARIPO, Brazil, Chile, GCC, Georgia, Malaysia, Morocco, OAPI, Philippines, and Tunisia.

Legal status and oppositions, if any, were retrieved from respective patent offices (to the extent that information was available).

Litigation data was retrieved from WestLaw, PACER, and pharma-related publicly available sources and updated throughout March 2015 using publicly available sources. The study differentiates between patents held by Sponsors and non-Sponsors. Sponsors are the entities developing the medicines and are filing for or already hold market authorization. Non-Sponsor entities include other pharmaceutical companies, public research institutes and other applicants. The patent position of the Sponsors is assessed. Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.

Wherever available, the application submitted under the WIPO PCT is used as a primary source, both because it is generally the favoured priority application for the pharmaceutical industry, and also because the WIPO International Search Report (ISR) include examiner references that are coded for relevance and for which initial rejections (an indicator of possible novelty issues) can be identified.

Thomson Reuters´ technical experts analysed the claims and determined whether the scope of each of the claims are broad or narrow. Where available, the outcome of the WIPO ISR on novelty and inventive step is described. It should be noted that quotes from the ISR are only examples and do not preclude objections or outcomes under national jurisdictions.

The expected time of expiration for all the patents was calculated and can be found in the Annexe.

US ORANGE BOOK

The updated Annex indicates which of the listed patents are contained in the US Orange Book of the US Federal Drug Administration (FDA). The US Orange Book lists the patents as submitted by the holder of the authorization with respect to new medicines authorized by the FDA for the US market. Under FDA rules the holder of the authorization has to notify certain patents, including formulation/composition patents; use patents for a particular

approved indication or method of using the product. Process patents for example do not need to be notified (FDA. Orange Book, 34th Edition 2014).

GEOGRAPHIC SCOPE

Family members of the Sponsor patent collection have been searched for in the following jurisdictions. It would have been beyond the scope of this study to include patent information of all WHO Member States, thus a selection was made taking into account disease burden, local manufacturing capacities and regional representation:

Argentina (AR), African Regional Intellectual Property Organization (AP), Australia (AU), Brazil (BR), Canada (CA), Chile (CL), China (CN), China, Hong Kong SAR (HK), Colombia (CO), Costa Rica (CR), Ecuador (EC), Egypt (EG), European Patent Office (EPO), Ethiopia (ET), Eurasian Patent Office (EAPO), Georgia (GE), India (IN), Indonesia (ID), Iran (Islamic Republic of) (IR), Israel, (IL), Japan, Jordan (JO), Malaysia (MY), Mexico (MX), Morocco (MA), New Zealand (NZ), Nigeria (NG), African Intellectual Property Organization (OA), Pakistan (PK), Patent Office of the Cooperation Council for the Arab States of the Gulf (GCC), Peru (PE), Philippines (PH), Republic of Korea (KR), Russian Federation (RU), Singapore (SG), South Africa (ZA), Thailand (TH), Tunisia (TN), Ukraine (UA), the United States of America (US), Uruguay (UY), and Viet Nam (VN).

FURTHER RESOURCES

The WHO publication *How to Conduct Patent Searches for Medicines: A Step-by-Step Guide* provides guidance on how to identify the patent status of medicines.[4] The draft *Guidelines for the examination of pharmaceutical patents: developing a public health perspective* provides detailed information on the different forms of patents in the pharmaceutical sector.[5] Material on the relationship between public health and intellectual property can be found in the document *Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade*.[6]

These publications as well as other relevant publications on issues related to public health and intellectual property can be found here: www.who.int/phi/publications/category/en/

More information on HCV and the recommended treatments can be found here: www.who.int/topics/hepatitis/en/

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[4] How to Conduct Patent Searches for Medicines: A Step-by-Step Guide. Delhi: World Health Organization; 2010 (http://www.wpro.who.int/publications/PUB_9789290223757/en/, April 2014).
[5] Guidelines for the examination of pharmaceutical patents: developing a public health perspective. Geneva: World Health Organization; 2006 (http://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf, April 2014).
[6] Promoting Access to Medical Technologies and Innovation. Intersections between public health, intellectual property and trade. Geneva: World Health Organization, World Trade Organization, World Intellectual Property Organization; 2013. (http://www.who.int/phi/promoting_access_medical_innovation/en/, April 2014).

SOFOSBUVIR (GS-7977)

Sofosbuvir (manufacturing code name GS-7977; formerly PSI-7977) is a viral polymerase nucleotide inhibitor that was approved in December 2013 by the United States Food and Drug Administration (FDA), and in January 2014 by the European Medicines Agency for the treatment of HCV infection. The WHO *Guidelines for the screening, care and treatment of persons with hepatitis C infection* recommend sofosbuvir in combination with ribavirin in genotypes 1, 2, 3 and 4 HCV infection, either with or without pegylated interferon (depending on the HCV genotype)[7]. Sofosbuvir in combination with ribavirin is the first interferon-free HCV treatment. The fact that sofosbuvir is all oral simplifies the treatment and will allow expansion in low resource settings with poor health infrastructure.

Sofosbuvir is marketed by Gilead Sciences, Inc. under the brand names Sovaldi and Virunon. In 2011, Gilead Sciences acquired Pharmasset Ltd., the company that developed the drug and filed the first patent in 2003. Sofosbuvir is a prodrug that is metabolized in the body to the active antiviral agent 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-monophosphate, a nucleotide analogue inhibitor of the HCV polymerase, which is critical for viral RNA replication. Sofosbuvir was invented by Pharmasset Ltd, and developed by Gilead Sciences (hereby referred to as the 'Sponsor').

CHEMICAL NAME

Systematic (IUPAC) name:

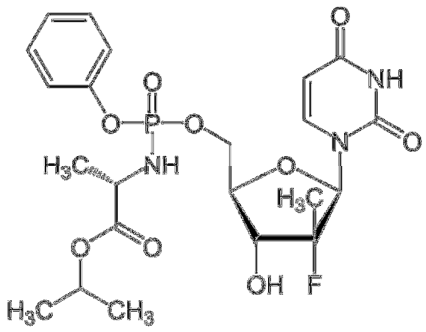
Isopropyl (2S)-2-[[[(2R,3R,4R,5R)-5-(2,4-dioxopyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-yl]methoxy-phenoxy-phosphoryl]amino]propanoate

MOLECULAR FORMULA

$C_{22}H_{29}FN_3O_9P$

[7] Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en, April 2014).

MOLECULAR STRUCTURE



SUMMARY

The search revealed patents filed with respect to sofosbuvir by the Sponsor as well as non-Sponsors.

The sofosbuvir Sponsor patent collection comprises 21 different patents (patent families) (see Patents 1 to 21 in Annex 1).

Patents 1 and 2 are primary patents claiming the base compound through a Markush claim, wherein Patent 2 relates to the sofosbuvir prodrug as marketed. Patent 1 and Patent 2 family members are involved in pre-grant opposition and litigation cases that dispute their novelty and inventive step.

Patents 3, 4 and 13 cover processes to make sofosbuvir and therefore if granted will require competitors to design around these patents and use other production processes.

Patent 5 is a product-by-process patent, claiming the sofosbuvir prodrug by a process of preparation, thereby, where granted, preventing competitors from making sofosbuvir prodrug by the process claimed or from importing sofosbuvir that was manufactured using this process.

Patents 6, 9, 10, 11, 12, 14, 15, 16, and 19 claim specific derivatives of sofosbuvir. Seeking subsequent patents on derivatives of existing drugs is a common strategy of companies (i.e., obtaining multiple patents that cover various aspects of the same product).

Patent 7 claims sofosbuvir for the use in combination therapy with other anti HCV drugs (ledipasvir and PSI7851).

Patents 8 and 20 are formulation patents, claiming the pharmaceutical dosage form (pharmaceutical composition).

Patents 17, 18, and 21 are method of use patents, claiming sofosbuvir and derivatives for use in the treatment of HCV infection.

Additional patents have been filed by the Sponsor which are partly disclosed in the License Agreement (see under LICENSE AGREEMENTS) as well as a huge number of non-Sponsor entities.

Note: The search also revealed two patents that are relevant for all seven reports. Patent applications WO2013059630A1 and WO2013059638A1 inter alia claim the use of combinations of unnamed direct-acting antiviral agents for treating HCV, where the treatment does not include administration of interferon or ribavirin, and the treatment lasts between 8-12 weeks. The description and the dataset for these two patents can be found in the Working Paper on ombitasvir (Patents No 3 and 4). These patents are in litigation. Detailed information can be found in the Working Paper on sofosbuvir under Patent No 2.

LICENSE AGREEMENTS

Gilead Sciences has signed licensing agreements with eight Indian generic manufacturers (Cadila Healthcare Ltd., Cipla Ltd., Hetero Labs Ltd., Mylan Laboratories Ltd., Natco Pharma, Ranbaxy Laboratories Ltd., Sequent Scientific Ltd., Strides Arcolab Ltd.) who under these agreements can produce and sell generic sofosbuvir and the combination of ledipasvir/sofosbuvir and GS5816 in 91 countries. They can also combine sofosbuvir with other hepatitis treatments.[8] The license agreements contain information about sofosbuvir patents. **Some but not all of the patents listed in the license agreement are included in this patent landscape. Additional patents disclosed in the license agreement include patents on the solid dispersion formulation, and the combination of two antiviral compounds.** A copy of the draft agreement is publicly available.[9]

[8] Gilead, Chronic Hepatitis C Treatment Expansion, Factsheet, September 2014, http://www.gilead.com/~/media/Files/pdfs/other/HCVGenericAgreementFactSheet.pdf
[9] http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_(FINAL).pdf

SOFOSBUVIR PATENT SITUATION

SPONSOR PATENTS

Patent searches revealed 21 Sponsor patents (referred to as Patents 1 to 21 in the following analysis section and Annex 1).

Patents 1 and 2 are the primary patents, claiming the base compound, wherein Patent 2 relates to the sofosbuvir prodrug as marketed. Patents 3 to 22 are secondary patents. Patents were filed under the name of Pharmasset (specifically patents 1, 2, 3, 4, 5, 6, 17, and 19) and Gilead Sciences. All patents are now owned by Gilead Sciences and remain in the name of the Sponsor entity Gilead Sciences.

PATENT 1: MODIFIED FLUORINATED NUCLEOSIDE ANALOGUES

Patent application WO2005003147A2 (primary patent) discloses the base compound of sofosbuvir. Sofosbuvir is a nucleoside derivative and the patent claims a general structural formula (Markush structure) and specific compounds. Compositions are also claimed, as well as methods of treatment, the use of methyl nucleosides or a pharmaceutically acceptable salt thereof, and a prodrug for the treatment of HCV infection in humans. It also claims the use of sofosbuvir for treatment of various other viral infections in humans.

The patent has a broad scope in its claimed compositions and their applicability. Most importantly, the patent claims a general structural formula of sofosbuvir as well as its various substituents.

As per the WIPO ISR, the application has entered into the European national phase. The ISR report illustrates that claims 1-55 of WO2005003147A2 were subject to amendment in light of prior art.

Litigation / Opposition on Patent

1. On 13 January 2015 the Indian Patent Office rejected Gilead's application 6087/DELNP/2005 on the basis that it failed section 3(d) of India's Patent Act. Opposition to the application was filed by generic pharmaceutical company Natco and non-for-profit organisation I-MAK. Gilead has filed an appeal against this decision. The case is pending.

2. In February 2012, the USPTO initiated an interference involving an Idenix patent application that was pending (United States patent application 12/131,868) covering certain 2'-methyl, 2'-fluoro nucleoside compounds, and a patent granted to Gilead (US 7,429,572) that was related to the same nucleoside compounds. The USPTO Appeals Board ruled that Gilead had filed its patent No. 7,429,572 first. In January 2013, the Appeals Board determined that Idenix is not entitled to priority of invention and decided in favor of Gilead.

Idenix challenged the decision in the District Court of Delaware on 29 January 2014. The case was brought for review by the Patent Trial and Appeal Board (PTAB) of the USPTO for correction of the decision and judgment of priority. The case is currently active (Case No. 1:14-cv-00109).

3. In December 2013, the USPTO declared a second patent interference between Idenix's U.S. Patent 7,608,600 and Gilead's United States publication US20080070861A1, both related to the use of 2'-methyl-2'-fluoro nucleoside compounds to treat HCV infections. No further information is available.

4. On 1 December 2013, Idenix announced that it filed a separate patent infringement and interference lawsuit in the United States District Court in Wilmington, Delaware (Idenix U.S. Patent 7,608,600 and Gilead U.S. Patent 8,415,322). The case is still active (Case No. 1:13-cv-01987).

5. In August 2013, Idenix Pharmaceuticals filed a request with the Chinese Patent Office's Patent Re-examination Board to invalidate Gilead's Chinese Patent CN100503628C.

PATENT 2: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

This patent is listed in the US Orange Book with patent numbers US8580765, US7964580, US8334270.

Patent application WO2008121634A2 claims a general structural formula (Markush) and several phosphoramidate prodrugs of nucleoside derivatives, their salts, hydrates, solvates, stereoisomers and crystalline forms and processes for their preparation. Methods of use are also claimed by administering the above to treat HCV. The compounds are disclosed to be HCV NS5B polymerase inhibitors. WO2008121634A2 relates to the sofosbuvir prodrug as marketed.

As per the WIPO ISR, not all claims of WO2008121634A2 meet the novelty and inventive step requirement in light of prior art.

Litigation / Opposition on Patent 2

1. On 23 February 2015, separate oppositions to the patent EP2203462 were made by the Intellectual Property Service (IPS), ZBM Patents, Satada Arzneimittel AG, and Actavis Group. IPS requested that the patent be revoked as the patent does not involve an inventive step (contrary to Article 56 of the European Patent Convention (EPC)), the invention was insufficiently disclosed (contrary to Article 83 of the EPC), and it contains subject matter which extends beyond the content of the application as filed (contrary to Article 123(2) of the EPC). ZBM also opposed the patent based on the reason that the patent extends beyond the content of the application as filed.

2. On 20 February 2015, separate oppositions to the patent were made by Teva Pharmaceutical Industries Ltd, Generics UK Ltd (trading as Mylan), and Pharmaceutical Works Polpharma S.A.

3. On 19 February 2015, separate oppositions to the patent EP2203462 were made by Ellis IP Ltd and Holm Herbert. The reasons outlined in Ellis IP Ltd included that the patent is contrary to Articles 56, 84 and 123(2) of the EPC as described above.

4. On 10 February 2015, French NGO Médecins du Monde (MdM) filed a 'brief in opposition' to the European Patent Office for the patent EP2203462 on the basis that 'the molecule itself is not sufficiently innovative'. MdM is challenging the patent as means to provide further access to the medicine and allow generic brands to create the same drug.

5. I-MAK, a United States-based not-for-profit group has filed a pre-grant opposition against Gilead's Indian patent application (3658/KOLNP/2009) on the grounds of lack of novelty and obviousness. I-MAK also claims that sofosbuvir in IN200903658P2 is merely a new form of a known substance that does not result in an enhancement of its efficacy. Lack of novelty is established based on Gilead Sciences´ earlier patent WO2005/003147, which discloses both the parent structure of sofosbuvir and the stabilized phosphate prodrug form.

6. Plaintiff Gilead Sciences, Inc. filed a patent infringement lawsuit against Abbott Laboratories, Inc. and AbbVie, Inc. (collectively "Abbott") on 18 December 2013 in the United States District Court for the District of Delaware (Case no 1:13-cv-02034). The Gilead and Abbott patents involved are US8088368B2, US8492386B2, US8466159B2, US8273341B2, US8575118B2, US7964580B2, US8334270B2, and US8580765B2, with the last three relating to Gilead Sciences Patent 2.

7. The original complaint is sealed. According to a redacted complaint, the defendants falsely and knowingly represented to the USPTO that they invented the methods of treating HCV that were, in fact, invented by the plaintiffs. The plaintiffs requested the court to issue a declaratory judgment that claims 13–16 of the '159 and '386 patents are invalid. The plaintiffs also ask the court to issue a declaratory judgment that the '159 and '386 patents are unenforceable, alleging misconduct of the defendant[10].

8. In a Joint Status Report dated 21 January 2015, the plaintiff seeks restitution and damages for the defendants' conduct as described above, and a declaration as to the invalidity, non-infringement and unenforceability of a number of patents.

[10] The full text of the redacted complaint is available on / through PACER.

PATENT 3: STEREOSELECTIVE SYNTHESIS OF PHOSPHORUS CONTAINING ACTIVES

Patent application WO2011123668A2 is a process patent with some claims referring to a compound in the form of a Markush structure The process comprises the preparation of sofosbuvir containing phosphorus. The process affords enantiomers or diastereomers of compounds having improved pharmacokinetic parameters relative to the active substance. Thus, claims are broad in nature and competitors may have to invent around this process.

As per the WIPO ISR, several process-related claims cannot be considered novel.

PATENT 4: NUCLEOSIDE PHOSPHORAMIDATES

Patent application WO2011123645A2 is a process patent for the preparation of the active compound. The patent covers a crystalline structure of nucleoside phosphoramidates, a general structural formula (Markush structure) of nucleoside phosphoramidates, and a process of preparation of the active compound. Nucleoside phosphoramidates are used for the treatment of HCV infection. As per the WIPO ISR, several claims related to crystalline structures cannot be considered novel.

PATENT 5: N- [(2 ' R) -2 ' -DEOXY-2 ' -FLUORO-2 ' -METHYL-P-PHENYL-5 ' -URIDYLYL] -L-ALANINE 1-METHYLETHYL ESTER AND PROCESS FOR ITS PRODUCTION

This patent is listed in the US Orange Book with patent number US8633309.

The patent application WO2010135569A1 contains product-by-process claims. A product-by-process claim is directed to a product that is defined by its process of preparation. This application claims diastereoisomeres of two specific nucleoside phosphoramidate prodrugs, their solvates, and polymorphic forms, as well as processes for their preparation and novel intermediates.

As per the WIPO ISR, the application does not meet the requirement for unity of invention, i.e. it relates to not only one invention, but a group of closely related inventions. The subject matter of independent claim 1, 18-21 and dependent claims 2-6 of WO2010135569A1 is new as it shows novelty and involves inventive steps.

PATENT 6: PURINE NUCLEOSIDE PHOSPHORAMIDATE

This patent application WO2011123672A1 claims a specific derivative of sofosbuvir. The patent covers a purine nucleoside phosphoramidate or hydrate thereof in crystalline or crystal-like form.

As per the WIPO ISR, all claims are new and inventive. However, claims 7-13 and 18-19 appear to be identical or lacking correct dependency.

PATENT 7: METHODS FOR TREATING HEPATITIS C VIRUS

Patent application WO2013040492A2 relates to combinations of therapeutic molecules (sofosbuvir, ledipasvir, PSI-7851) exhibiting synergistic effects, oral formulation, tablet formulation, dosing regimes, and methods of use for treating HCV infection.

As per the WIPO ISR, the subject matter of several claims (1,2, 10,11, 15-16, 19-21, 24, 33-38) is not inventive in light of prior art.

This patent is listed in the ledipasvir report Patent No. 5

PATENT 8: COMPOSITIONS AND METHODS FOR TREATING HEPATITIS C VIRUS

This patent is listed in the US Orange Book with patent number US8889159.

Patent application WO2013082003A1 claims a pharmaceutical composition comprising sofosbuvir and at least one excipient to treat HCV infection, a unit dosage form of about 400 mg of sofosbuvir, and a method to prepare a tablet of sofosbuvir.

Application WO2013082003A1 is in early prosecution.

PATENT 9: CONDENSED IMIDAZOLYLIMIDAZOLES AS ANTIVIRAL COMPOUNDS

Patent application WO2013075029A1 covers sofosbuvir derivatives. A Markush structure and specific imidazolylimidazole derivatives, their salts, prodrugs, compositions and combinations comprising them are claimed. The compounds, disclosed as HCV NS5A inhibitors, are claimed to be useful for the treatment of HCV infections.

As per the WIPO ISR, three documents have been cited as prior art against WO2013096512A1. One prior art document of particular relevance, WO2012068234A2, is by Gilead Sciences itself, and is relevant to claims 1-42.

PATENT 10: THIOPHEN-2-CARBOXYLIC ACID DERIVATIVES USEFUL AS INHIBITORS OF FLAVIVIRIDAE VIRUSES

Patent application WO2013010112A1 covers sofosbuvir derivatives. A Markush structure and specific substituted thiophen-2-carboxylic acid derivatives, their salts, esters, and compositions and combinations comprising them, are claimed. The compounds are claimed to be useful for the treatment of HCV infection in a mammal.

As per the WIPO ISR, two documents have been cited against the relevant claims 1-7,9,11,12, 19-28 of WO2013096512A1. The ISR report suggests that claims 1-7, 9 and 1-14 do not fulfill the requirements of novelty and claims 1-28 do not fulfill the inventive step.

PATENT 11: PYRAZINE AND IMIDAZOLIDINE DERIVATIVES AND THEIR USES TO TREAT HEPATITIS C

Patent application WO2012103113A1 covers specific sofosbuvir derivatives. A Markush structure and pyrazine and imidazolidine compounds and their stereoisomers and salts, pharmaceutical compositions containing them and a process for their preparation are claimed. The compounds are claimed to be useful for the treatment of viral infections, in particular HCV.

A WIPO ISR for this PCT application is not available. The examination history of this PCT application reveals that communication has been dispatched and the application is deemed to be withdrawn because of non-payment of the filing fee/search fee in time.

PATENT 12: ANTIVIRAL COMPOUNDS

Patent application WO2012068234A2 covers specific sofosbuvir derivatives. A Markush structure and new substituted imidazole compounds and their salts and prodrugs, pharmaceutical compositions and combinations comprising them are claimed. The compounds are used in pharmaceutical compositions useful for treating HCV or diseases associated with HCV.

As per the WIPO ISR, the PCT application does not meet the requirement of unity of invention. Several of the 324 claims are not novel (claim 6, 12-15, 19-22, 25-26, 31, 125-128, 155, 169, 177, and 178 completely; and claims 1, 43, 44, 46-49, 51-57, 62, 63, 83, 84, 111, 113, 115, 162, 163, 166, 170, 191, 225-324 partially).

PATENT 13: METHODS FOR THE PREPARATION OF DIASTEROMERICALLY PURE PHOSPHORAMIDATE PRODRUGS

Patent application WO2012012465A1 is a process patent claiming methods for preparing diastereomerically pure phosphoramidate prodrugs (Markush structure).

As per the WIPO ISR, all 36 claims meet the requirement of novelty and industrial applicability. However, claims 1-7 of the present application lack inventive steps.

PATENT 14: 1'-SUBSTITUTED-CARBA-NUCLEOSIDE PRODRUGS FOR ANTIVIRAL TREATMENT

Patent application WO2011150288A1 covers specific sofosbuvir derivatives. A Markush structure of a carba-nucleoside prodrug and compositions comprising prodrugs of the carba-nucleoside, or their salts and esters, is claimed. The compounds are used in pharmaceutical compositions for inhibiting HCV RNA-dependent RNA polymerase.

As per the WIPO ISR, all 23 claims of the present PCT application meet the requirement of novelty, inventive steps and industrial applicability.

Recently, a European patent (EP2576534B1) has been granted for this PCT application after the applicant amended the claims and restricted to composition claims only.

All claims of corresponding United States patent application US8415308B2 were allowed for grant.

PATENT 15: HETEROCYCLIC FLAVIVIRIDAE VIRUS INHIBITORS

Patent application WO2011146817A1 covers specific sofosbuvir derivatives. A Markush structure and new heterocyclic compounds, their salts, pharmaceutical compositions and combinations comprising them are claimed. The invention is also related to methods of use, as well as processes and intermediates useful for preparing such compounds. The compounds are useful for treating HCV infections.

As per the WIPO ISR, claim 1 relates to an extremely large number of possible compounds that have not been searched by the examiner. Specific compounds of claims 3, 5-10, and 22-23 have been searched and these fulfil the requirements of novelty, but are deemed to be obvious in light of prior art.

PATENT 16: CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT

Patent application WO2010093608A1 covers specific sofosbuvir derivatives. A Markush structure and novel substituted thieno[3,4-d]pyrimidine derivatives, their salts, esters, a process for their preparation, and compositions comprising them are claimed. The compounds are disclosed to be HCV RNA-dependent RNA polymerase (RdRp) inhibitors, useful for the treatment of viral infections.

As per the WIPO ISR, all 29 claims of the present PCT application meet the requirement of novelty, inventive steps and industrial applicability. Recently, a European patent EP2396340B1 has been granted for this PCT application.

PATENT 17: ABBREVIATED HCV THERAPY FOR HCV INFECTED PATIENTS WITH IL28B C/C GENOTYPE

United States patent application US20120107278A1 is a method of use patent. It claims the use of a combination of direct-acting antiviral, pegylated IFN α-2a, and ribavirin for the treatment of an HCV-infected patient with a specific DNA sequence variation in chromosome 19. Also claimed is a method of detecting a DNA sequence variation (rs12979860 SNP of chromosome 19) in HCV-infected patient. Sofosbuvir is a direct-acting antiviral, but not specifically claimed.

According to the USPTO Patent Application Information Reference system, the United States application is in examination and the present application has received final rejection for several claims based on obviousness as these claims are obvious variations (not identical copies) of claims of another patent or application of the same assignee, and are not patentable.

PATENT 18: COMBINATION OF ANTI-HCV COMPOUNDS WITH RIBAVIRIN FOR THE TREATMENT OF HCV

Patent application WO2011156757A1 claims a dosing regimen comprising the combination of an anti-HCV agent or its pharmaceutically acceptable salts, and ribavirin (but not interferon). It also claims where the combination exhibits synergistic effects in treating HCV infection. Further claimed are compositions and kits. The anti HCV compounds are selected from an NS3 protease inhibitor, NS4B inhibitor, nucleoside NS5B polymerase inhibitor (here sofosbuvir), non-nucleoside NS5B polymerase inhibitor, NS5A inhibitor, or an HCV entry inhibitor.

A WIPO ISR is not available. The examination history of this PCT application reveals that the constituency application is deemed to be withdrawn because of non-payment of filing fee/search fee in time.

PATENT 19: COMPOUNDS

Patent application WO2012075140A1 covers specific sofosbuvir derivatives. A Markush structure of spiro-nucleosides, their pharmaceutically acceptable salts, isomers, metabolites, deuterides, a process of preparation of spiro-nucleosides, compositions comprising them, and a method of treatment of HCV infection using spiro-nucleosides, is claimed.

As per the WIPO ISR, two prior art documents have been cited against relevant claims (claims 1, 2, 29, 39-49 of WO2012075140A1). Also the ISR reveals that the PCT application does not meet the requirement of unity of invention, as the search authority considers that there are ten inventions covered by the claims in the present application.

PATENT 20: NUCLEOSIDE PHOSPHORAMIDATES

This patent is listed in the US Orange Book with patent number US8618076.

United States patent US8618076B2 covers a crystalline form of specific nucleoside phosphoramidate. The compound is useful for the treatment of HCV infection.

PATENT 21: METHODS AND COMPOSITIONS FOR TREATING HEPATITIS C VIRUS

Patent application WO2013066748A1 covers a composition and a method of treatment of HCV infection using GS-7977 (sofosbuvir) and ribavirin.

An International Search Report (ISR) is yet to be published.

<u>Other Litigation Cases</u>

1. On 14 March 2014, Idenix Pharmaceuticals filed a patent infringement lawsuit against Gilead Sciences in France, Germany and in the United Kingdom. Idenix argued that Gilead infringes its European patent EP1523489, which covers nucleosides for treating HCV. It is seeking remedies with respect to Gilead's marketing and sale of drugs that contain sofosbuvir, which it believes infringes the patent. Current status is unknown.

2. In December 2013, Idenix Pharmaceuticals filed a patent infringement lawsuit in the United States District Court in Boston, Massachusetts against Gilead. The patents-in-suit include Idenix United States Patents 6,914,054 and 7,608,597.

3. Gilead Sciences filed an impeachment action on the Canadian Federal Court to invalidate the Idenix CA2490191 patent, which is the Canadian patent corresponding to Idenix United States Patent No. 7608600.

4. Gilead Sciences filed a suit against Idenix Pharmaceuticals in Australia to invalidate a granted Idenix patent covering certain 2'-methyl-2'-fluoro nucleoside compounds and their use in treating HCV or other Flaviviridae viruses.

5. In September 2012 Gilead Sciences filed a suit in Norway against Idenix Pharmaceuticals to invalidate Idenix's co-owned Norwegian patent NO330755 covering certain 2'-methyl-2'-fluoro nucleoside compounds and their use in treating HCV or other Flaviviridae viruses. Idenix filed a counter claim that a Gilead patent covering similar subject matter was invalid and unenforceable. The Oslo District Court in Norway decided on 21 March 2014 that Idenix is not entitled to priority of invention and decided in favor of Gilead. The court found the Idenix patent to be invalid. Idenix announced that it intends to file an appeal to challenge the decision.

6. F. Hoffmann-La Roche Ltd. filed an arbitration case against Gilead Sciences. Roche is claiming control of sofosbuvir based on a 2004 collaboration with Pharmasset. On 14 August 2014 the arbitration panel ruled in favor of Gilead, determining that Gilead has exclusive rights to sofosbuvir over Roche.

7. Merck Sharp & Dohme, MSD filed a patent infringement lawsuit against Gilead in the United States District Court for the Northern District of California, seeking a 10% royalty based on two patents ('499 and '712). In response, Gilead stated that its HCV drug would not infringe the patents, and that the patents failed to meet the standards for patentability. On 3 September 2013, Gilead asked the Court to issue a declaratory judgment that its HCV drug would not infringe two Merck Sharpe & Dome patents, or to deem the patents invalid. The case is still active (Case No: 3:13-cv-04057).

NON-SPONSOR PATENTS

As of March 2014, there was competition for patents on sofosbuvir that have been filed by 52 non-Sponsor entities, including AstraZeneca, Boehringer-Ingelheim GmbH, Bristol-MyersSquibb, GlaxoSmithKline, F. Hoffmann La Roche, Merck Sharpe & Dome and Novartis.

As of March 2014, a total of 168 inventions (patent families) were found, most relating to product (100), followed by method of use (26) and formulation (15).

Patents of non-Sponsor entities are included in the complete data collection in form of an Excel file that can be made available on demand. Please send any requests to: phidepartment@who.int.

ANNEX – SOFOSBUVIR PATENT SITUATION

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Subject Matter	Patent application WO2005003147A2 discloses the base compound of sofosbuvir (primary patent).	Patent application WO2008121634A2 relates to the sofosbuvir prodrug as marketed.	Patent application WO2011123668A2 is a process patent.	Patent application WO2011123645A2 is a process patent for the preparation of the active compound.	Patent application WO2010135569A1 is a product by process patent.	Patent application WO2011123672A1 claims a specific derivative of sofosbuvir.	Patent application WO2013040492A2 covers a composition and a method of treatment using a sofosbuvir, PSI-7851, or ledipasvir. This patent is the same as Patent 5 in the ledipasvir report.	Patent application WO2013082003A1 claims a pharmaceutical composition comprising sofosbuvir and at least one excipient.
Applicant	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Pharmasset Ltd.	Gilead Sciences Inc.	Gilead Sciences Inc.
Int'l Patent Publication Number	WO2005003147A2	WO2008121634A2	WO2011123668A2	WO2011123645A2	WO2010135569A1	WO2011123672A1	WO2013040492A2	WO2013082003A1
Priority Number	US2003474368P	US20070909315P US20070982309P US20080053015	US2010319548P	US2010319513P	US2009179923P	US2010319548P	US2011535885P	US2011564500P
Listed in US Orange Book[11]	No	Patent Nos: US8580765, US7964580, US8334270	No	No	Patent No: US8633309	No	No	Patent No: US8889159
Expected expiry[a]	20 Apr 2024	25 Mar 2028	30 Mar 2031	30 Mar 2031	19 May 2030	30 Mar 2031	13 Sep 2032	26 Nov 2032

[11] The US Orange Book lists the patents as submitted by the holder of the authorization in line with Federal Drug Administration (FDA) Form 3542. This includes formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents, FDA. Orange Book, 34th Edition 2014.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
PATENT STATUS								
ARIPO (AP)[b g]	No application identified	No patent or application listed in the license agreement[h]	Examined and objection to patentability issued. Awaiting Applicants response AP201206535	Pending AP2012006543D0	No patent or application listed in the license agreement[h]	No application identified	Pending AP2014007575	Pending AP2012007699
Argentina (AR)	Pending AR82068A2 Pending AR82067A2 Pending AR82066A2 Pending AR82064A2 Pending AR44566A1	Pending AR66898A1	Pending AR80819A1	Pending AR80870A1	Pending AR82937A1	Pending AR81813A1	N/A	N/A
Australia (AU)	Granted AU2004253860B2	Pending AU2012241173A1 Granted AU2008232827B2	Pending AU2011235044A1	Pending AU2011235112A1	Granted AU2010249481B2	N/A	Pending AU2012308295A1	N/A
Brazil (BR)[g]	Pending BR200410846A	Pending PI0809654-6 Pending PI0823519-8	N/A	Granted BR1120120249231	N/A	N/A	N/A	Granted BR1120140127395

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Canada (CA)	Pending CA2734066A1 Pending CA2734055A1 Pending CA2734052A1 Pending CA2733842A1 Granted CA2527657C	Granted CA2682230A1	Pending CA2794671A1	Pending CA2794669A1	Pending CA2763151A1 Pending CA2819700A1	Pending CA2849694A1	Pending CA2840242A1	N/A
Chile (CL)[g]	No application identified	Granted CL2008000902A1	Granted CL2011000718	No application identified	Pending CL201000520 Pending 2013000903 (Divisional from CL201000520)	Pending CL20110000717	Pending CL2014000630A1	Pending CL2014001397
China (CN)	Pending CN1816558A Granted CN100503628C	Pending CN101918425A	Pending CN102906102A Pending CN104017020A	Pending CN102858790A	Pending CN102459299A Pending CN104292256A	N/A	Pending CN104244945A	N/A
China, Hong Kong SAR (HK)	Pending HK1155752A0 Pending HK1155751A0 Pending HK1155458A0 Pending HK1155457A0	Pending HK1150450A0	Pending HK1181775A0	Pending HK1178171A0	Pending HK1169414A0 Pending HK1182114A0 Pending HK1182938A0	Pending HK1181774A0	N/A	N/A
Colombia (CO)	Pending CO5660270A2	Pending CO6260023A2	Pending CO6630166A2	Pending CO6630167A2	Pending CO6470789A2	N/A	Pending CO6930366A2	N/A
Costa Rica (CR)	N/A	N/A	Pending CR20120534A	Pending CR20120532A	N/A	N/A	Pending CR20140177A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Ecuador (EC)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Egypt (EG)	N/A	N/A	N/A	Pending 1955/2011 Pending 1659/2012	N/A	N/A	Pending 392/2014	Pending 864/2014
Ethiopia (ET)	N/A	No patent or application listed in the license agreement[h]	N/A	No patent or application listed in the license agreement[h]	N/A	N/A	No patent or application listed in the license agreement[h]	No patent or application listed in the license agreement[h]
EAPO (EA)[c]	N/A	No patent or application listed in the license agreement[h]	Pending EA201290988A1	Pending EA201290993A1	Pending EA201171417A1 Pending EA201370186A1	N/A	Pending EA201490588A1	No patent or application listed in the license agreement[h]
EPO (EP)[d]	Pending EP2604620A1 Pending EP2345661A1 Pending EP2345659A1 Withdrawn EP2345658A1 Pending EP2345657A1 Pending EP1633766A2	Granted EP2203462B1 Pending EP2792680A1 Pending EP2801580A1 Pending EP2824109A1 Pending EP2826784A1	Granted EP2552931B1	Pending EP2552930A2	Pending EP2432792A1 Pending EP2610264A3	Pending EP2552933A1 Pending EP2609923A3 Pending EP2752422A1	Pending EP2709613A2	Pending EP12795307
GCC[e g]	No application identified	No application identified	No application identified	No application identified	No application identified	Pending GC2011-18617	No application identified	Pending GC2012-22917
Georgia (GE)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
India (IN)	Pending IN201102079P1 2079/DELNP/2011 Pending IN201101871P1 1871/DELNP/2011 Pending IN201101870P1 1870/DELNP/2011 Refused - appeal pending IN200506087P1 6087/DELNP/2005	Pending IN200903658P2 3658/KOLNP/2009	N/A	Pending 9149/CHENP/2012 [h]	Pending 4972/KOLNP/2011	N/A	Pending 2956/DELNP/2014[h]	Pending 4542/DELNP/2014
Indonesia (ID)	Granted ID28288	No patent or application listed in the license agreement[h]	N/A	Pending W0020124454[h]	No patent or application listed in the license agreement[h]	N/A	Pending P00201402133[h]	Pending P00201403478[h]
Iran (Islamic Republic of) (IR)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Israel (IL)	Granted IL211375A Granted IL210367A Granted IL172259A	Pending IL222810D0 Pending IL217228A Pending IL201239A	N/A	Pending IL222099	Pending IL216492	N/A	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Japan (JP)	Rejected JP2011201882A Pending JP2011190264A Withdrawn JP2011190263A Granted JP05266357B2 Granted JP04958158B2	Granted JP05318085B2 Granted JP5539419B2 Pending JP2015024998A Pending JP2014196305A	Pending JP2013527145A	Pending JP2013523767A	Pending JP2012527477A Pending JP2015028060A	Pending JP2013525277A	Pending JP2014526516A	N/A
Jordan (JO)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Malaysia (MY)[g]	Granted MY138477A	Granted MY147409A	N/A	N/A	Pending MY2011005625P	N/A	N/A	Pending MY2014001520P
Mexico (MX)	Granted MX275935B	Pending MX296818B Pending MX2009010401A	Pending MX2012011324A	Pending MX2012011171A	Pending MX2011012417A	N/A	Pending MX2014003145A	N/A
Morocco (MA)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	Pending 36906	Pending 37103
New Zealand (NZ)	Granted NZ543867A	Granted NZ599206A Granted NZ579880A	N/A	N/A	Pending NZ596635	N/A	N/A	N/A
Nigeria (NG)	N/A	No patent or application listed in the license agreement[h]	N/A	No patent or application listed in the license agreement[h]	No patent or application listed in the license agreement[h]	N/A	N/A	No patent or application listed in the license agreement[h]
OAPI[f g]	No application identified	No application identified	Granted 16115	Granted 16103	No application identified	No application identified	Pending 1201400117	Pending 1201400229

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Pakistan (PK)[g]	No application identified	No application identified and no patent or application listed in the license agreement[h]	No application identified	Pending 233/2011 Pending 748/2012	No application identified and no patent or application listed in the license agreement[h]	No application identified	Pending 880/2011	Pending 803/2012
Peru (PE)	N/A	N/A	Pending PE20130151A1	Pending PE20130183A1	N/A	N/A	Pending PE10562014A1	N/A
Philippines (PH)[g]	Granted PH12005502136	Pending PH2009501847	No application identified	No application identified	No application identified	No application identified	Pending PH2014500557	Pending PH2014501133
Republic of Korea (KR)	Granted KR883703B1	Granted KR101432860B1 Pending KR20120034801A Pending KR20150008929A	Pending KR20130064064A	Pending KR20120138242A	Pending KR20120034662A	N/A	Pending KR20140096029A	N/A
Russian Federation (RU)	Granted RU2358979C2	Granted RU2478104C2 Pending RU2012152811A	N/A	N/A	N/A	N/A	N/A	N/A
Singapore (SG)	Granted SG117252	Pending SG179445A1 Granted SG155711	Pending SG184323A1	Pending SG184324A1	Pending SG176197A1	N/A	N/A	N/A
South Africa (ZA)	Granted ZA200509521A	Granted ZA200906647 Pending ZA201200310	Granted ZA201207800	Granted ZA201207799A Pending ZA201400249	Granted ZA201108749 Allowed ZA201301620	N/A	Pending ZA201402534	Pending ZA201403903 ZA201404061
Tunisia (TN)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6	Patent 7	Patent 8
Thailand (TH)	N/A	N/A	Pending TH1201005229	Pending TH1201005189	N/A	N/A	N/A	N/A
Ukraine (UA)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
The United States (US)	Granted US8415322B2 Granted US7429572B2 Pending US20080253995A1 Pending US20080070861A1 Pending US20090004135A1 Pending US20090036666A1 Pending US20120245335A1	Granted US8580765B2 Granted US8334270B2 Granted US7964580B2 Granted US8906880B2 Granted US8735372B2 Granted US8957046B2 Pending US20140187511A1	Granted US8859756B2	Granted US8859756B2	Pending US20130165401A1 Granted US8629263B2 Granted US8633309B2 Granted US8642756B2 Pending US20140121366A1	Granted US8563530B2	Pending US20130243726A1	Granted US8889159B2
Uruguay (UY)	N/A	N/A	N/A	Pending UY33311A	N/A	Pending UY33310A Pending UY33312A	N/A	Pending UY34474A
Viet Nam (VN)	N/A	No patent or application listed in the license agreement[h]	Pending VN32717A	Pending VN33365A	No patent or application listed in the license agreement[h]	N/A	Pending 39534	Pending 1-201401861[h]

	Patent 9	Patent 10	Patent 11	Patent 12	Patent 13	Patent 14	Patent 15	Patent 16
Subject Matter	Patent application WO2013075029A1 covers sofosbuvir derivatives be HCV NS5A inhibitors	Patent application WO2013010112A1 covers sofosbuvir derivatives.	Patent application WO2012103113A1 covers specific sofosbuvir derivatives.	Patent application WO2012068234A2 covers specific sofosbuvir derivatives.	Patent application WO2012012465A1 is a process patent claiming methods for preparing diastereomerically pure phosphoramidate prodrugs (Markush structure).	Patent application WO2011150288A1 covers specific sofosbuvir derivatives.	Patent application WO2011146817A1 covers specific sofosbuvir derivatives.	Patent application WO2010093608A1 covers specific sofosbuvir derivatives.
Applicant	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.	Gilead Sciences Inc.
Int'l Patent Publication Number	WO2013075029A1	WO2013010112A1	WO2012103113A1	WO2012068234A2	WO2012012465A1	WO2011150288A1	WO2011146817A1	WO2010093608A1
Priority Number	US2011560654P	US2011507544P	US2011435528P	US2010414818P	US2010365621P	US2010349597P	US2010347215P	US2009151248P
Listed in US Orange Book[12]	No	No	No	No	No	No	No	No
Expected expiry[a]	15-Nov-32	12-Jul-32	23-Jan-32	15-Nov-31	18-Jul-31	25-May-31	19-May-31	8-Feb-30
PATENT STATUS								
ARIPO (AP)[b g]	Pending AP201306877D0	No application identified	No application identified	No application identified	Pending AP201306665D0	No application identified	No application identified	Granted AP2922A

[12] The US Orange Book lists the patents as submitted by the holder of the authorization in line with Federal Drug Administration (FDA) Form 3542. This includes formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents, FDA. Orange Book, 34th Edition 2014.

	Patent 9	Patent 10	Patent 11	Patent 12	Patent 13	Patent 14	Patent 15	Patent 16
Argentina (AR)	N/A	N/A	Pending AR85016A1	Pending AR083711A1	N/A	Pending AR084389A1	N/A	N/A
Australia (AU)	Pending AU2012318253A1	Pending AU2012280959A1	N/A	Pending AU2011328980A1	Pending AU2011282241A1	N/A	Pending AU2011255452A1	Pending AU2010213873A1
Brazil (BR)[g]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Canada (CA)	Pending CA2815082A1	Pending CA2840445A1	N/A	Pending CA2817840A1	Pending CA2804375A1	N/A	Pending CA2797872A1	Pending CA2751277A1
Chile (CL)[g]	Pending CL2013001428A1	N/A	N/A	N/A	Pending CL2013000076A1	N/A	N/A	Pending CL2011001906
China (CN)	Pending CN103328480A	N/A	N/A	N/A	Pending CN103052646A	N/A	N/A	Pending CN102348713A
China, Hong Kong SAR (HK)	N/A	N/A	N/A	N/A	Pending HK1182394A0	Granted HK1182387A1	Pending HK1181033A0	Granted HK1163108A1
Colombia (CO)	N/A	N/A	N/A	N/A	Pending CO6680607A2	N/A	N/A	Pending CO6420354A2
Costa Rica (CR)	Pending CR20130231A	N/A	N/A	N/A	Pending CR20130063A	N/A	N/A	N/A
Ecuador (EC)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Egypt (EG)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethiopia (ET)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
EAPO (EA)[c]	Pending EA201390576A1	N/A	N/A	N/A	Pending EA201390133A1	N/A	N/A	Pending EA201190110A1

	Patent 9	Patent 10	Patent 11	Patent 12	Patent 13	Patent 14	Patent 15	Patent 16
EPO (EP)[d]	Pending EP2635588A1	Pending EP2734515A1	Pending EP12702714	Pending EP2640719A2	Granted EP2596004B1	Granted EP2576534B1	Pending EP2571882A1	Granted EP2396340B1 Pending EP2719701A1
GCC[e g]	No application identified	No application identified	Pending GC2012-20325	No application identified	No application identified	No application identified	No application identified	No application identified
Georgia (GE)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified
India (IN)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Pending IN201106065P1 6065/DELNP/2011
Indonesia (ID)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Iran (Islamic Republic of) (IR)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Israel (IL)	Pending IL226345D0	N/A	N/A	Pending IL226346D0	Pending IL224045	N/A	N/A	Pending IL214396A
Japan (JP)	N/A	Pending JP2014520862A	N/A	Pending JP2013542996A	Pending JP2013537527A	Pending JP2013512264 Pending JP2013528184A	Pending JP2013526581A	Pending JP2012517444A Pending JP2014185183A
Jordan (JO)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Malaysia (MY)[g]	Adverse Preliminary Exam MY2014001415P	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mexico (MX)	Pending MX2013005575A	N/A	N/A	N/A	Pending MX2013000656A	N/A	N/A	Pending MX2011008409A

	Patent 9	Patent 10	Patent 11	Patent 12	Patent 13	Patent 14	Patent 15	Patent 16
Morocco (MA)[g]	Granted MA34727B1	No application identified	No application identified	No application identified	Granted MA34471B1	No application identified	No application identified	No application identified
New Zealand (NZ)	N/A	N/A	N/A	N/A	N/A	N/A	Pending NZ603310A	Pending NZ594370A
Nigeria (NG)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
OAPI[f g]	Pending 1201300262	No application identified	No application identified	No application identified	Granted 16292	No application identified	No application identified	Granted 15545
Pakistan (PK)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified
Peru (PE)	Pending PE11632014A1	N/A	N/A	N/A	Pending PE20130807A1	N/A	N/A	Pending PE20120257A1
Philippines (PH)[g]	Pending PH2013500976	No application identified	No application identified	No application identified	Pending PH2013500033	No application identified	No application identified	No application identified
Republic of Korea (KR)	Pending KR20140096239A	N/A	N/A	Pending KR20140033316A	Pending KR2013130690A	N/A	N/A	Pending KR2011116046A
Russian Federation (RU)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Singapore (SG)	Pending SG190786A1	N/A	N/A	Pending SG190785A1	Pending SG186831A1	N/A	N/A	Pending SG173186A1
South Africa (ZA)	N/A	N/A	N/A	N/A	Granted ZA201300135A	N/A	N/A	Granted ZA201106230A
Tunisia (TN)[g]	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified	No application identified
Thailand (TH)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ukraine (UA)	Pending UA201306068A	N/A	N/A	N/A	Pending UA201301999A	N/A	N/A	N/A

	Patent 9	Patent 10	Patent 11	Patent 12	Patent 13	Patent 14	Patent 15	Patent 16
The United States (US)	Granted US8940718B2 Granted US8575135B2 Granted US8921341B2 Pending US20130164260A1 Pending US20140309432A1	Granted US8741946B2	Abandoned US2012202794A1	Pending US20140018313A1	Pending US20130281686A1	Granted US8415308B2	Granted US8815858B2	Granted US8012942B2
Uruguay (UY)	N/A	N/A	Pending UY33875A	Pending UY33735A	N/A	Pending UY33414A	N/A	N/A
Viet Nam (VN)	N/A	N/A	N/A	N/A	Pending VN33756A	N/A	N/A	Pending VN30328A

	Patent 17	Patent 18	Patent 19	Patent 20	Patent 21
Subject Matter	US patent application US20120107278A1 is a method of use patent.	Patent application WO2011156757A1 claims a dosing regimen comprising the combination of an anti-HCV agent or its pharmaceutically acceptable salts, ribavirin (but not interferon).	Patent application WO2012075140A1 covers specific sofosbuvir derivatives.	US patent US8618076B2 covers crystalline form of specific nucleoside phosphoramidate.	Patent application WO2013066748A1 covers a composition and a method of treatment of HCV infection using GS-7977 (sofosbuvir) and ribavirin.
Applicant	Pharmasset Ltd	Gilead Sciences Inc.	Pharmasset Ltd	Gilead Sciences Inc.	Gilead Sciences Inc.
Int'l Patent Publication Number	US20120107278A1	WO2011156757A1	WO2012075140A1	US8618076B2	WO2013066748A1
Priority Number	US2010408304P	US2010353460P	US2010417946P	US2009179923P	US2011553481P
Expected expiry[a]	30-Oct-31	9-Jun-31	29-Nov-31	30-Mar-31	25-Oct-32
Listed in US Orange Book[13]	No	No	No	Yes US8618076	No
PATENT STATUS					
ARIPO (AP)[b g]	No application identified	No application identified	No application identified	No application identified	No application identified
Argentina (AR)	N/A	Pending AR084393A1	Pending AR084044A1	N/A	Pending AR088580A1

[13] The US Orange Book lists the patents as submitted by the holder of the authorization in line with Federal Drug Administration (FDA) Form 3542. This includes formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents, FDA. Orange Book, 34th Edition 2014.

	Patent 17	Patent 18	Patent 19	Patent 20	Patent 21
Australia (AU)	N/A	N/A	Pending AU2011336632A1	N/A	Pending AU2012332827A1
Brazil (BR)[g]	N/A	N/A	N/A	N/A	N/A
Canada (CA)	N/A	N/A	Pending CA2818853A1	N/A	Pending CA2853495A1
Chile (CL)[g]	N/A	N/A	N/A	Pending CL2011000716	N/A
China (CN)	N/A	N/A	N/A	N/A	Pending CN104244947A
China, Hong Kong SAR (HK)	N/A	N/A	N/A	N/A	N/A
Colombia (CO)	N/A	N/A	N/A	N/A	N/A
Costa Rica (CR)	N/A	N/A	N/A	N/A	N/A
Ecuador (EC)	N/A	N/A	N/A	N/A	N/A
Egypt (EG)	N/A	N/A	N/A	N/A	N/A
Ethiopia (ET)	N/A	N/A	N/A	N/A	N/A
EAPO (EA)[c]	N/A	N/A	N/A	N/A	N/A
EPO (EP)[d]	N/A	Pending EP11726033	Pending EP2646453A1	N/A	Pending EP1278726A1 Pending EP2776024A1

	Patent 17	Patent 18	Patent 19	Patent 20	Patent 21
GCC[e g]	No application identified	No application identified	No application identified	No application identified	Pending GC2012-22601
Georgia (GE)[g]	No application identified	No application identified	No application identified	No application identified	No application identified
India (IN)	N/A	N/A	N/A	N/A	N/A
Indonesia (ID)	N/A	N/A	N/A	N/A	N/A
Iran (Islamic Republic of) (IR)	N/A	N/A	N/A	N/A	N/A
Israel (IL)	N/A	N/A	N/A	N/A	N/A
Japan (JP)	N/A	N/A	Pending JP2013544286A	N/A	Pending JP2014532657A
Jordan (JO)	N/A	N/A	N/A	N/A	N/A
Malaysia (MY)[g]	N/A	N/A	N/A	N/A	N/A
Mexico (MX)	N/A	N/A	N/A	N/A	N/A
Morocco (MA)[g]	No application identified	No application identified	No application identified	No application identified	No application identified
New Zealand (NZ)	N/A	N/A	N/A	N/A	N/A
Nigeria (NG)	N/A	N/A	N/A	N/A	N/A
OAPI[f g]	No application identified	No application identified	No application identified	No application identified	No application identified
Pakistan (PK)[g]	No application identified	No application identified	No application identified	No application identified	No application identified

	Patent 17	Patent 18	Patent 19	Patent 20	Patent 21
Peru (PE)	N/A	N/A	N/A	N/A	N/A
Philippines (PH)[g]	No application identified	No application identified	No application identified	No application identified	No application identified
Republic of Korea (KR)	N/A	N/A	N/A	N/A	N/A
Russian Federation (RU)	N/A	N/A	N/A	N/A	N/A
Singapore (SG)	N/A	N/A	N/A	N/A	N/A
South Africa (ZA)	N/A	N/A	N/A	N/A	N/A
Tunisia (TN)[g]	No application identified	No application identified	No application identified	No application identified	No application identified
Thailand (TH)	N/A	N/A	N/A	N/A	N/A
Ukraine (UA)	N/A	N/A	N/A	N/A	N/A
United States (US)	Pending US20120107278A1	Abandoned US20110306541A1	Granted US8841275B2 Pending US2015018300A1	Pending US2013288997A1 Granted US8618076B2 Granted US8735569B2	Pending US2013109647A1
Uruguay (UY)	N/A	Pending UY33445A	N/A	N/A	Pending UY34420A
Viet Nam (VN)	N/A	N/A	N/A	N/A	N/A

[a] If granted and not subject to patent term extension.

[b] **The African Regional Intellectual Property Organization (ARIPO) includes the following countries:** Botswana, Ghana, Gambia, Kenya, Liberia, Lesotho, Malawi, Mozambique, Namibia, Sudan, Sierra Leone, Swaziland, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe.

[c] **The Eurasian Patent Organization (EAPO) includes the following countries:** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation, Tajikistan and Turkmenistan.

[d] **The European Patent Office (EPO) includes the following countries:** Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxemburg, Latvia, Malta, Monaco, Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovenia, Slovakia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Turkey and the United Kingdom.

[e] **The Patent Office of the Cooperation Council for the Arab States of the Gulf** (**Gulf Cooperation Council - GCC) includes the following countries**: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and United Arab Emirates.

[f] **The African Intellectual Property Organization (OAPI) includes the following countries:** Benin, Burkina Faso, Cameroon, Central African Republic, Chad, The Congo, Equatorial Guinea, Gabon, Guinea, Guinea Bissau, Côte d'Ivoire, Mali, Mauritania, Niger, Senegal and Togo.

[g] Information directly received or retrieved from the patent office.

[h] Information from Appendix 2 of the License Agreement. The draft agreement can be found on: http://keionline.org/sites/default/files/GILD_Sof_License_Agmt_(FINAL).pdf

GLOSSARY

INTERFERENCE PROCEEDING: An interference proceeding is a proceeding to determine the priority issues of multiple patent applications. Based on the (previous) first-to-invent system of the United States, a party which has failed to file a patent application on time is allowed to challenge the inventorship of another party which has a granted or pending patent.

N/A: Patent information was not available for this country at the time the patent searches were conducted.

NOTICE OF ALLOWANCE: During a USTPO examination, if it appears to the examiner that the applicant is entitled to a patent under the law, a notice of allowance is sent to the applicant. The notice of allowance specifies a sum constituting the issue fee which must be paid within a given time from the date of mailing of the notice of allowance to avoid abandonment of the application.

PATENT FAMILY MEMBER: All patent publications that relate to the same basic patent (that is, invention) are members of this patent family. In the present study patent families are based on the Derwent World Patent Index (DWPI).

PENDING or GRANTED: Indicates a patent's legal status.

PRIORITY NO: Earliest application number.

SPONSOR: The term "Sponsor" refers to the entities that are developing the medicines and are holding or filing for market authorization. Note that a Sponsor is not necessarily the patent assignee or applicant.

THE WIPO INTERNATIONAL SEARCH REPORT (ISR): After an applicant files a PCT application with WIPO, a search is conducted by an authorised International Searching Authority (ISA) to find the most relevant prior art documents regarding the claimed subject matter. The search results in an International Search Report (ISR), together with a written opinion regarding patentability.